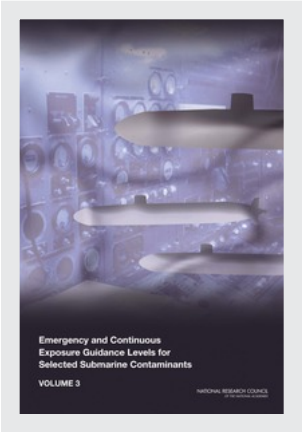

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Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants

VOLUME 3

Committee on Emergency and Continuous Exposure Guidance Levels
for Selected Submarine Contaminants

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

A submarine is an enclosed and isolated environment when submerged. Its crew works, eats, and sleeps in this environment and is exposed to air contaminants 24 h/day, unlike workers in a typical occupational environment, who have a respite from workplace exposures at the end of the workday or workweek. To protect the health of submariners, the U.S. Navy has developed 1-h and 24-h emergency exposure guidance levels (EEGLs) and 90-day continuous exposure guidance levels (CEGLs) for a number of chemical contaminants.

In 1995, the Navy began reviewing and updating submarine exposure guidance levels and asked the Committee on Toxicology (COT) of the National Research Council (NRC) to conduct an independent review of several chemicals. As a result of the Navy's initial request, NRC convened a committee that reviewed and published two reports on 21 chemicals. As a follow-on activity to that work, the Navy requested review of an additional five chemicals. Accordingly, this third volume provides the committee's rationale and recommendations for EEGLs and CEGLs for acetaldehyde, hydrogen chloride, hydrogen fluoride, hydrogen sulfide, and propylene glycol dinitrate.

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by 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 of 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 thank the following for their review of this report: John R. Balmes, University of California, San Francisco; Alan H. Hall, Toxicology Consulting and Medical Translating Services, Inc.; Wendy J. Heiger-Bernays, Boston University School of Public Health; Charles H. Hobbs, Lovelace Respiratory Research Institute; Nu-May Ruby Reed, California Environmental Protection Agency; Laura Van Winkle, University of California, Davis; and James G. Wagner, Michigan State University.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of the report was overseen by E. Eugene McConnell, ToxPath, Inc. Appointed by NRC, he was responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of the report rests entirely with the committee and the institution.

The committee is grateful for the assistance of the NRC staff in preparing this report: Ellen Mantus, project director; James Reisa, director of the Board on Environmental Studies and Toxicology; Heidi Murray-Smith, associate program officer; Mirsada Karalic-Loncarevic, manager, Technical Information Center; Norman Grossblatt, senior editor; Korin Thompson, program assistant (up to November 2008); and Panola Golson, senior program assistant. Finally, I thank the members of the committee for their dedicated efforts throughout the development of this report.

David Dorman, *Chair*
Committee on Emergency and Continuous
Exposure Guidance Levels for Selected
Submarine Contaminants

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Summary

Submariners live in an enclosed and isolated environment when at sea on a submerged submarine. Unlike workers who have respites from occupational exposures at the end of a shift or workweek, submariners are potentially exposed to air contaminants 24 h/day while their submarine is submerged. To protect submariners from potential adverse health effects associated with air contaminants, the U.S. Navy has established 1-h and 24-h emergency exposure guidance levels (EEGLs) and 90-day continuous exposure guidance levels (CEGLs) for a number of the contaminants.

EEGLs are defined as ceiling concentrations (concentrations not to be exceeded) of chemical substances in submarine air that will not cause irreversible harm to crew health or prevent the performance of essential tasks, such as closing a hatch or using a fire extinguisher, during rare emergency situations lasting 1-24 h. Exposures at the EEGLs may induce reversible effects, such as ocular or upper respiratory tract irritation, and are therefore acceptable only in emergencies, when some discomfort must be endured. After 24 h of exposure, the CEGLs would apply. CEGLs are ceiling concentrations designed to prevent immediate or delayed adverse health effects or degradation in crew performance that might result from continuous exposure to chemical substances lasting up to 90 days.

In December 1995, the Navy began reviewing and updating the submarine exposure guidance levels. Because the National Research Council (NRC) Committee on Toxicology (COT) had previously reviewed and provided recommendations for those and other types of exposure guidance levels, the Navy requested that COT review or when necessary develop EEGLs and CEGLs for a variety of substances. As a result of the Navy's request, NRC convened a committee in 2002 that reviewed and published two reports on 21 chemicals.[1,2] As a

[1]NRC (National Research Council). 2007. Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants: Volume 1. Washington, DC: National Academies Press.

follow-on activity to that work, the Navy requested review of an additional five chemicals, and NRC convened a second Committee on Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants in 2008.

THE COMMITTEE AND ITS CHARGE

Members of the committee were selected for their expertise in inhalation toxicology, neurotoxicology, regulatory toxicology, veterinary pathology, respiratory pathology, pharmacokinetics, pulmonary and occupational medicine, and human-health risk assessment. The committee was asked to review the U.S. Navy's current and proposed 1-h and 24-h EEGLs and 90-day CEGLs for selected submarine contaminants and, where possible, to develop EEGLs and CEGLs for those selected chemicals that do not have existing or proposed levels. The committee was also asked to identify data gaps and to make recommendations for future research. Specifically, the Navy asked the committee to review guidance levels for acetaldehyde, hydrogen chloride, hydrogen fluoride, hydrogen sulfide, and propylene glycol dinitrate.

APPROACH TO STUDY

In conducting its evaluations, the committee reviewed relevant human and animal data and used data-selection criteria described in the NRC report *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals*.[3] Where possible, primary references were used to derive the exposure guidance levels. Secondary references were used to support the estimates derived and the selection of critical end points. Whenever possible, studies that followed accepted standard scientific methods were selected as key studies (studies used to derive the exposure guidance levels). Inhalation-exposure studies were used to derive the EEGL and CEGL values; data on other routes of exposure were considered when that was appropriate. Human studies were preferred over animal studies. When epidemiologic and human experimental studies were available, preference typically was given to human experimental studies because they were conducted in a controlled laboratory setting and allowed measurement of personal exposure and health effects relevant for derivation of exposure guidance levels. The committee recognizes the need to consider

[2]NRC (National Research Council). 2008. Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants: Volume 2. Washington, DC: National Academies Press.

[3]National Research Council. 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

the statistical power of a study involving a small number of subjects. However, the committee did not develop criteria for assessing the adequacy of a study's statistical power, because individual studies, whether human or animal, were never used in isolation to derive an EEGL or CEGL value. When appropriate human data were not available, standard laboratory animal studies were used. A weight-of-evidence approach was used to select key studies and to ensure that the selected data were consistent with the overall scientific database.

For derivation of the EEGL and CEGL values, the committee followed basic guidance provided by the NRC report *Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-Term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance Level (CEGL) Documents*[4] but also considered the guidance for developing similar exposure levels provided in more recent NRC reports. Data on acute or short-term inhalation and ocular irritancy provided the basis of the EEGLs, whereas data on repeated inhalation exposure data provided the basis of the CEGLs, and the effects of cumulative exposures were considered in deriving the CEGL. The most sensitive end points were emphasized for derivation of both exposure levels. The committee considered only health end points relevant to healthy young men on the assumption that no women are serving as permanent crew on submarines.

When the key studies, health end points, and exposure levels were identified, the application of uncertainty factors was considered in extrapolating from animals to humans and in extrapolating from lowest-observed-adverse-effect levels to no-observed-adverse-effect levels. When necessary, other factors were applied to account for critical data gaps or for potentially relevant variations in susceptibility.

COMMITTEE RECOMMENDATIONS

In this report, the committee recommends 1-h and 24-h EEGLs and 90-day CEGLs for acetaldehyde, hydrogen chloride, hydrogen fluoride, hydrogen sulfide, and propylene glycol dinitrate. The recommendations are listed in Table S-1, and the Navy's current values are included in the table for comparative purposes. The basis of the committee's derivations and the specific recommendations for research needed to improve the confidence of the derived exposure levels are provided in the individual chemical profiles.

Most of the values derived by the committee are similar to or slightly higher than the current U.S. Navy values. However, the 24-h EEGL and 90-day CEGL derived by the committee for hydrogen sulfide were slightly lower than

[4]National Research Council. 1986. Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-Term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance Level (CEGL) Documents. Washington, DC: National Academy Press.

TABLE S-1 Comparison of U.S. Navy's Current Exposure Guidance Levels with Those Recommended by the Committee

Chemical	Exposure Level	Current U.S. Navy Value, ppm	Committee Recommended Value, ppm
Acetaldehyde	1-h EEGL	10	25
	24-h EEGL	6	12.5
	90-day CEGL	2	2
Hydrogen chloride	1-h EEGL	5	9
	24-h EEGL	2	3
	90-day CEGL	1	1
Hydrogen fluoride	1-h EEGL	2	3
	24-h EEGL	1	1
	90-day CEGL	0.1	0.04
Hydrogen sulfide	1-h EEGL	10	10
	24-h EEGL	3	2.8
	90-day CEGL	1	0.8
Propylene glycol dinitrate	1-h EEGL	0.15	0.2
	24-h EEGL	0.02	0.02
	90-day CEGL	0.01	0.004

the Navy values, and the 90-day CEGLs for hydrogen fluoride and propylene glycol dinitrate derived by the committee were about half the Navy's values. The Navy may want to reconsider its 90-day CEGLs for hydrogen fluoride and propylene glycol dinitrate.

RESEARCH RECOMMENDATIONS

Since publication of the NRC reports *Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Volumes 1 and 2,* efforts have been made to characterize the submarine atmosphere better. However, the committee emphasizes the importance of a continuing occupational-health program and the need to monitor the submarine atmosphere and to maintain appropriate engineering controls to minimize the crew's exposure to air contaminants.

The committee did not address exposure to chemical mixtures. The potential for antagonistic, additive, or synergistic interactions between contaminants in the submarine environment is subject to substantial uncertainty, remains largely unexamined, and needs to be studied. The committee recommends that

the Navy examine event situations to determine toxicologically significant mixtures to which the crew might be exposed in acute excursions. That is, what systems could fail and what mixtures would be yielded as a result?

As in the earlier reports, several of the chemicals evaluated in this report are sensory irritants. The derivation of quantitative environmental and occupational exposure limits for sensory irritants is fraught with difficulty because measures of ocular and respiratory tract irritation experienced by human subjects are often subjective. The results of controlled human exposures to many sensory irritants typically use such descriptors as "mild" or "mild to moderate," and the data on sensory-irritation thresholds can be highly variable. Research is needed to quantify the diverse methods and end points used in sensory-irritation studies so that the data can be used in public-health and occupational-health risk assessment with greater confidence.

Finally, as noted earlier, the submarine is a unique environment in which workers are potentially exposed 24 h/day over periods of weeks or months. Few experimental studies examine continuous exposure, and more studies that replicate the submarine environment need to be funded and conducted.

1

Introduction

Submariners live in isolated, confined, and often crowded conditions when at sea. They must adjust to an 18-h day (6 h on duty and 12 h of training, other related activities, and free time) and are continuously exposed to air contaminants in their environment. To protect submariners from the potential adverse health effects associated with air contaminants, the U.S. Navy has established 1-h and 24-h emergency exposure guidance levels (EEGLs) and 90-day continuous exposure guidance levels (CEGLs) for a number of the contaminants.

In December 1995, the Navy began reviewing and updating submarine exposure guidance levels (Crawl 2003). Because the National Research Council (NRC) Committee on Toxicology (COT) had previously reviewed and provided recommendations for those and other types of exposure guidance levels (NRC 1984a,b,c; 1985a,b; 1986a; 1987; 1988a; 1994; 1996a,b; 2000a,b,c; 2002a,b; 2003), the Navy requested that COT review or if necessary develop EEGLs and CEGLs for 21 chemical substances. As a result of the Navy's request, NRC convened a committee that reviewed those 21 chemicals and published two reports on them (NRC 2007, 2008). As a follow-on activity, the Navy requested review of an additional five chemicals, and NRC convened a second Committee on Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants in 2008.

THE COMMITTEE'S CHARGE

Members of the committee were selected for their expertise in inhalation toxicology, neurotoxicology, regulatory toxicology, veterinary pathology, respiratory pathology, pharmacokinetics, pulmonary and occupational medicine, and human-health risk assessment. See Appendix A for biographic information on the committee. The committee was asked to review the Navy's current and proposed 1-h and 24-h EEGLs and 90-day CEGLs for selected submarine contami-

nants and, if possible, to develop EEGLs and CEGLs for selected chemicals that do not have existing or proposed levels. The committee was also asked to identify data gaps and to make recommendations for future research. Specifically, the Navy asked the committee to review guidance levels for acetaldehyde, hydrogen chloride, hydrogen fluoride, hydrogen sulfide, and propylene glycol dinitrate. See Appendix B for a verbatim statement of task.

POPULATION CHARACTERISTICS

An estimated 30,000 submariners are on active duty in the U.S. Navy (Cassano 2003). Permanent crew members on U.S. submarines are all male and are 18-48 years old. Before entry into the submarine service, candidates receive comprehensive physical and psychologic examinations and are rejected if any major medical problems—such as heart disease, asthma, or chronic bronchitis—are noted (U.S. Navy 1992, 2001). Submariners are also required to undergo a complete physical examination every 5 years (Capt. D. Molé, U.S. Navy, personal commun., May 28, 2003); they may be disqualified from submarine duty if any medical problems are noted at that time or during active duty (Cassano 2003). Thus, the population that serves on U.S. submarines is, in general, quite healthy.

Studies that have evaluated mortality patterns in U.S. submariners support the conclusion that submariners are healthy. Charpentier et al. (1993) examined a cohort of 76,160 submariners who served on U.S. nuclear-powered submarines during the period 1969-1982. They compared mortality in the submariners with that in the general adult male population of the United States and found that the standardized mortality ratio (SMR) for total mortality was significantly less than 1.[1] The SMR was also significantly lower than that expected in a military population. The SMRs for specific causes of mortality were also less than 1. SMRs exceeded 1 for only two causes: malignant neoplasms of the central nervous system (SMR, 1.03) and motor-vehicle accidents (SMR, 1.06). The results reported by the study authors were supported by a study of Royal Navy submariners, who must meet stringent physical requirements similar to those of the U.S. Navy (Inskip et al. 1997).

Morbidity patterns in U.S. Navy submariners also indicate a healthy population. Thomas et al. (2000) evaluated the rates of medical events in crews on 136 submarine patrols over 2 years (1997-1998). Injury was the most common medical-event category, followed by respiratory illness (primarily upper respiratory infections) and then skin problems, such as minor infections and ingrown toenails. Other medical events included ill-defined symptoms, infectious diseases, digestive disorders, ear and eye complaints, and musculoskeletal condi-

[1]An SMR indicates whether mortality in a given population is greater (SMR > 1) or less (SMR < 1) than that in a comparison population.

tions. The categories just listed account for about 90% of the 2,044 medical events reported.

Although recent data indicate that U.S. submariners are a healthy population, some might be sensitive to particular air contaminants because of genetic predisposition or conditions arising during active duty. For example, Sims et al. (1999) reported that asthma led to the disqualification each year of 0.16% of the active-duty personnel serving in the Atlantic Fleet Submarine Force (the authors considered the asthma cases to be mild).

Tobacco smokers might be more or less sensitive to some air contaminants. Smoking on U.S. submarines is permitted only in specified areas. The percentage of U.S. submariners who smoke is difficult to estimate because no broad survey has been conducted. Sims et al. (1999) estimated a prevalence of smoking of 36% on the basis of data on eight submarines. However, Thomas et al. (2000) estimated that the prevalence might be as low as 22% on the basis of survey data collected from one submarine in 1997. The Navy has indicated that the percentage of submariners who smoke most likely ranges from 15% to 30% (Cmdr. W. Horn, U.S. Navy, personal commun., August 7, 2003). However, smoking policies on board submarines vary because they are determined by the commanding officer.

One other aspect of the population that could affect its sensitivity to chemical exposure is consumption of alcoholic beverages. However, no alcohol is allowed on board a submarine, so there is no expected consumption of alcoholic beverages while the crew is on board (Cmdr. G. Chapman, U.S. Navy, personal commun., May 29, 2009).

THE SUBMARINE ENVIRONMENT

The U.S. submarine fleet is composed mostly of two types of submarines (Thomas et al. 2000). Table 1-1 provides some distinguishing characteristics of the crews and patrols of the two submarine types.

When submerged, a submarine is an enclosed and isolated environment. Submariners work, eat, and sleep in that environment and potentially are exposed to air contaminants 24 h/day. A submarine differs from typical occupational settings in which workers have respites from workplace exposures at the end of their shifts or workweeks.

Operation of a closed vessel can lead to accumulation of air contaminants (NRC 1988b). Major sources of air contaminants on a submarine include cigarette-smoking, cooking, and the human body. Other sources include control equipment, the power train, weapons systems, batteries, sanitary tanks, air-conditioning and refrigeration systems, and a variety of maintenance and repair activities.

Several onboard methods are used to maintain a livable atmosphere and remove air contaminants (NRC 1988b). Oxygen generators add oxygen to the air

TABLE 1-1 Characteristics of Crew and Patrols for U.S. Navy Nuclear-Powered Submarines

Type[a]	Number and Size of Crew	Typical Patrol
Nuclear-powered attack submarines (SSN)	1 designated crew of 130 men	Irregular intervals between patrols; patrols of variable length
Nuclear-powered ballistic-missile submarines (SSBN)	2 rotating crews of 160 men each	Regularly scheduled patrols; 90-day cycle between ship and shore; patrols over 60 days long

[a]Note that there are three classes of attack submarines—Los Angeles, Seawolf, and Virginia—and one class of ballistic-missile submarines—Ohio. There are also two deep-diving specialized research submarines (one nuclear-powered and the other diesel-powered) that are in a class of their own (Capt. D. Molé, U.S. Navy, personal commun., January 15, 2004).
Source: Information from Thomas et al. 2000.

by electrolyzing seawater. The hydrogen that is generated in the process is discharged to the sea. Monoethanolamine scrubbers are used to remove carbon dioxide from the air. Carbon monoxide that is generated primarily by cigarette-smoking and hydrogen that is released in battery-charging are removed by a carbon monoxide–hydrogen burner that catalytically oxidizes the two components to carbon dioxide and water, respectively; hydrocarbons are also oxidized by this system. Activated-carbon filters help to remove high-molecular-weight compounds and odorants, and electrostatic precipitators help to remove particles and aerosols. Vent-fog precipitators are used in the engine room to remove oil mists generated there. Other means of minimizing air contaminants include restricting the materials that can be brought on board and limiting the types of activities, such as welding, that can be conducted at sea.

When the submarine is submerged, air is recirculated in a closed-loop system. The system is composed of the forward-compartment air-circulation system and the engine-compartment air-circulation system (R. Hagar, Naval Sea Systems Command, personal commun., April 2, 2003). Figure 1-1 is a generalized schematic of a nuclear-powered attack submarine. The forward-compartment air-circulation system contains most of the air-purification equipment and oxygen generators and is designed to condition the air to 80°F and 50% relative humidity. The forward compartment is divided into zones; the fan room serves as the mixing chamber. Stale air from the boat is exhausted to the fan room, and the fan room supplies treated air to the boat. The engine-compartment air-circulation system provides heating, cooling, and air distribution within the engine room and is designed to maintain its air temperature below 100°F. Electrostatic precipitators and other filters in this room treat its air. Air from the engine room is exhausted directly to the fan room, which supplies conditioned air directly to the engine room.

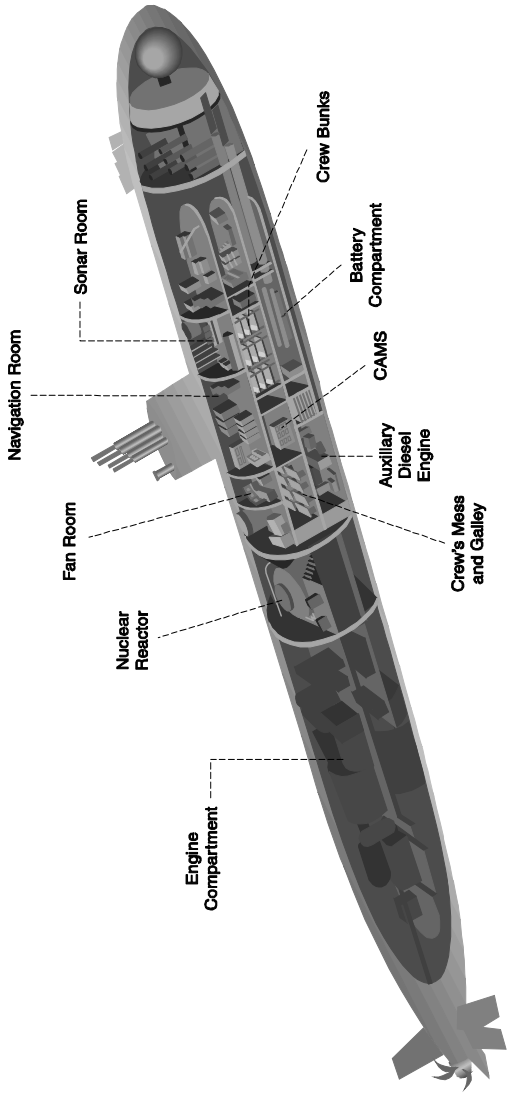

FIGURE 1-1 Generalized schematic of a nuclear-powered attack submarine. Source: Adapted from image courtesy of the Smithsonian/NMAH Transportation.

Special variations in the exhaust airflow path described above exist (R. Hagar, Naval Sea Systems Command, personal commun., April 2, 2003). Air discharged from the carbon monoxide–hydrogen burners and the carbon dioxide scrubbers is vented directly to the fan room. Many electronic cabinets have fan systems that also vent directly to the fan room, and air from the laundry dryers passes through lint screens and then to the fan room. About 50% of the air vented to the fan room passes through electrostatic precipitators, and air from the galley, scullery, pantry, and water closets goes through activated-charcoal filters before venting to the fan room. Cooking grease is removed from the range and fryer hoods by centrifugal force.

The central atmosphere monitoring system (CAMS) of the submarine uses an infrared spectrometer to measure carbon monoxide and a mass spectrometer to measure oxygen, nitrogen, carbon dioxide, hydrogen, water vapor, and Freons 11, 12, and 114 (NRC 1988b). A newer version of CAMS (CAMS MK II) can monitor the following trace species: acetone; aliphatic hydrocarbons (sum of masses 57, 71, 99, and 113); aromatic hydrocarbons (sum of masses 91, 105, 119, 133, and 147); benzene; Freons 12, 114, and 134a; isobutylene; methanol; methyl chloroform; silicone; and trichloroethylene. Fan-room air is monitored continuously, and air in other onboard locations is analyzed on a rotating basis.

Portable devices are routinely used to monitor submarine air (Hagar 2003; NRC 1988b). Photoionization detectors monitor total hydrocarbon concentrations, although they are not used in submarines equipped with the newer version of CAMS. A portable oxygen detector verifies oxygen concentrations weekly. Colorimetric detector tubes are used weekly to measure concentrations of acetone, ammonia, benzene, carbon dioxide, carbon monoxide, chlorine, hydrazine, hydrochloric acid, methyl chloroform, monoethanolamine, nitrogen dioxide, ozone, sulfur dioxide, toluene, and total hydrocarbons. During battery-charging, portable detectors are also used to monitor hydrogen concentrations. Suspected fluorocarbon or torpedo-fuel leaks are assessed with portable devices that have photoionization detectors. Retrospective passive monitoring of the submarine air provides 30-day time-weighted average concentrations of volatile organic compounds, ozone, acrolein, aldehydes, amines, and nitrosamines. Exposure data on compounds addressed in this report are presented in the individual chapters.

THE COMMITTEE'S APPROACH TO ITS CHARGE

The committee reviewed relevant human and animal data and used data-selection criteria described in *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001). Specifically, the committee's approach to data selection included the following elements:

- Whenever possible, primary references (published or unpublished study reports) were used to derive exposure guidance levels. Secondary references were used to support the levels derived and the selection of critical end points.
- Whenever possible, studies that followed accepted standard scientific methods were selected as key studies for deriving exposure guidance levels. Evaluation of study quality required the professional expertise and judgment of the committee.
- Inhalation-exposure studies were used to derive exposure guidance levels. Data on other exposure routes (oral and dermal) were considered, especially in evaluating pharmacokinetics, tissue dose, metabolism, and mechanisms of toxicity.
- Human studies were preferred for deriving exposure guidance levels. The committee considered human data from accidental exposures, experimental studies, and epidemiologic studies to be valuable in determining the effects of chemical exposure. When epidemiologic and human experimental studies were available, a preference typically was given to the latter because these were conducted in a controlled laboratory setting and allowed measurement of personal exposure and evaluation of end points relevant to derivation of exposure guidance levels. The committee recognizes that one potential problem with experimental studies is the statistical power of a study to detect an effect in the small number of subjects typically used. That design problem often exists in studies of humans or large animals, such as nonhuman primates and dogs. However, the committee did not set a threshold for statistical power, for two reasons. First, data presented in manuscripts or technical reports were often inadequate to allow the committee to perform independent calculations to determine the power of an experiment. Second, derivation of the EEGLs and CEGLs was never based solely on a single study; multiple key studies were always supported by other human experimental studies, epidemiologic studies, or animal studies (see last bulleted item). To the best of the committee's knowledge, the data used were not obtained from uninformed or coerced subjects.
- When high-quality human data were not available, standard laboratory animal studies were used to derive exposure guidance levels. The animal species used were those on which there were historical control data and those which were most relevant to humans.
- A weight-of-evidence approach was used to select key studies that ensured that selected data were consistent with the overall scientific database and incorporated what was known about the biologic effects of a chemical on pertinent organ systems.

The committee followed basic procedures provided by *Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-Term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance Level (CEGL) Documents* (NRC 1986b) but also considered the

procedures for developing similar exposure levels provided in more recent reports (NRC 1992, 2001). The committee evaluated chemicals individually and did not address exposures to chemical mixtures. It recommends that empirical data that characterize mixtures found in submarine air be evaluated when they become available. It considered only health end points relevant to healthy young men on the assumption that women do not serve as permanent crew on submarines. In deriving EEGLs and CEGLs, the committee assumed that the confined conditions on a submarine keep the crew from achieving maximal exercise. It also assumed that a submarine is operated at an internal pressure near 1 atm. The specific approaches adopted by the committee for developing EEGLs and CEGLs are outlined below.

Emergency Exposure Guidance Levels

NRC (1986b) defines EEGLs as ceiling concentrations (concentrations not to be exceeded) of chemical substances that will not cause irreversible harm to crew health or prevent the performance of essential tasks, such as closing a hatch or using a fire extinguisher, during rare emergency situations that last 1-24 h. Exposures at the EEGLs may induce reversible effects, such as ocular or upper respiratory tract irritation, and they are acceptable only in emergencies when some discomfort must be endured. After 24 h of exposure, CEGLs would apply.

To develop 1-h and 24-h EEGLs, the committee reviewed relevant human and animal toxicity data and considered all health end points reported. The EEGLs were based on acute or short-term inhalation and ocular-irritation data, and the most sensitive end points were emphasized. The committee considered conducting benchmark-dose or benchmark-concentration modeling, but the datasets were often not amenable for doing so, and points of departure were based on lowest observed-adverse-effect levels (LOAELs) or no-observed-adverse-effect levels (NOAELs) from human or animal studies.

In deriving EEGLs, the committee used uncertainty factors that ranged from 1 to 10. Those factors accounted for interspecies differences (extrapolation from animal to human populations, if applicable), intraspecies differences (possible variations in susceptibility that might be applicable to the healthy male population considered), extrapolations from a LOAEL to a NOAEL, and weaknesses or critical gaps in the databases. The committee strove for consistency, but its overarching goal was a thorough case-by-case review of available data. Selection of uncertainty factors for each chemical reflects the committee's best judgment of the data on toxicity and mode of action. Because an uncertainty factor of 3 represents a logarithmic mean (3.16) of 10, the committee considered the product of two uncertainty factors of 3 to equal a composite uncertainty factor of 10, which is consistent with current risk-assessment practices (NRC 2001; EPA 2002).

Continuous Exposure Guidance Levels

NRC (1986b) defines CEGLs as ceiling concentrations of chemical substances designed to prevent immediate or delayed adverse health effects or degradations in crew performance that might result from continuous chemical exposures lasting up to 90 days. To derive CEGLs, the committee used the basic approach outlined for developing EEGLs; relevant data were reviewed, sensitive end points evaluated, and appropriate uncertainty factors applied. The method differed only in that inhalation studies with repeated exposures were used, when available, as the primary basis of CEGL development. The effects of cumulative exposure were taken into account by using a weight-of-evidence approach.

Carcinogenic Substances

For known and suspected human carcinogens, the U.S. Department of Defense sets military exposure levels to avoid a theoretical excess cancer risk of greater than 1 in 10,000 exposed persons (NRC 1986b). For chemicals that have been designated as known or suspected human carcinogens by the International Agency for Research on Cancer or by the U.S. Environmental Protection Agency, the committee evaluated the theoretical excess cancer risk resulting from exposure at the 90-day CEGLs. It considered deriving the cancer risk resulting from exposure at the 24-h EEGLs but concluded that such estimates would involve too much uncertainty. Additional information on cancer risk is provided in individual chapters as appropriate. The committee notes that COT typically has not proposed CEGLs for carcinogenic substances (NRC 1986b) but acknowledges that there is value in conducting such evaluations and has proposed 90-day CEGLs for known and suspected human carcinogens.

Comparison with Other Regulatory Standards or Guidance Levels

In its evaluations, the committee considered relevant inhalation exposure standards or guidance levels put forth by NRC and other agencies or organizations. However, it notes that the submarine EEGLs and CEGLs differ from typical public-health and occupational-health standards in three important ways. First, public-health standards are developed to protect sensitive populations—such as children, the elderly, and others with chronic health conditions who might be particularly sensitive—whereas EEGLs and CEGLs are developed for a healthy adult male population with little variation in physical qualifications. Second, occupational-health standards are designed for repeated exposure throughout a working lifetime on the assumption that workers are exposed 8 h/day, 5 days/week for a working lifetime. Submariners can be exposed 24 h/day with no relief from exposure during submergence. In a typical submariner's career, a 10-year assignment to active sea duty would result in about 4.5-5 years of

cumulative exposure in the enclosed submarine environment (Capt. V. Cassano, U.S. Navy, personal commun., December 16, 2003). Third, EEGLs allow for the development of reversible health effects that would not prevent the performance of essential tasks; such health effects might not be considered acceptable in setting conventional occupational-health or public-health exposure standards.

The committee considered the submarine escape action levels (SEALs) and the spacecraft maximum allowable concentrations (SMACs) to be useful for comparison with EEGLs and CEGLs. SEALs are developed for disabled submarines and allow moderate, rather than only minimal, reversible effects (NRC 2002a). SMACs are probably the most comparable with EEGLs and CEGLs because SMACs are developed with similar criteria and address adverse effects in a healthy population in an isolated and confined environment. However, SMACs are developed for an older male and female population that experiences the conditions of microgravity during exposure.

ORGANIZATION OF REPORT

This report contains the committee's rationale and recommendations with respect to EEGLs and CEGLs for acetaldehyde, hydrogen chloride, hydrogen fluoride, hydrogen sulfide, and propylene glycol dinitrate. Each chapter summarizes the relevant toxicologic and epidemiologic studies of a substance, selected chemical and physical properties, toxicokinetic and mechanistic data, and published regulatory and guidance levels for inhalation exposure. The committee's recommendations for exposure guidance levels and for the research needed to define and support the recommendations are also provided. The chemical profiles presented in this report are not comprehensive toxicologic profiles. The profiles focus on data that are particularly relevant to the derivation of EEGLs and CEGLs. References to recent authoritative reviews of the toxicology of some of the chemicals addressed in this report are provided.

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2

Acetaldehyde

This chapter summarizes the relevant epidemiologic and toxicologic studies of acetaldehyde. Selected chemical and physical properties, toxicokinetic and mechanistic data, and inhalation-exposure levels from the National Research Council and other agencies are also presented. The committee considered all that information in its evaluation of the U.S. Navy's 1-h, 24-h, and 90-day exposure guidance levels for acetaldehyde. The committee's recommendations for acetaldehyde exposure levels are provided at the end of this chapter with a discussion of the adequacy of the data for defining the levels and the research needed to fill the remaining data gaps.

PHYSICAL AND CHEMICAL PROPERTIES

Acetaldehyde is a colorless, flammable liquid with a pungent, fruity odor (HSDB 2005). Ruth (1986) reported an odor threshold ranging from 0.0001 to 2.3 ppm and an irritating concentration of 50 ppm. Selected physical and chemical properties are shown in Table 2-1.

OCCURRENCE AND USE

Acetaldehyde is used primarily as a chemical intermediate in the production of such products as herbicides, insecticides, fungicides, pharmaceuticals, flavors, fragrances, dyes, plastics, and synthetic rubber (IARC 1985). Small quantities are used as a food additive. It is an intermediate in the respiration of higher plants and thus a natural component of many fruits and vegetables (EPA 2007). It is also a metabolite of ethanol and sugar metabolism in humans, and it is endogenously produced in humans from amino acid metabolism and from

Table 2-1 Physical and Chemical Properties of Acetaldehyde

Synonyms	Acetic aldehyde, ethanal, ethyl aldehyde
CAS registry number	75-07-0
Molecular formula	CH_3CHO
Molecular weight	44.05
Boiling point	21°C
Melting point	–123.5°C
Flash point	–38.9°C (closed cup)
Explosive limits	Lower limit, 4.1%; upper limit, 55% by volume
Specific gravity	0.788 at 16°C
Vapor pressure	902 mmHg at 25°C
Solubility	Miscible with water and most common organic solvents
Conversion factors	1 ppm = 1.8 mg/m^3; 1 mg/m^3 = 0.56 ppm

Sources: Budavari et al. 1989, HSDB 2005.

anaerobic metabolism of glucose by intestinal microflora (NRC 1994). Acetaldehyde is eliminated in expired air of fasted humans at 17 µg/h (NRC 1994).

Acetaldehyde is a component of tobacco smoke. The amount of acetaldehyde generated depends on the type of cigarette. Results of several studies indicate a range in the amount of acetaldehyde in the smoke of 400-1,400 µg/cigarette (IARC 1985; Hoffmann and Hecht 1990), although results of one study indicate a much lower emission of acetaldehyde from low-tar cigarettes (90-270 µg/cigarette; IARC 1985). Acetaldehyde is also a component of automobile exhaust and is generated by the combustion of wood and plastics (IARC 1985). Several studies have measured acetaldehyde concentrations in ambient air in the United States; results range from nondetectable to 69 ppb (IARC 1985).

Acetaldehyde concentrations have been measured on nuclear-powered submarines. Raymer et al. (1994) reported the results of air sampling at three locations over 6 h during the missions of two submarines. Acetaldehyde concentrations ranged from 78 to 130 ppb on an attack submarine and from 210 to 250 ppb on a ballistic-missile submarine. Holdren et al. (1995) reported the results of a similar sampling exercise (two submarines, three locations, and sampling duration of 6 h). Concentrations ranged from 46.6 to 97.2 ppb on a nuclear-powered attack submarine and from 103.9 to 118.0 ppb on a ballistic-missile submarine. Hagar (2008) reported data representing 228,960 h (318 patrols) on 23 attack submarines and 77,760 hours (108 patrols) on 10 ballistic-missile submarines. Acetaldehyde concentrations were determined with passive monitoring and averaged 16 ppb (range, 1-110 ppb) on the attack submarines and 5 ppb (range,

1-16 ppb) on the ballistic-missile submarines. The most recent data (Hagar 2008) collected on three attack submarines indicated an acetaldehyde concentration of 250-350 ppb. Few details on collection of the data were provided.

SUMMARY OF TOXICITY

Acetaldehyde toxicity has been reviewed in several publications (IARC 1985, 1999; EPA 1987; NRC 1994; WHO 1995; Heck 1997; Environment Canada and Health Canada 2000; ACGIH 2001; EC 2004; HEI 2007; NASA, unpublished material, 2007; Dorman et al. 2008). Mucosal irritation is the sensitive effect of acute exposure to acetaldehyde; eye irritation is more sensitive than nose or throat irritation. Eye irritation has been reported in human volunteers at concentrations as low as 50 ppm, whereas concentrations greater than 100-200 ppm are typically required for nose or throat irritation (Silverman et al. 1946; Sim and Pattle 1957; Muttray et al. 2009). Increasing air concentrations result in deeper penetration of acetaldehyde vapor in the respiratory system, which causes bronchiolitis obliterans (as reported after accidental high-dose occupational exposures) or bronchoconstriction in asthmatics. Acetaldehyde, like formaldehyde and acrolein, is chiefly a portal-of-entry toxicant that targets the upper respiratory mucosa, but it is considerably less potent than these two other aldehydes.

No systemic effects or effects on the olfactory epithelium or other portions of the respiratory tract were reported after repeated subchronic exposure of rats at 50 ppm (Dorman et al. 2008). Continuous 24-h exposure of mice at 125 ppm for 14 days (Oyama et al. 2007) and repeated subchronic exposure of rats to acetaldehyde at 150 ppm or greater result in nasal lesions and increasing olfactory neuron loss and degeneration and thinning of the olfactory epithelium with increasing concentration and exposure duration. Repeated subchronic exposure of rats at higher concentrations (such as those greater than 500 ppm) has also resulted in inflammation, hyperplasia, and squamous metaplasia of the respiratory epithelium; moderate to severe lesions of the olfactory epithelium with neuronal loss and hyperplasia result at 1,500 ppm (Dorman et al. 2008).

Chronic exposure of rats at 750 ppm or greater for 2 years is carcinogenic to the nasal mucosa (Woutersen et al. 1986). Data on humans are inadequate to assess carcinogenicity of inhaled acetaldehyde (EPA 1991; NTP 2005). Some evidence indicates that humans with genetic polymorphisms for reduced aldehyde dehydrogenase activity may be at higher risk for oral and esophageal cancers from consuming alcohol because the acetaldehyde from metabolism of the alcohol is not readily oxidized (NTP 2005; Baan et al. 2007).

Concentrations of toxicologic concern are related to resulting epithelial tissue concentrations, which depend on the rates of tissue absorption and metabolism of acetaldehyde by acetaldehyde dehydrogenases (Morris 1997a; Environment Canada and Health Canada 2000). High airborne concentrations result in saturation of acetaldehyde metabolism, which leads to apparent nonlinear

increases in nasal tissue concentration, tissue damage, and penetration of acetaldehyde beyond the nasal cavity to the larynx and trachea (Heck 1997; Morris 1997b).

Effects in Humans

Accidental Exposures

As noted above, acetaldehyde is a component of food flavorings and is added to various products, such as fruit juices and soft drinks. Its concentration in foods is generally up to 0.047% (IARC 1985). In a food-flavoring manufacturing facility using high concentrations of acetaldehyde, an index case of bronchiolitis obliterans was reported (Lockey et al. 2002); exposure involved the manual pouring of concentrated acetaldehyde into open mixing tanks (J. Lockey, University of Cincinnati, personal commun., July 11, 2009).

Experimental Studies

Human subjects were exposed to various individual chemicals for 15 min, including acetaldehyde at 25, 50, and 200 ppm (Silverman et al. 1946).[1] Several subjects strenuously objected to the vapor at 25 ppm, although whether this was because of odor or irritation is not stated. Silverman et al. (1946), however, stated that eye irritation appeared at 50 ppm with the majority of subjects reporting some eye irritation at that concentration. Those not reporting eye irritation had bloodshot eyes and reddened eyelids at 200 ppm. Nevertheless, the majority of subjects said that they would be willing to work an 8-h day at 200 ppm. Exposure to acetaldehyde at 134 ppm for 30 min resulted in mild upper respiratory irritation in 14 men (Sim and Pattle 1957). Data on sensory irritants, such as acrolein, indicate that a constant level of irritation is eventually reached. For example, in humans, the eye irritancy of acrolein increased from 15 to 40 min of exposure at 0.3 ppm and stayed constant from 40 to 60 min (Weber-Tschopp et al. 1977, cited in NRC 1994).

In a recent study (Muttray et al. 2009), 20 volunteers were exposed to acetaldehyde at 50 ppm and to ambient air using a crossover design for 4 h in an exposure chamber. Subjects reported no increase in irritating symptoms after exposure to acetaldehyde as measured by questionnaire. There was a nonsignificant increase in mucociliary transport time, but no change in olfactory threshold. In addition, there was no increase in the concentration of interleukins in nasal

[1]Silverman et al. (1946) exposed different subjects to a number of chemicals at various concentrations but did not report the specific number of subjects for each chemical exposure. They reported that an average of 12 subjects of both sexes were used for each solvent exposure.

secretion and no increase in mRNA levels of inflammatory factors in nasal epithelial cells.

An oral ethanol provocation test using a solution (300 mL) that contained ethanol at 10% and glucose at 5% was performed in Japanese asthmatics (Matsuse et al. 2007). Bronchoconstriction was noted in 21 of 46 asthmatics and corresponded with increased blood histamine and acetaldehyde concentrations and decreased enzymatic activity of acetaldehyde dehydrogenase 2 (ALDH2). An investigation of the direct effect of increasing concentrations of aerosolized acetaldehyde solutions (5, 10, 20, and 40 mg/mL) administered with a nebulizer was conducted in asthmatics with and without pretreatment with the antihistamine terfenadine and in healthy controls (Myou et al. 1993). Asthmatics had a significant decrease (more than 20%) in FEV_1 compared with healthy subjects and asthmatics pretreated with terfenadine. There was a significant correlation between the acetaldehyde concentration and the methacholine concentration needed to cause a 20% decrease in FEV_1. The authors concluded that acetaldehyde causes bronchoconstriction in asthmatics indirectly through histamine release (Myou et al. 1993). A later study demonstrated that acetaldehyde administered by nebulizer can increase nonspecific bronchial hyperresponsiveness as measured by methacholine provocation in asthmatics independently of histamine release (Myou et al. 1994). Various additional studies have shown the sensitivity of the asthmatic population to acetaldehyde exposure (Myou et al. 1995; Fujimura et al. 1999; Sanchez-Toril et al. 2000; Prieto et al. 2000, 2002a,b).

OEHHA (2008) converted the concentrations of inhaled acetaldehyde delivered by nebulizer in the various studies in milligrams per milliliter to approximate air concentrations in parts per million. The authors noted the uncertainty in the conversions related to inconsistencies in nebulizer delivery systems. Given the limitations, the acetaldehyde concentration producing a 20% reduction in FEV_1 in adult asthmatics was estimated to range from 286 to 692 ppm (geometric means). The lowest individual concentration was 59 ppm. Although the inhalation-challenge studies are difficult to relate to exposure to airborne acetaldehyde because of the method of administration (inhalation of nebulized solutions through the mouth), the studies indicate sensitivity to bronchoconstriction in asthmatics, particularly those with genetic impairment in ALDH2 activity. The calculated concentrations, however, overestimate the concentration that would reach the middle to lower respiratory tract in normal airborne exposures because the method of administration bypasses the upper respiratory tract and does not account for uptake there.

Occupational and Epidemiologic Studies

Mucous-membrane irritation was measured in workers exposed to two suppliers' cutting fluids that contained acetaldehyde and formaldehyde. The incidence of nasal irritation ranged from less than 10% after exposure to one of the cutting fluids to 30-40% after exposure to the other, but there was no consis-

tent correlation between reported symptoms and aldehyde concentrations in the fluids or in the ambient air according to the limited air-monitoring data (Jarvholm et al. 1995).

In a study of acetaldehyde-production workers, total cancer incidence was higher than in the background German population (Bittersohl 1974, cited in NRC 1994). Concentrations in the factory workroom after equipment leakages were 0.56-3.88 ppm (Bittersohl 1975, cited in ACGIH 2001). Of the nine cancers in the cohort of 220 workers, the incidences of oral cancer (two cases) and bronchial cancer (five cases) were highest (Bittersohl 1974, cited in NRC 1994). Major deficiencies of the study were the small number of subjects, the 100% smoking rate in those with cancer, and the presence of various confounding exposures, which made it impossible to evaluate the carcinogenic potential of acetaldehyde (Bittersohl 1974, cited in NRC 1994).

Effects in Animals

Acute Toxicity

Appelman et al. (1982) reported a 4-h LC_{50} in rats of 13,300 ppm, whereas a higher LC_{50} in rats of 20,000 ppm was reported for a 30-min exposure (Skog 1950, cited in ACGIH 2001). At 5,000 ppm for the first 30 min of exposure, rats showed dyspnea and excitation (Appelman et al. 1982). ALDH2-/- transgenic mice (representing ALDH2-deficient humans) demonstrated greater sensitivity to acetaldehyde after a 4-h exposure at 5,000 ppm than wild-type (ALDH2+/+) mice (Isse et al. 2005). ALDH2+/+ mice showed flushing, whereas ALDH2-/- mice showed tears, straggling gait, prone position, pale skin, abnormal deep respiration, dyspnea, and one death. Both types of mice showed crouching, bradypnea, and piloerection.

Studies of acute effects in laboratory animals have noted mucosal and sensory irritation, breathing-rate decreases mediated by the trigeminal nerve reflex (Alarie 1973), ciliostasis (Dalhamn and Rosengren 1971, cited in NRC 1994), and DNA-protein cross-link formation in the respiratory and olfactory mucosa (Lam et al. 1986). The acetaldehyde concentration resulting in a 50% reduction in respiratory rate (RD_{50}) in two mouse strains was reported to be about 2,800-2,900 ppm in 10 min compared with formaldehyde at about 3-5 ppm and acrolein at 1-1.4 ppm (Steinhagen and Barrow 1984). The RD_{50} in rats exposed to acetaldehyde vapor for the first 3 min was 3,046 ppm compared with formaldehyde at 10 ppm and acrolein at 9 ppm (Cassee et al. 1996). At the lowest acetaldehyde concentration tested (2,800 ppm), the immediate decrease in respiratory rate (to about 55% of normal) in the first 3 min was followed by partial recovery to about 90% of normal over the remainder of the 30-min exposure period and nearly full to full recovery in the 10-min period after exposure (Cassee et al. 1996). Within 30 min, an acetaldehyde concentration of about 560 ppm produced stasis of cilia in rabbit tracheal explants (Dalhamn and Rosengren 1971,

cited in NRC 1994). Acute exposure to acetaldehyde (for 6 h) resulted in increased DNA-protein cross-link formation in the nasal respiratory mucosa of rats at 1,000 and 3,000 ppm but not at 100 or 300 ppm (Lam et al. 1986). No such increase was found in the nasal olfactory mucosa after a single 6-h exposure, but a significant increase occurred at 1,000 ppm after repeated exposure 6 h/day for 5 days.

Repeated Exposure and Subchronic Toxicity

A 90-day inhalation study in hamsters used exposure concentrations of 390-4,560 ppm 6 h/day, 5 days/week (Kruysse et al. 1975). At the highest concentration, effects included severe histopathologic changes in the respiratory tract, irritation of the eyes and nose, growth retardation, increased numbers of erythrocytes, and increased heart and kidney weights. No toxic effects were reported at 390 ppm.

Rats exposed to acetaldehyde at 5,000 ppm 6 h/day, 5 days/week for 4 weeks showed growth reduction, more neutrophils and fewer lymphocytes in blood, reduced urine production with increased urine specific gravity, increased lung weights, and severe degeneration with hyperplasia and metaplasia of the nasal, laryngeal, and tracheal epithelium (Appelman et al. 1982). At 1,000 and 2,200 ppm, growth reduction and increased urine production in males was observed. Moderate to severe degeneration of the nasal olfactory epithelium with hyperplasia or metaplasia was observed in most animals at 2,200 ppm, whereas slight to moderate degenerative changes of the nasal olfactory epithelium without hyperplasia or metaplasia were observed in most animals at 1,000. Minimal epithelial changes of the larynx and trachea were also observed at 2,200 ppm. At 400 ppm, degeneration of the nasal olfactory epithelium was slight to moderate in most animals, without hyperplasia or metaplasia but with loss of microvilli, thinning and disarrangement of epithelial cells, and occasional loss of sensory cells. Thus, increasing acetaldehyde concentrations were associated with more severe epithelial lesions and effects deeper into the respiratory tract, going beyond the nasal cavity at 2,200 ppm.

A follow-up study examined the effect of variable vs fixed exposure concentrations of acetaldehyde in male rats (Appelman et al. 1986). Exposure concentrations were 110, 150, or 500 ppm 6 h/day, 5 days/week for 4 weeks. At the highest concentration, animals were divided into three groups, each of which was exposed to one of the following daily exposure regimens: (1) one 6-h exposure, (2) two 3-h exposures separated by 1.5 h with no exposure, or (3) same as regimen 2 but with four 5-min peak exposures (6 times the exposure concentration) during each 3-h exposure. Regimen 3 was used for the 110-ppm group of rats, and regimens 1 and 2 for the 150-ppm group. Rats exposed at 500 ppm showed degeneration of the olfactory epithelium with little difference among the three exposure regimens. The group exposed at peaks of 3,000 ppm showed irritation, excitation, a reduction in body-weight gain, and greater reduction in

the phagocytotic index of lung macrophages. No effects related to acetaldehyde exposure were observed in the rats exposed at 150 ppm or exposed at 110 ppm with a peak of 660 ppm. The investigators concluded that the fixed, variable, or peak exposure regimens tested had little effect on the toxicity of acetaldehyde to nasal epithelial cells.

Another 4-week study examined pulmonary effects in nonsensitized or ovalbumin-sensitized guinea pigs that were challenged with an ovalbumin aerosol at the end of 4 weeks of exposure to acetaldehyde 6 h/day, 5 days/week (Lacroix et al. 2002). The acetaldehyde concentration was intended to be a low, environmentally relevant concentration of 200 ppb (0.2 ppm). However, the chamber concentration varied widely, and the exposure concentrations were lognormally distributed with a geometric mean of 149.9 ppb for the nonsensitized group and 221.9 ppb for the sensitized group, both with a geometric standard error of the mean of 0.6. Histopathology results were summarized briefly without details. Nonsensitized guinea pigs reportedly showed slight irritation (metaplasia or hyperplasia) of the respiratory epithelium of the nasal cavity, trachea, and lungs. Sensitized guinea pigs showed moderate irritation of the trachea and lungs. Nonsensitized guinea pigs also showed a significant increase in alveolar macrophages, which indicated pulmonary inflammation.

The results of the Lacroix et al. study are inconsistent with the rest of the literature. No other studies report histopathologic lesions beyond the nasal cavity into the trachea and lungs after exposure to a concentration as low as 0.2 ppm. Observations in the control (ambient-air) group are not described, so it is not possible to evaluate fully whether the effects were related to acetaldehyde exposure, husbandry conditions, or other factors. In addition to the wide variation in chamber concentrations, the sample-collection and analytic methods are described incompletely with respect to sample validation (such as collection efficiency and method for generating standard curves) and limits of detection. Thus, the results do not appear to be reliable for setting an exposure guidance level.

A subchronic study in rats (Dorman et al. 2008) investigated the concentration-response relationship for acetaldehyde-induced nasal lesions, nasal epithelial cell proliferation, and DNA-protein cross-link formation. Rats were exposed to acetaldehyde at 0, 50, 150, 500, or 1,500 ppm 6 h/day, 5 days/week for up to 65 days of exposure. No treatment-related systemic toxicity or effects on body-weight gain or on the trachea or lungs were observed. Histologic examinations of the olfactory epithelium showed no effects at 50 ppm, relatively little olfactory neuronal loss at 150-500 ppm, and moderately severe lesions at 1,500 ppm. The severity of olfactory neuronal loss increased with exposure duration from 4 to 65 days. Increased olfactory epithelial cell proliferation was also reported at the highest concentration. Exposures at 500 and 1,500 ppm resulted in inflammation, hyperplasia, and squamous metaplasia of the respiratory epithelium (Dorman et al. 2008). In contrast with the observations of Lam et al. (1986) at 1,000 ppm, no effect of acetaldehyde on DNA-protein cross-link formation was observed, even at 1,500 ppm.

Oyama et al. (2007) exposed wild-type (ALDH2+/+) and ALDH2-/- knockout mice to acetaldehyde at 0, 125, and 500 ppm 24 h/day for 14 days. ALDH2-/- mice, particularly at the highest concentration, showed greater erosion of the nasal respiratory epithelium; hemorrhage of the nasal subepithelium; hemorrhage of the nasal cavity; degeneration of the respiratory epithelium in larynx, pharynx, and trachea; erosion of the dorsal skin; and higher acetaldehyde blood concentration than the wild-type mice. Relatively few effects on the olfactory epithelium were reported; one of five wild-type and knockout mice showed slight degeneration of cells at 500 ppm. Some of the effects were increased in wild-type mice compared with controls, primarily at 500 ppm. Fewer effects were reported in the mice compared with controls at 125 ppm, and knockout and wild-type mice were more similar in response.

Chronic Toxicity

Feron (1979, cited in EPA 1991 and ACGIH 2001) conducted a 52-week study in hamsters exposed to acetaldehyde at 1,500 ppm 7 h/day, 5 days/week. Treatment-related effects included epithelial hyperplasia, metaplasia of the nasal mucosa, inflammation of the nasal cavity and trachea, growth retardation, slight anemia, increased urinary glutamic-oxaloacetic transaminase activity, increased protein content, and increased kidney weights without pathologic changes. No evidence of carcinogenicity was reported. Because only one concentration was used, no evaluation of a dose-response relationship or no-effect level was possible.

In a 52-week study (7 h/day, 5 days/week) in hamsters, acetaldehyde concentrations were gradually reduced from 2,500 ppm to 1,650 ppm (Feron et al.1982, cited in EPA 1991 and ACGIH 2001). The combined tumor incidence in the larynx (carcinoma in situ, squamous cell carcinoma, and adenosquamous carcinoma) was significantly higher in the exposed group than in the controls. Simultaneous exposure to acetaldehyde and benzo[a]pyrene (administered intratracheally) increased malignant respiratory tract tumors over those in animals exposed to air or acetaldehyde alone by a factor of 3-5.

Woutersen et al. (1986) exposed rats to acetaldehyde at 0, 750, and 1,500 ppm for up to 28 months. They also exposed rats at 3,000 ppm but gradually decreased this concentration over the course of the study to about 1,000 ppm by day 359 because of signs of morbidity (such as severe growth reduction) and early mortality. All treatment groups showed non-neoplastic changes (degeneration, hyperplasia, and metaplasia) and adenocarcinomas of the olfactory epithelium. The two highest-exposure groups also showed squamous cell carcinomas of the respiratory epithelium and hyperplasia and keratinized squamous metaplasia of the laryngeal epithelium. In addition, the highest-exposure group showed rhinitis and sinusitis.

Reproductive Toxicity in Males

No studies that reported male reproductive toxicity of acetaldehyde were located.

Immunotoxicity

The immune system is not reported to be a critical target of acetaldehyde toxicity. No immunologic effects are reported below concentrations that cause respiratory toxicity (Environment Canada and Health Canada 2000). Mice showed an 8% increase in bactericidal activity of alveolar macrophages after a single 3-h exposure to acetaldehyde at 204 ppm but a 15% reduction after repeated exposure at 180 ppm 3 h/day for 5 days (Aranyi et al. 1986). Neither exposure regimen affected mortality from streptococcal infection. Various in vitro tests have indicated effects on immune-system cells, but concentrations used in the cell cultures are much higher than what would result in the body from air concentrations causing initial upper respiratory system effects (reviewed by WHO 1995).

The study by Lacroix et al. (2002) investigated the potential for acetaldehyde to increase pulmonary allergic responses in guinea pigs. Ovalbumin-sensitized guinea pigs exposed to acetaldehyde at 200 ppb 6 h/day, 5 days/week for 4 weeks showed no changes in biologic measures associated with inflammatory or allergic responses. As noted above, inconsistency with other studies and insufficient description of methods and results limit the usefulness of that study.

Genotoxicity

According to reviews by WHO (1995), NRC (1994), HEI (2007), and Morris (1997a), acetaldehyde is mutagenic in mammalian cells in several (although not all) in vitro systems without exogenous metabolic activation (for example, chromosomal aberrations and sister-chromatid exchanges). Addition of NAD^+ and ALDH to human lymphocyte cultures reduces sister-chromatid exchanges induced by acetaldehyde (Obe et al. 1986, cited in WHO 1995), presumably by oxidizing acetaldehyde. The available evidence indicates that acetaldehyde primarily produces clastogenic effects and sister-chromatid exchanges, but evidence indicating that acetaldehyde causes genetic mutations is sparse (Morris 1997a). A study using an in vitro system involving separated alleles in yeast indicated that acetaldehyde may play a role in mutations of tumor-suppressor gene *TP53*, which is involved in human esophageal cancers (Paget et al. 2008).

In vivo, acetaldehyde induced sister-chromatid exchanges in bone marrow of hamsters after intraperitoneal injection (HEI 2007) and increased micronucleus frequency in reticulocytes in mice after inhalation of acetaldehyde vapor

(Kunugita et al. 2008) but did not increase micronucleus frequency in mouse early spermatids after intraperitoneal injection (WHO 1995). Although several in vitro studies indicate that acetaldehyde can react with DNA in forming DNA-protein and DNA-DNA cross-links (Morris 1997a), studies demonstrating such formation in vivo are few and required high concentrations of acetaldehyde. The in vivo study in rats by Lam et al. (1986) suggested that acetaldehyde at 1,000 ppm can react with DNA and proteins to form stable adducts (Lam et al. 1986; WHO 1995). Dorman et al. (2008) and Stanek and Morris (1999), however, did not observe DNA-protein cross-link formation at 1,500 ppm in rats. Inhibition of ALDH had no effect in inducing DNA-protein crosslink formation at 1,500 ppm (Stanek and Morris 1999).

Standard bacterial test systems (Ames) with or without exogenous metabolic activation have generally had negative or equivocal results for genotoxicity, although acetaldehyde has resulted in reverse mutations in some tests that used *Escherichia coli* (IARC 1985; WHO 1995).

Carcinogenicity

The International Agency for Research on Cancer (IARC) listed acetaldehyde as possibly carcinogenic in humans (category IIB) on the basis of evidence from animal studies. Increased incidences of oral, throat, and esophageal cancers were found after heavy alcohol intake by people who had genetic polymorphisms of an enzyme involved in the metabolism of acetaldehyde (IARC 1999). As a metabolite of alcohol, acetaldehyde was discussed at an IARC meeting about the carcinogenicity of alcoholic beverages. On the basis of mechanistic evidence, the IARC working group concluded that acetaldehyde derived from alcoholic beverages contributed to causing malignant esophageal tumors in humans who are deficient in ALDH2 (Baan et al. 2007; Lachenmeier and Sohnius 2008).

The U.S. Environmental Protection Agency (EPA 1991) has also classified acetaldehyde as a B2 or probable human carcinogen by inhalation on the basis of sufficient animal data (nasal tumors in rats and laryngeal tumors in hamsters). The human evidence was judged to be inadequate on the basis of the epidemiologic study of workers by Bittersohl (1974, cited in EPA 1991) because of the lack of age adjustment of the incidence and several other methodologic limitations, such as exposures to other chemicals, smoking (all the incident cases were in smokers, according to Bittersohl 1975, as cited in ACGIH 2001), "short duration, small number of subjects, and lack of information on subject selection, age, and sex distribution." EPA (1991) relied on the finding of significantly increased laryngeal tumors in hamsters exposed to acetaldehyde at a time-weighted average concentration of 2,028 ppm 7 h/day, 5 days/week for 52 weeks (Feron et al. 1982, cited in EPA 1991) and on exposure-related increases in multiple types of nasal-cavity tumors in rats exposed to acetaldehyde at 0, 750, or 1,500 ppm or at an initial concentration of 3,000 ppm that was gradually

decreased to 1,000 ppm 6 h/day, 5 days/week for up to 28 months (Woutersen et al. 1986). Squamous cell carcinomas of the nasal respiratory epithelium showed clear concentration-related increases, whereas adenocarcinomas of the olfactory epithelium were highest in the middle-concentration group, possibly because of high mortality and competing squamous cell carcinomas in the high-concentration group.

TOXICOKINETIC AND MECHANISTIC CONSIDERATIONS

Toxicokinetic and mechanistic data on acetaldehyde have been reviewed in several publications (WHO 1995; Morris 1997a; Environment Canada and Health Canada 2000; EC 2004; HEI 2007; Deitrich et al. 2007). As a highly reactive, electrophilic compound, acetaldehyde readily binds with tissues and with sulfhydryl moieties of free proteins and nonprotein sulfhydryl groups, such as cysteine and glutathione. Acetaldehyde binding to intracellular thiols (cysteine and glutathione) may prevent binding to proteins, peptides, and DNA. Conjugation with thiols can result in various intermediates and later elimination of thioethers and disulfides in the urine. Inhaled acetaldehyde is largely retained at the initial site of contact with little increase in blood concentrations except at high airborne concentrations that exceed the capacity of respiratory tissues for binding and metabolism. Once aldehydes are absorbed after inhalation or ingestion, their primary reported metabolism and detoxification pathway is oxidation to acetate via the NAD^+-dependent enzyme, ALDH. Acetate is further metabolized to carbon dioxide and water or enters the two-carbon pool for molecular synthesis reactions.

Of the 19 known ALDH enzymes in humans, only a few are involved in aldehyde oxidation for which genetic polymorphisms can result in hereditary defects in metabolism of normal endogenous substrates (Deitrich et al. 2007). Most notably, polymorphism in the ALDH2 gene affects the mitochrondrial enzyme primarily responsible for oxidation of ethanol-derived acetaldehyde. A common polymorphism of that gene inhibits enzymatic activity, and this has resulted in reduced clearance of acetaldehyde in both homozygotic and heterozygotic people. Such people are protected from alcohol abuse (because of the unpleasant effects of acetaldehyde accumulation) but may be more at risk for esophageal, pharyngeal, and oral cancer (Deitrich et al. 2007; Kunugita et al. 2008). The frequency of polymorphisms for slow clearance of acetaldehyde may be as high as 50% in some populations (for example, Japanese) (Kunugita et al. 2008).

Other enzymes (such as aldehyde oxidase, xanthine oxidase, cytochrome P450 oxidase, and glyceraldehyde-3-phosphate dehydrogenase) may also play a role in acetaldehyde metabolism, but their contribution to total metabolic activity is small (Deitrich et al. 2007).

Although the liver is the primary location of ALDH activity, it is also present in other tissues. ALDH has been shown to be present in the noses of rats,

hamsters, mice, and guinea pigs and is thought to be a detoxification pathway for inhaled aldehydes (Morris 1997a,b). ALDH activity in the respiratory tract of rats is primarily in the nasal respiratory epithelium (particularly in ciliated epithelial cells) and in Clara cells of the lower bronchioles; there is low activity in the tracheal epithelium and virtually no activity in the olfactory epithelium (Bogdanffy et al. 1986). Morris (1997b) reported that in all four rodent species studied, uptake of acetaldehyde in the upper respiratory tract was 2-3 times more efficient at 1-10 ppm than at 1,000 ppm; this suggests a saturable process for acetaldehyde removal in the tissues. The rank order among mice, rats, hamsters, and guinea pigs in scrubbing efficiency of acetaldehyde in the upper respiratory tract differed between high and low concentrations, and this makes extrapolation of toxicity from high to low concentrations in rodents complex. Capacity limitation of nasal metabolism occurs when the rate of acetaldehyde delivered to the nasal tissues exceeds the total metabolic capacity of the tissues (Morris 1997b) or such protective mechanisms as binding to intracellular thiols (Environment Canada and Health Canada 2000). Thus, above some critical concentration, tissue concentrations of acetaldehyde increase as deposition exceeds metabolism (Heck 1997). Morris and Blanchard (1992) noted that the acetaldehyde deposition rate exceeds the rate of metabolism at 100 ppm and 1,000 ppm but not at 1 ppm or 10 ppm. A decrease in mucosal absorption in the upper airways also results in more penetration to lower airways.

Much of the observed decrease in the efficiency of uptake of acetaldehyde in rats between 10 and 100 ppm is thought to be attributed to saturation of metabolism because the concentration dependence disappears after pretreatment with an ALDH inhibitor (Morris 1999). Humans with the inactive variant of ALDH2 may have a lower critical concentration for saturation of acetaldehyde removal, which results in increased tissue concentrations in the upper respiratory tract, greater potential for systemic absorption, and deeper penetration at lower concentrations than in those with the active form of this enzyme. Using a knockout-gene mouse model to represent ALDH2-deficient humans, Oyama et al. (2007) showed greater effects on the upper respiratory tract and higher blood acetaldehyde concentrations in ALDH2-/- mice than in wild-type mice after exposure to acetaldehyde at 125 ppm or 500 ppm for 24 h/day for 14 days. At 125 ppm, blood acetaldehyde concentrations measured in three ALDH2-/- mice were about 1.4 times higher than those in three wild-type mice; however, at 500 ppm, blood acetaldehyde concentrations were 5 times higher in ALDH2-/- mice than in wild-type mice. In a previous study by the same group (Isse et al. 2005), the difference in blood acetaldehyde concentrations after exposure at 5,000 ppm for 4 h was about a factor of 2. Although blood acetaldehyde concentrations were not reported for the control (clean-air) group, blood acetaldehyde concentrations in wild-type mice were relatively unchanged between 125 and 500 ppm (1.65 μM and 1.72 μM, respectively) (Oyama et al. 2007). After the 4-h exposure at 5,000 ppm, blood acetaldehyde concentrations in wild-type mice ranged from 80 to 227 μM (Isse et al. 2005), indicating saturation of acetaldehyde metabolism

and tissue binding in the respiratory tract and greater systemic absorption at this higher concentration.

The difference in blood acetaldehyde concentrations between wild-type and ALDH2-deficient mice appears to be nonlinear over the air acetaldehyde concentration range examined. At the lower concentration of 125 ppm, the difference is less than a factor of 2, but it increases to a factor of 5 at 500 ppm, reflecting a reduced capacity of removal of acetaldehyde in ALDH2-/- mice because of impaired metabolic activity (Oyama et al. 2007). At the high concentration (5,000 ppm), the difference in blood acetaldehyde concentration decreases to a factor of 2 as the metabolic capacity of the respiratory tissues is also exceeded in the wild-type mice (Isse et al. 2005).

Related research by Kunugita et al (2008) showed that exposure to acetaldehyde at 125 and 500 ppm for 2 weeks resulted in higher mutagenicity (micronucleus frequency in reticulocytes) in the ALDH2-deficient mice than in the wild-type mice and controls. Micronucleus frequencies were similar between wild-type mice and controls at both concentrations and about 1.5 times higher and 1.75 times higher in deficient mice at 125 and 500 ppm, respectively.

Using the cytokinesis-block micronucleus assay on peripheral lymphocytes from blood samples from 47 healthy Korean subjects, Kim et al. (2005) showed that application of 0 mM, 0.5 mM, and 1.5 mM of acetaldehyde to lymphocytes in vitro increased the micronucleus frequencies in a dose-dependent manner. At the highest concentration, a 2-fold increase in micronucleus frequency over baseline (0 mM) was observed in lymphocytes from subjects with wild-type genotype ($ALDH2^1$) compared with a 3-fold increase in micronucleus frequency in lymphocytes from heterozygotes ($ALDH2^1/ALDH2^2$) and a 3.5-fold increase in micronucleus frequency in lymphocytes from homozygotes ($ALDH2^2/ALDH2^2$). The relative difference between the homozygotes and the wild-type was thus about 1.75 fold.

INHALATION EXPOSURE LEVELS FROM THE NATIONAL RESEARCH COUNCIL AND OTHER ORGANIZATIONS

A number of organizations have established or proposed acceptable exposure limits or guidelines for inhaled acetaldehyde. Selected values are shown in Table 2-2.

COMMITTEE RECOMMENDATIONS

The committee's recommended EEGLs and CEGL for acetaldehyde are shown in Table 2-3. The current U.S. Navy values (R. Hagar, Naval Sea Systems Command, personal commun., August 5, 2008) are provided for comparison.

TABLE 2-2 Selected Inhalation Exposure Levels for Acetaldehyde from the National Research Council and Other Agencies[a]

Organization	Type of Level	Exposure Level (ppm)	Reference
Occupational			
ACGIH	TLV-ceiling	25	ACGIH 2001
NIOSH	REL	Ca[b]	NIOSH 2005
OSHA	PEL-TWA	200	29 CFR 1910.1000
Spacecraft			
NASA	SMAC		NRC 1994
	1-h	10	
	24-h	6	
	30-day	2	
	180-day	2	
General public			
NAC (interim)	AEGL-1 (1-h)	45	EPA 2006
	AEGL-2 (1-h)	270	
	AEGL-1 (8-h)	45	
	AEGL-2 (8-h)	110	

[a]Comparability of EEGLs and CEGLs with occupational-exposure and public-health standards or guidance levels is discussed in Chapter 1 ("Comparison with Other Regulatory Standards or Guidance Levels").
[b]Potential occupational carcinogen.
Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AEGL, acute exposure guideline level; NAC, National Advisory Committee; NASA, National Aeronautics and Space Administration; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; SMAC, spacecraft maximum allowable concentration; TLV, Threshold Limit Value; TWA, time-weighted average.

TABLE 2-3 Emergency and Continuous Exposure Guidance Levels for Acetaldehyde

Exposure Level	Current U.S. Navy Values (ppm)	Committee Recommended Values (ppm)
EEGL		
1-h	10	25
24-h	6	12.5
CEGL		
90-day	2	2

Abbreviations: CEGL, continuous exposure guidance level; EEGL, emergency exposure guidance level.

1-Hour EEGL

The 1-h EEGL is based on human ocular and nasal irritation. As discussed above, Muttray et al. (2009) evaluated the protectiveness of the German occupational level for acetaldehyde and exposed 20 human subjects to acetaldehyde at 50 ppm for 4 h. They found no self-reported increase in irritating symptoms, a nonsignificant increase in mucociliary transport time but no change in olfactory threshold, no increase in the concentration of interleukins in nasal secretion, and no increase in mRNA levels of inflammatory factors in nasal epithelial cells. Their results differed from those in the study of Silverman et al. (1946), in which several subjects objected to acetaldehyde at 25 ppm (reason not specified) and most of the subjects (about 12) reported some eye irritation at 50 ppm. However, the recent study used a stronger crossover design, included various clinical and subclinical measures of irritation or inflammatory effects, and involved more people. It is possible that neither study included people who were more sensitive, such as those who were ALDH2-deficient.

ALDH2-deficient people may be more sensitive because of decreased acetaldehyde metabolism in epithelial tissues. Therefore, an uncertainty factor of 2 was applied to the 50-ppm exposure level to yield a 1-h EEGL of 25 ppm. The uncertainty factor is based on the difference between blood acetaldehyde concentrations in ALDH2-deficient and wild-type mice at low air concentrations (a factor of about 1.4 at 125 ppm; Oyama et al. 2007), evidence of micronucleus formation in reticulocytes of ALDH2-deficient and wild-type mice (a factor of about 1.5 at 125 ppm; Kunugita et al. 2008), and in vitro evidence in human lymphocytes from people who were ALDH2-deficient and people who had normal ALDH activity levels (a factor of about 1.75; Kim et al. 2005). Although those measures of the effect of ALDH2 deficiency are more systemic, ALDH activity in some epithelial tissues will affect the rate of acetaldehyde removal and thus the degree of irritation. Evidence from the above studies showing a reduction in the difference between impaired and normal ALDH2 activity with a decrease in air acetaldehyde concentration indicates that the difference may be even lower than a factor of 1.4-1.5 at 50 ppm compared with that at 125 ppm. Thus, an uncertainty factor of 2 should help to account for other potential differences in sensitivity among individuals. Any potential irritation at 25 ppm would be expected to be mild and not to interfere with duties during a 1-h emergency.

24-Hour EEGL

The basis of the 24-h EEGL is the study conducted by Oyama et al. (2007) in which ALDH2-deficient and wild-type mice were exposed to acetaldehyde 24 h/day for 14 days. The lowest exposure concentration used in the study (125 ppm) was associated primarily with nasal epithelial lesions, which tended to be more severe in the ALDH2-deficient mice (that is, ALDH wild-type mice showed fewer effects in terms of number of tissues, types of pathologic effects,

and number of animals showing effects). Lesions after 1 day are expected to be minimal compared with those after 2 weeks of exposure, and the variation in response between rats and humans with respect to such direct irritation was expected to be less than a full factor of 10. Therefore, an uncertainty factor of 3 to extrapolate from a lowest observed-adverse-effect level (LOAEL) to a no-observed-adverse-effect level (NOAEL) and an interspecies uncertainty factor of 3 to extrapolate from rats to humans were used to yield a total uncertainty factor of 10. An additional intraspecies uncertainty factor for variation within humans was not included because the sensitive ALDH2-deficient mice were used. The resulting 24-h EEGL is 12.5 ppm, which is half the 1-h EEGL based on irritation in humans and one-fourth of the NOAEL for eye irritation in the human study by Muttray et al. (2009). Furthermore, the 24-h EEGL should be protective against nasal lesions, which develop at higher exposures associated with greater irritation and more prolonged exposure.

90-Day CEGL

The subchronic study in rats by Dorman et al. (2008) was selected as the basis of a 90-day CEGL because of the study's comprehensive evaluation of the lower dose-response range and modeling of corresponding tissue concentrations to relate to 24-h continuous air concentrations for humans. The study showed a NOAEL of 50 ppm for olfactory epithelial effects.

Dorman et al. (2008) estimated a reference concentration for acetaldehyde based on the 50-ppm NOAEL in rats (see Figure 2-1). According to EPA (1994) guidelines, a reference concentration is intended to be protective in continuous exposure up to a lifetime for the general public, including sensitive populations. EPA's reference concentration for acetaldehyde includes a conversion of the air exposure concentration in rats to a human-equivalent concentration in an attempt to address the anatomic and physiologic differences between rats and humans (EPA 1991). Rather than using the EPA default cross-species ratio for reactive gases, Dorman et al. (2008) used a physiologically based pharmacokinetic (PBPK) model in rats to relate the NOAEL concentration of 50 ppm to a nasal tissue concentration in rats. The rat tissue concentration was divided by an uncertainty factor of 30 to extrapolate it to a human nasal tissue concentration. Dorman et al. (2008) then used a PBPK model for humans to provide the corresponding acetaldehyde concentration in air for a 24-h daily exposure (0.4 ppm). Dorman et al. (2008) also calculated the reference concentration by converting the rat nasal tissue concentration to a human-equivalent air concentration by using the PBPK model in humans and then applying the uncertainty factor of 30 (see Figure 2-1). That approach yielded approximately the same reference concentration as calculated by the other approach. Dorman et al. (2008) did not apply an additional uncertainty factor for extrapolating subchronic to chronic exposure because no additional damage would be expected for a longer duration

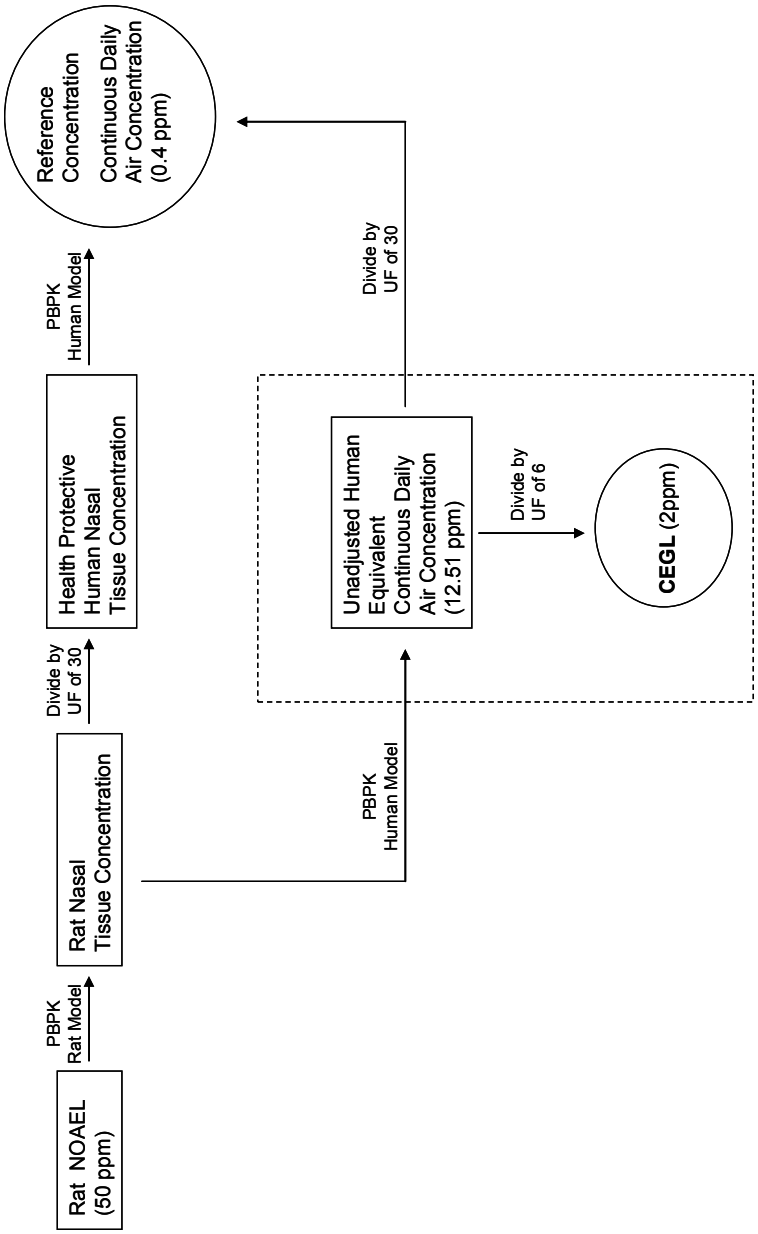

FIGURE 2-1 Calculation of the acetaldehyde reference concentration by Dorman et al. (2008). The pathway in the box shows the committee's calculation of the CEGL.

of exposure at the NOAEL for epithelial tissue injury (D. Dorman, North Carolina State University College of Veterinary Medicine, personal commun., December 4, 2008).

The reference concentration derived by Dorman et al. (2008) is intended to be protective of the general public. The uncertainty factor used to extrapolate to human exposures may differ between submariners and the general population. Dorman et al. (2008) used a combined uncertainty factor of 30 composed of a factor of 3 for pharmacodynamic differences between rats and humans (the model accounted for pharmacokinetic differences) and a factor of 10 for variation among humans (D. Dorman, North Carolina State University College of Veterinary Medicine, personal commun., December 4, 2008). However, because the submariner population is considered to be healthier and less susceptible than the general population, the committee used a factor of 2 instead of 10 for variation in humans based on the ALDH2-deficient polymorphism. Differences in human sensitivity to acetaldehyde are expected to be less variable at low air concentrations because it is associated with direct tissue effects at the site of entry rather than systemic effects. The combined uncertainty factor is 6 on the basis of a factor of 3 for pharmacodynamic differences between rats and humans and a factor of 2 for intraindividual variation.

Because Dorman et al. (2008) found little difference between application of the uncertainty factor to the rat tissue concentration calculated by the PBPK model in rats and application of the uncertainty factor to the human-equivalent air concentration calculated by the PBPK model in humans, the committee used the human-equivalent air concentration as a starting point to calculate the CEGL to avoid the need to rerun the model. Thus, an uncertainty factor of 6 was applied to the human-equivalent air concentration of 12.51 to yield a CEGL of 2 ppm.[2]

CARCINOGENICITY ASSESSMENT

EPA (1991) calculated an inhalation unit risk factor for assessing risks to the general public with the linearized multistage model based on the data on nasal cavity tumors in rats (Woutersen and Appelman 1984, cited in EPA 1991; Woutersen et al. 1985, cited in EPA 1991; Woutersen et al. 1986). The resulting unit risk value is 2.2×10^{-6} per microgram of acetaldehyde per cubic meter, assuming 24-h daily exposure for a lifetime. Implicit in that risk value is the assumption of no threshold dose below which the cancer risk is negligible. Given a total exposure time for a submariner over his career of 5 years and the U.S.

[2]The committee notes that a peer-reviewed HEC value was used here to derive the CEGL, whereas HEC values were not used in other EEGL and CEGL derivations because no other peer-reviewed values were available and only a default method would have been available to calculate the values.

Navy's acceptable cancer risk of 1×10^{-4} (NRC 1986), the corresponding acetaldehyde concentration is 0.35 ppm.[3]

That concentration is about 0.18 the calculated 90-day CEGL based on noncancer effects. The EPA cancer risk assessment is based on the assumption that the tumors observed in animals at high doses can be extrapolated to lower doses with no threshold for negligible cancer risk. However, as for formaldehyde (NRC 2007), considerable evidence indicates that the mechanism of action for tumor formation at high concentrations is related to cytotoxicity, hyperplasia, and cellular proliferation in the nasal cavity. Given the mutagenicity of acetaldehyde, lower doses could be associated with a risk of cancer through some genotoxic mechanism, although no specific models have been developed to assess such risk for acetaldehyde. Lower doses would not have cell proliferation to amplify the genotoxic effects and therefore would be associated with a substantially lower risk of tumor formation. The toxicokinetic and mechanistic evidence suggests that the dose-response relationship for acetaldehyde toxicity may also be nonlinear as the activity of ALDH becomes saturated; this would allow tissue concentrations to increase more rapidly. As a result, the cancer risk at lower doses would be less than predicted based on extrapolation from high doses. DNA-protein cross-link formation, which has been used to model low-dose formaldehyde cancer risk (Conolly et al. 2003), was not shown to demonstrate a dose-response relationship for acetaldehyde concentrations of 50-1,500 ppm (Dorman et al. 2008). Stanek and Morris (1999) likewise found no evidence of increased DNA-protein cross-link formation in rats exposed at 1,500 ppm even with administration of an ALDH inhibitor.

Dorman et al. (2008) note that rats and mice may be more predisposed to nasal lesions (and thus nasal tumors) than humans. Rats and mice are obligate nose breathers in which a larger portion of the nasal cavity (50% vs 10% in humans) is lined with olfactory mucosa. The network of ethmoid turbinates in the caudal region of the nasal cavity in rats also greatly expands the surface area of the olfactory mucosa and decreases air flow. Those factors in combination increase the concentration of acetaldehyde delivered to the olfactory mucosa. Lower ALDH activity in the olfactory epithelium in rats (Bogdanffy et al. 1986) would also make this tissue more susceptible to injury from acetaldehyde. Consequently, the 90-day CEGL based on protection of submariners from noncancer effects of acetaldehyde should also be protective against cancer.

DATA ADEQUACY AND RESEARCH NEEDS

Although data for assessing NOAELs for the different acetaldehyde guidance levels are available, uncertainties in setting exposure limits for submariners include the relative paucity of studies available for defining the lower limits for

[3] $[1 \times 10^{-4}\ (1\ \mu g/m^3 / 2.2 \times 10^{-6})]\ (70/5) = 636\ \mu g/m^3$ or $0.636\ mg/m^3$ (0.35 ppm).

eye irritation, the relative effect of ALDH2 polymorphisms in increasing sensitivity to irritation, and the chronic injury at low airborne concentrations of acetaldehyde. More research on carcinogenic mechanisms of inhaled acetaldehyde at low doses is needed to evaluate the potential carcinogenic risk at low concentrations.

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3

Hydrogen Chloride

This chapter summarizes the relevant epidemiologic and toxicologic studies of hydrogen chloride. It presents selected chemical and physical properties, toxicokinetic and mechanistic data, and inhalation-exposure levels from the National Research Council and other agencies. The committee considered all that information in its evaluation of the U.S. Navy's 1-h, 24-h, and 90-day exposure guidance levels for hydrogen chloride. The committee's recommendations for hydrogen chloride exposure levels are provided at the end of this chapter with a discussion of the adequacy of the data for defining the levels and the research needed to fill the remaining data gaps.

PHYSICAL AND CHEMICAL PROPERTIES

Hydrogen chloride is a colorless, corrosive, nonflammable gas with a pungent odor (Budavari et al. 1989). Leonardos et al. (1969) determined the odor threshold of hydrogen chloride to be 10 ppm by using a standardized procedure, a trained odor panel, and high-purity hydrogen chloride; the odor was described by the panel as "pungent." A wide range of odor thresholds (HSDB 2008) have since been reported. On the basis of a literature review, Amoore and Hautala (1983) reported the odor threshold as 0.77 ppm. The irritating concentration has been reported as 33 ppm (Ruth 1986).

Hydrogen chloride is highly soluble in water and forms hydrochloric acid. Because hydrogen chloride is so hygroscopic, airborne hydrogen chloride is typically an aerosol of hydrochloric acid. Selected physical and chemical properties are shown in Table 3-1.

TABLE 3-1 Physical and Chemical Properties of Hydrogen Chloride

Synonyms	Anhydrous hydrochloric acid
CAS registry number	7647-01-0
Molecular formula	HCl
Molecular weight	36.47
Boiling point	–85.05°C
Melting point	–114.22°C
Flash point	NA
Explosive limits	NA
Specific gravity	1.268 at 25°C (air = 1.000)
Vapor pressure	35,424 mmHg at 25°C
Solubility	67.3 g/100 g of water at 30°C; soluble also in some polar organic solvents, such as methanol, ethanol, and ether
Conversion factors	1 ppm = 1.49 mg/m^3; 1 mg/m^3 = 0.67 ppm

Abbreviation: NA, not available or not applicable.
Sources: Budavari et al. (1989), HSDB (2008).

OCCURRENCE AND USE

Hydrogen chloride is found naturally in the environment, is produced by the digestive system of most mammals, is a byproduct of many industrial processes, and is used primarily to synthesize inorganic and organic chemicals, such as chlorine, ethylene dichloride, and methyl chloride (Hisham and Bommaraju 2005).

Hydrogen chloride has been measured in the submarine atmosphere. Data collected on three nuclear-powered attack submarines indicate a range of 1-3 ppb (Hagar 2008). Whether the reported concentrations are representative of the submarine fleet is not known; few details were provided about the conditions on the submarines when the samples were taken. The committee located no other exposure data for the submarine environment. Hydrogen chloride emissions in the submarine are thought to arise from decomposition of halogenated hydrocarbons and refrigerants (Hagar 2008).

SUMMARY OF TOXICITY

The toxicity of hydrogen chloride has been the subject of a number of reviews (NRC 1987; EPA 1995; Lam and Wong 2000; NRC 2002, 2004; ACGIH 2003). At high concentrations, hydrogen chloride is an irritant to the mucous membranes, eyes, and skin. Accidental exposure to gaseous products or mix-

tures containing high concentrations of hydrogen chloride can result in a spectrum of chronic effects, including recurrent acute respiratory illnesses and asthma. Prolonged hypoxemia is noted in case reports, but details of exposure duration are unknown. The maximum tolerable concentration in prolonged exposure of humans has been reported as 10 ppm, with a maximum tolerable concentration for a few hours of 10-50 ppm (Henderson and Hagard 1943). Respiratory tract effects in laboratory animals range from mild to moderate irritation at low concentrations (less than 100 ppm) to nasal lesions at moderate concentrations (100-500 ppm) and pulmonary damage at high concentrations (greater than 500 ppm). Death can result from severe pulmonary injury. Hydrogen chloride can cause functional and morphologic respiratory tract injuries, depending on exposure concentration and duration (Darmer et al. 1974; Hartzell et al. 1985; Burleigh-Flayer et al. 1985; Kaplan et al. 1988, 1993a, cited in NRC 2004; Stavert et al. 1991). Because of its high water solubility, most hydrogen chloride that is inhaled should be absorbed in the upper respiratory tract (Morris and Smith 1982), and this should result in low availability for systemic toxicity. However, hepatic, myocardial, and renal damage was observed in laboratory animals after repeated exposure at high concentrations (Machle et al. 1942). Those effects may be attributed to disturbances in acid-base metabolism or to reduction in blood oxygen concentrations resulting from pulmonary damage. Data on the genotoxicity, immunotoxicity, and male reproductive toxicity of hydrogen chloride exposure are either nonexistent or too sparse to support conclusions. Neither epidemiologic studies nor lifetime animal cancer bioassays have yielded evidence of an association between hydrogen chloride exposure and cancer (Bond et al. 1991; IARC 1992; Sellakumar et al. 1985).

Effects in Humans

Accidental Exposures

Accidental exposure can occur when hydrogen chloride is the sole agent or the dominant agent in a mixture, such as one produced by combustion of polyvinyl chloride. Published reports describe immediate skin, eye, and respiratory tract irritation, particularly in the nose, pharynx, larynx, and tracheobronchial tree. The reports described below do not include exposure concentrations, so they are of little use in setting exposure guidelines; they are provided as secondary, supportive evidence of the outcomes observed in quantitative animal exposure studies.

A 41-year-old nonsmoking nonatopic man with stable, mild asthma developed rapidly progressive bronchospasm and acute respiratory failure requiring mechanical ventilation after cleaning a pool for 1 h with a product that contained hydrochloric acid. Severe asthma requiring oral corticosteroids and repeated hospitalizations persisted a year after the accident (Boulet 1988). A 57-year-old man with a 12-pack-year cigarette-smoking history developed irritant-induced

asthma after exposure to a hydrochloric acid and phosgene mixture (Tarlo and Broder 1989).

Finnegan and Hodson (1989) provided an overview of the 47 cases of hydrogen chloride fume inhalation in the registry of the poison center of Guy's Hospital, London. Exposure sources, durations, and circumstances were not specified. The dominant initial symptoms were nausea and vomiting, with bronchospasm in those with a history of asthma and one report of laryngospasm. Symptoms typically resolved in a week. Rosenthal et al. (1978) reported persistent hypoxemia lasting for months in one of 11 workers exposed to a gaseous mixture of hydrogen chloride, phosphorus oxychloride, phosphorus pentachloride, oxalyl chloride, and oxalic acid. Evidence of alveolar injury in the workers included reduction in diffusion capacity (three workers) and a finding of lung rales on physical examination (two workers).

The following case is presented in detail because of the extensive clinical characterization of persistent hypoxemia, which indicated the ability of mixed hydrogen chloride vapor and mist to cause delayed-onset deep lung or parenchymal injury. The case also illustrates a propensity for recurrent acute respiratory illness after such an injury. A chemical factory released vapors that contained an unknown high concentration of hydrogen chloride, water, and trace amounts of phosphorous trichloride. The release resulted in a 15-min exposure of a 34-year-old woman who was working on her boat in an open marina 300 ft away. As reported by Finnegan and Hodson (1989), the strength of the mixture caused the paint on the boat to blister. The woman was hospitalized on the same day for symptoms of skin, eye, and respiratory tract irritation and for tachypnea, facial erythema, and hoarseness. She was discharged on the third day but readmitted with dyspnea while talking and with hypoxemia without hypercapnea, corrected with 24-28% oxygen. Further evaluation to identify the cause of the hypoxemia showed a normal anatomic shunt of 3.2%, a normal ventilation-perfusion scan (which excluded pulmonary thromboembolism), and normal total lung capacity but reduced residual volume. Exercise challenge during this interval showed marked desaturation (from 94% to 82%). The hypoxemia persisted for a month despite treatment with prednisone, salbutamol, and beclomethasone. Hypoxemia recurred during two later viral infections that required hospitalization.

A neighborhood exposure occurred when a container truck leaked 200 gal of hydrochloric acid while parked 150 ft from a mobile-home park; hydrogen chloride was later found in nearby ditches and a pond (Kilburn 1996). The acute illness among the investigating officer and residents included burning and tearing eyes, burning throat, headache, chest pain, shortness of breath, and influenza-like complaints. Follow-up assessment 20 months after the exposure compared findings between 45 adults and 24 children living in the zone of the cloud of fumes and 56 adults and 39 children living in a similar mobile-home court 1.4 miles from the site. The exposed group showed more respiratory symptoms, such as phlegm production and shortness of breath, than the reference group. After adjustment for sex, age, height, and cigarette-smoking, exposed adults

showed lower mean forced vital capacity (FVC; 70% vs 79%) and lower forced expiratory volume at 1 s (FEV_1; 61% vs 72%). Self-reports of mood state showed greater tension, depression, anger, extreme fatigue, and confusion and lower vigor in the exposed group.

Dyer and Esch (1976) performed a clinical study of 170 firefighters who were exposed one to four times to polyvinyl chloride thermal degradation products. Acute symptoms included pain in the throat, neck, and anterior part of the chest; dyspnea; severe headache; dizziness; and irregular pulse. Electrocardiography showed that 20% had extrasystoles. Twelve firefighters required hospitalization and treatment with oxygen, bronchodilators, antihistamines, and decongestants. None had to retire because of permanent airway disorders.

Markowitz et al. (1989) conducted a retrospective cohort study of 80 firefighters exposed in 1985 to burning polyvinyl chloride; they used 15 unexposed firefighters as control subjects. Air analysis during a recreation of the polyvinyl chloride combustion showed the primary decomposition products to be hydrogen chloride (6,800 ppm), carbon monoxide (9,300 ppm), carbon dioxide (26,000 ppm), and methane (1,760 ppm). Smaller quantities of benzene (146 ppm) and other organic compounds, primarily acetylene (420 ppm), were detected. The concentrations of nitric oxide, nitrogen dioxide, methyl pyrrole, and an unidentified chlorinated agent were 3-6 ppm. Phosgene, vinyl chloride, dioctylphthalate, and polychlorinated biphenyls were not detected. One hour after the fire began, firefighters reported rashes and eye irritation. Five to 6 weeks after the incident, symptoms with a higher relative risk in exposed firefighters included eye irritation, skin irritation, rash or itching, sore throat, headache, restlessness, dizziness, blurred vision, stomach pain, tingling or numbness, dry mouth, chest pain, wheezing, coughing, shortness of breath, increased thirst, muscle or joint pain, tiredness, and daytime drowsiness.

Promisloff et al. (1990) reported the development of reactive-airways dysfunction syndrome (RADS) in three Philadelphia police officers after exposure to toxic fumes from a roadside truck accident. The accident resulted in a large chemical spill and fire on a major highway. Exposures were to sodium hydroxide and hydrochloric acid generated by hydrolysis of silicon tetrachloride and trichlorosilane. Exposure concentrations were not discussed. In summary, the officers developed persistent coughing and headache within hours of exposure and exertional dyspnea and wheezing later. Inhalation challenge showed airway hyperreactivity to methacholine; exercise challenge showed no oxyhemoglobin desaturation. Initial spirometry was normal, but an accelerated decline in function (decreases in FEV_1 and FEV_1/FVC%) occurred over the following year.

Experimental Studies

Human exposure studies performed in laboratories in the late 1800s and first half of the 1900s remain an important source of hydrogen chloride exposure-response information (Table 3-2). A limitation of the data is that the meth-

ods and results are reported in less detail than current practice dictates. Elkins (1959) recommended a maximum allowable concentration of 5 ppm on the basis of immediate symptoms of nose and throat irritation. Lower concentrations might have promoted tooth decay but were not considered to be harmful. All concentrations above 10 ppm were reported as highly irritating, although some workers adapted over time. Workplace exposure measurements included 16 ppm in waste carbonizing, 11 ppm in acid dipping, and 23 ppm in tanning processes.

Henderson and Hagard (1943) reported that hydrogen chloride at 35 ppm caused irritation of the throat on short exposure, and 10 ppm was the maximum concentration tolerable for prolonged exposure. The maximum concentration tolerable for a few hours was 10-50 ppm, the maximum concentration tolerable for 1 h was 50-100 ppm, and concentrations of 1,000-2,000 ppm were reported as dangerous for even short exposure.

Heyroth (1963) cited an 1889 dissertation that reported that work is impossible when one inhales hydrogen chloride at 50-100 ppm, difficult but possible at 10-50 ppm, and undisturbed at 10 ppm.

Stevens et al. (1992) exposed 10 18- to 25-year-old asthmatics to low concentrations of hydrogen chloride (0.8 and 1.8 ppm) in a controlled human exposure study. The subjects were exposed three times: once to filtered air, once to hydrogen chloride at 0.8 ppm, and once to hydrogen chloride at 1.8 ppm. Exposures were separated by at least a week. The 45-min exposure was evenly divided into two periods of exercise separated by a period of rest. The exercise consisted of walking on a treadmill at 2 mph with an inclination of 10%. The subjects reported no increases in respiratory symptoms and had insignificant changes in pulmonary function between pre-exposure and postexposure measurements. There was a significant rise in oral ammonia concentrations—a finding that was counterintuitive in that the authors had expected a slight decrease because of neutralization caused by the inhaled acid gas. The authors concluded that people who had mild asthma had no adverse respiratory effects of exposure to hydrogen chloride at low concentrations.

Occupational and Epidemiologic Studies

Kremer et al. (1995) conducted a cross-sectional study to evaluate the relationship between occupational exposure to low concentrations of airway irritants and airway responsiveness to histamine, a marker of airway hyperreactivity. Of a cohort of 688 male workers, 119 were potentially exposed to acid mists containing sulfur dioxide and hydrogen chloride vapors and aerosols of sulfate and hydrogen chloride. Company policies prevented employment of workers who might be exposed to the acid mists if they had a suspected history of asthma-like symptoms during the 5-year period before the study. Time-weighted average (7-h, TWA) concentrations were determined by personal sampling and indicated maximum concentrations of 0.3 mg/m^3 for sulfur dioxide vapor, of 2.1 mg/m^3

TABLE 3-2 Hydrogen Chloride: Human Exposure Studies

Concentration (ppm)	Duration	Effect	Reference
0.77	Unspecified	Geometric mean of odor thresholds	Amoore and Hautala 1983
1-5	Unspecified	Odor threshold	Heyroth 1963
10	Unspecified	Odor threshold	Leonardos et al. 1969
< 5	Unspecified	Apparently not harmful, may promote tooth decay	Elkins 1959
≥ 5	Unspecified	Immediately irritating	Elkins 1959
> 10	Occupational	Highly irritating, but workers developed some tolerance	Elkins 1959
10	Prolonged	Maximum tolerable	Henderson and Hagard 1943
10-50	A few hours	Maximum tolerable	Henderson and Hagard 1943; Jacobs 1967
35	Short	Throat irritation	Henderson and Hagard 1943
50-100	1 h	Maximum tolerable	Henderson and Hagard 1943; Jacobs 1967
1,000-2,000	Short (less than 1 h)	Dangerous	Henderson and Hagard 1943; Jacobs 1967

for hydrogen chloride aerosol, and of 0.5 mg/m^3 for sulfate aerosol. For some work operations, peak hydrogen chloride vapor exposures of up to 40 mg/m^3 (27 ppm) occurred (averaging a few minutes). There was a trend toward a reduced prevalence of histamine reactivity in the acid-mist group; however, the mixed exposure and pre-employment selection bias limit the usefulness of this study in the present analysis.

Possible carcinogenic effects of hydrogen chloride were evaluated with a nested case-control study of 308 lung-cancer cases and 616 comparison workers among a cohort of 19,608 chemical-manufacturing employees (Bond et al. 1991). Exposure reconstruction was performed by an industrial hygienist familiar with plant operations. The duration of hydrogen chloride exposure was calculated by summing the time spent on jobs with a TWA greater than zero. Cumulative exposure was derived by multiplying the time spent on each job by the midpoint of the TWA range for that job and summing across all jobs. Workers were then classified into four exposure groups: 0, 0.1-3.9, 4-12.4, and at least 12.5 ppm-years. There was no association between hydrogen chloride exposure and lung cancer whether analyzed by duration of exposure, cumulative exposure, highest average exposure, or latency.

Coggon et al. (1996) assessed the risk of cancer from inhalation of mineral-acid mists with a cohort study and a nested case-control study of 15 men with upper aerodigestive tumors in a 93% follow-up sample of 4,401 men employed since 1950 at two battery plants and two steel works in Britain. The 15 upper aerodigestive cancers included four of the lip, three of the larynx, two of the tongue, one of the nasal sinus, two of the gum or retromolar area, two of the pharynx or nasopharynx, and one of the tonsil. The odds ratio (OR) was doubled for cumulative acid exposure, measured according to whether a person had worked for over 5 years in jobs with exposures in excess of 1 mg/m^3 (OR, 2.0; 95% confidence interval [CI], 0.4-10). There was no dose-response relationship for risk related to maximum exposure to acid mists. There was no information on smoking and alcohol consumption in the cohort, but the authors stated that lung cancer in men with definite exposure to acid mists was close to expectation (standardized mortality ratio, 0.98; 95% CI, 0.78-1.22).

Effects in Animals

Acute Toxicity

Acute exposures of laboratory animals to hydrogen chloride were summarized in reviews by NRC (1987, 2002, 2004), Lam and Wong (2000), and ACGIH (2003). A number of LC_{50} values have been calculated for exposure times ranging from 5 to 60 min in rats and mice (Higgins et al. 1972, cited in NRC 2004; MacEwen and Vernot 1972, cited in NRC 1987; Darmer et al. 1974; Wohlslagel et al. 1976, cited in NRC 2004; Vernot et al. 1977; Anderson and Alarie 1980, cited in NRC 2004). Mice appear to be more sensitive than rats to

the lethal effects of hydrogen chloride. For a 60-min exposure, the LC_{50} values in mice were 1,108 ppm (Wohlslagel et al. 1976, cited in NRC 2004) and 1,322 ppm (MacEwan and Vernot 1972, cited in NRC 2004). NRC (2004) combined rat and mouse LC_{50} data for exposures of 1-100 min and, on the basis of regression analysis, determined that n = 1 was appropriate for application of the relationship $C^n \times t = k$, where C = concentration, t = time, and k = constant, defined by ten Berge et al. (1986) for time-scaling.

Nonhuman primates, guinea pigs, rabbits, rats, and mice have been used in a number of nonlethal single-exposure investigations of hydrogen chloride. Baboons (n = 1, 2, or 3) were exposed to a range of hydrogen chloride concentrations for 5-15 min to assess respiratory effects and the potential of hydrogen chloride to impair escape behavior (Kaplan 1987; Kaplan et al. 1985, cited in NRC 1987, 2004; Kaplan et al. 1986, cited in NRC 2002; Kaplan et al. 1988). Concentrations of 16,570 and 17,290 ppm (5 min) caused severe dyspnea and resulted in delayed death due to pneumonia and pulmonary edema (Kaplan et al. 1985, cited in NRC 1987, 2004). At 500, 5,000, or 10,000 ppm (15 min), respiratory rate and minute volume were increased, arterial oxygen decreased (5,000 and 10,000 ppm), but lung function was normal when measured 3 days and 3 months after exposure (Kaplan et al. 1988). Irritant effects ranged from coughing and frothing at the mouth at lower concentrations (810-940 ppm) to profuse salivation, blinking, and head-shaking at higher concentrations (16,570-17,290 ppm), but there was no loss of escape capability at 11,400 or 17,290 ppm. No sign of irritation was observed in a baboon exposed to hydrogen chloride at 190 ppm for 5 min (Kaplan et al. 1985, cited in NRC 1987, 2004). It should be noted that individual baboons may have been used for more than one exposure (NRC 2004).

Four groups of investigators have studied the effects of acute (15-30 min) hydrogen chloride exposure in guinea pigs (Kaplan et al. 1993b, cited in NRC 2004; Malek and Alarie 1989; Burleigh-Flayer et al. 1985; Machle et al. 1942). Results were not always consistent among studies, perhaps because of the different study designs and end points monitored. Hydrogen chloride was shown to be a sensory and pulmonary irritant at exposure concentrations of 320-1,380 ppm (Burleigh-Flayer et al. 1985). Kaplan et al. (1993b, cited in NRC 2004) observed a decrease in respiratory rate at 520 or 3,940 ppm but little effect on blood gases and a decrease in arterial pH in animals exposed only at 3,940 ppm.

Malek and Alarie (1989) focused on time to incapacitation by using a chamber exercise-wheel apparatus. Guinea pigs exercised on the wheel for 10 min before the start of hydrogen chloride exposure. The authors observed gasping and death in guinea pigs exposed at 586 ppm. Hydrogen chloride concentrations of 140 and 162 ppm caused coughing, gasping, and incapacitation; time to incapacitation was 16.5 and 1.3 min, respectively. Guinea pigs exposed at 107 ppm showed only mild irritation (details were not provided) and were not incapacitated during the 30 min of exposure.

Machle et al. (1942) exposed groups of three guinea pigs and three rabbits to hydrogen chloride at various concentrations (about 34-14,000 ppm) and for

various times (5 min to 6 h). Animals that survived 2 months or longer were killed. Detailed results were not provided, but no animals survived exposure to hydrogen chloride at 679 ppm for 6 h. At lower concentrations, mild inflammatory reactions with some peribronchial fibrosis and lymph node hyperplasia were observed in the guinea pigs. Lobular pneumonia and pulmonary abscesses were observed in rabbits exposed at lower concentrations. However, no pathologic changes (presumably in lungs, liver, kidneys, and heart) were observed in animals exposed at the lowest concentration studied (34 ppm 6 h/day, 5 days/week for 4 weeks).

Several scientists reported acute hydrogen chloride exposure studies in rats that resulted in nonlethal effects. Exposures to hydrogen chloride at 11,800 ppm and higher for 5 min produced extreme irritation of the mucous membranes, eyes, and respiratory tract (Darmer et al. 1974; Kaplan et al. 1986, cited in NRC 2002). Rats did not lose their ability to escape via a signal-avoidance task unless the exposure concentration of hydrogen chloride were high enough to induce death (87,600 ppm) (Kaplan 1987, cited in ACGIH 2003; Kaplan et al. 1988, cited in ACGIH 2003). Irritation of the eyes, mucous membranes, and respiratory tract and erythema occurred when animals were exposed at 1,800-4,500 ppm for 1 h, and 20% or higher mortality occurred when rats were exposed at 2,600 ppm or higher for 1 h (Wohlslagel et al. 1976, cited in NRC 2002). Concentration-related decreases in respiratory rate and minute volume were observed after 30-min exposures at 200 ppm and higher (Hartzell et al. 1985). The RD_{50} (the concentration that produces a 50% decrease in respiratory frequency) was determined to be 560 ppm. Stavert et al. (1991) showed dramatic differences in response to hydrogen chloride exposure between nose-breathing rats and mouth-breathing rats. The mouth-breathing rats were fitted with a mouthpiece attached to an endotracheal tube. At 1,300 ppm for 30 min, 46% of the mouth-breathing rats and 6% of the nose-breathing rats died. Survivors were killed 24 h after exposure, and their nasal cavities, tracheas, and lungs were examined microscopically. Epithelial-cell necrosis and severe inflammation were observed in the tracheas of mouth-breathing rats, but the findings were limited to the nasal cavities of nose-breathing rats. Similarly, lung weights were increased in the mouth-breathing rats compared with control animals, but not in the nose-breathing rats. In summary, functional respiratory effects were observed in rats after 30-min exposure to hydrogen chloride at 200 ppm or higher, and lethality was observed in mouth-breathing rats exposed at 1,300 ppm for the same duration.

Mice appear to be more sensitive to acute hydrogen chloride exposures than rats (Higgins et al. 1972, cited in NRC 2004). In general, mice die at hydrogen chloride concentrations that are about one-third of the concentrations that kill rats. Studies in mice by Doub (1933, cited in NRC 2002), Darmer et al. (1974), Wohlslagel et al. (1976, cited in NRC 2002, 2004), Lucia et al. (1977), Barrow et al. (1977, 1979), and Kaplan et al. (1993b) yielded the following observations:

- *5-min exposures*. Hydrogen chloride produced severe irritation of the mucous membranes and eyes and some irritation of exposed skin at concentrations of 3,200 ppm or higher.
- *10-min exposures*. Hydrogen chloride is a sensory irritant with an RD_{50} of 309 ppm. A decrease in respiratory rate was observed above 40 ppm, and small superficial ulcerations were observed in respiratory epithelium of the nasal cavity near its junction with squamous epithelium at a concentration as low as 17 ppm. As the concentration of hydrogen chloride increased, the mucosal ulcerations increased in severity and extent, gradually extending up the sides and septum of the nasal cavity.
- *15-min exposures*. Hydrogen chloride produced a decrease in respiratory rate at 475 ppm or higher followed by 50% or greater mortality after exposure. The time between exposure and death was inversely related to exposure concentration. No abnormal histopathologic findings were observed in the respiratory tract (nares to lungs) of the 475-ppm exposure group, but causes of death were not stated.
- *30-min exposures*. Hydrogen chloride produced severe irritation of the mucous membranes and some irritation of exposed skin at concentrations of 410 ppm or higher.
- *60-min exposures*. Hydrogen chloride produced irritation of the mucous membranes and eyes, respiratory distress, corneal opacity, and erythema at concentrations of 560 ppm or higher. Twenty percent mortality was observed at 560 ppm.

In summary, minimal microscopic lesions were observed in the nasal cavities of mice exposed to hydrogen chloride at 17 ppm for 10 min, but this information was not consistent with results of other studies, which showed no lesions at 475 ppm for 15 min. However, mortality was observed in mice exposed to hydrogen chloride at 475 ppm for 15 min or at 560 ppm for 1 h. A slight decrease in respiratory rate occurs at 40 ppm, and the RD_{50} was 309 ppm.

Repeated Exposures and Subchronic Toxicity

A few inhalation studies of hydrogen chloride that used more than a single exposure have been performed in laboratory animals. Buckley et al. (1984) investigated the induction of respiratory tract lesions in mice after exposure to chemical sensory irritants. Histopathologic lesions were observed in the nasal cavity after exposure to hydrogen chloride at 310 ppm 6 h/day for 3 days. Lesions included exfoliation, erosion, ulceration, and necrosis of the nasal respiratory epithelium. However, nasal cavity lesions were minimal in the olfactory epithelium, and no effects were observed in the lungs of mice exposed to hydrogen chloride. In a 4-week study by Machle et al. (1942), no histopathologic lesions (presumably in the lungs, liver, kidneys, and heart) were observed in three rabbits, three guinea pigs or one monkey exposed to hydrogen chloride at 34

ppm 6 h/day, 5 days/week. However, several months elapsed after exposure before all animals were killed and examined for histologic effects.

A 90-day inhalation toxicity study was conducted by Toxigenics (1984). Both sexes of F344 and Sprague-Dawley rats (31 males and 21 females per strain per group) and B6C3F1 mice (31 males and 21 females per group) were subjected to whole-body exposure to hydrogen chloride at 0, 10, 20, or 50 ppm 6 h/day, 5 days/week for 13 weeks. An interim necropsy of 15 males and 10 females per group took place the day after the fourth exposure. End points included clinical observations, body weight, hematologic findings, serum chemistry, urinalysis findings, and histopathologic lesions of selected tissues. All 50-ppm exposure groups had a reduction in body-weight gain, which was observed after as few as four exposures. Minimal to mild rhinitis was observed in rats in all groups exposed to hydrogen chloride. The degree of rhinitis was concentration- and duration-dependent and was confined to the anterior portion of the nasal cavity. There were no changes in hematologic, serum chemistry, or urinalysis measures or histopathologic findings beyond the nasal cavity in the exposed rats compared with control rats.

In mice, body-weight gain was decreased in the 50-ppm exposure group. Histopathologic lesions (minimal to mild intracytoplasmic "eosinophilic globules") were observed in the epithelial cells lining the nasal turbinates of mice in all groups exposed to hydrogen chloride. Effects were more prevalent in females than in males, and eosinophilic globules were not observed in male mice in the 20-ppm and 10-ppm groups. Mice in the 50-ppm group also had minimal lesions of the lips (ulcerative cheilitis). There were no changes in hematologic, serum chemistry, or urinalysis measures or histopathologic findings beyond the nasal cavity and perioral areas in exposed mice compared with control mice.

The results of the 90-day study indicate that 10 ppm is a lowest observed-adverse-effect level (LOAEL) in light of the minimal rhinitis and minimal eosinophilic globules in nasal turbinates observed in rats and mice, respectively.

Chronic Toxicity

The study conducted by Sellakumar et al. (1985) provides the only inhalation toxicity data on exposures to hydrogen chloride lasting more than 90 days (data reported at an interim stage in Albert et al. 1982). A single group of 100 male Sprague-Dawley rats was exposed to hydrogen chloride at 10 ppm 6 h/day, 5 days/week for 128 weeks (lifetime). The group exposed only to hydrogen chloride was part of a larger study that involved exposure of four additional groups of rats to air only (control group), to formaldehyde at 15 ppm, to a mixture of hydrogen chloride at 10 ppm and formaldehyde at 15 ppm, and to vapors of hydrogen chloride at 10 ppm and formaldehyde at 15 ppm that were not mixed but were introduced simultaneously and separately into the exposure chamber. End points included daily clinical observations, body weights, gross necropsy findings, and histopathologic findings of the nasal cavity, trachea, lar-

ynx, lung, kidneys, testes, and other organs in which gross lesions were observed. Only results for the respiratory tract were presented in detail. The incidences of epithelial or squamous-cell hyperplasia (in 62 of 99 animals) and squamous-cell metaplasia (in nine of 99 animals) in the nasal cavity of rats exposed only to hydrogen chloride were greater than incidences observed in air-only control animals (51 of 99 and five of 99, respectively). Incidences of tracheal hyperplasia (in 26 of 99) and laryngeal hyperplasia (in 22 of 99) were increased in the rats exposed only to hydrogen chloride compared with air-only control rats (six of 99 and two of 99, respectively). For developing an inhalation reference concentration for hydrogen chloride, the U.S. Environmental Protection Agency considered a concentration of 10 ppm in this study as a LOAEL (EPA 1995).

Reproductive Toxicity in Males

No data on male reproductive toxicity of hydrogen chloride were found in the literature. Results of repeated inhalation exposure studies in rats and mice (Toxigenics 1984) did not reveal histopathologic effects in male reproductive organs.

Immunotoxicity

No data on immunotoxicity of hydrogen chloride were found in the literature.

Genotoxicity

Genotoxicity studies of hydrogen chloride are sparse. There are no in vivo genotoxicity inhalation studies of hydrogen chloride, such as a mouse micronucleus assay. Results of an adenovirus SA7 transformation assay of Syrian hamster embryo cells with hydrochloric acid concentrations of 31-500 µg/mL were negative (Casto and Hatch 1978, cited in Heidelberger et al. 1983). However, at a concentration of 25 µg/well, hydrochloric acid was positive in an *Escherichia coli* DNA-repair assay (McCarroll et al. 1981); and at a concentration of 100 ppm for 24 h, chromosomal nondisjunction was induced in *Drosophila melanogaster* (RTECS 2008).

Carcinogenicity

Sellakumar et al. (1985) performed a lifetime study of exposure of male Sprague-Dawley rats to hydrogen chloride. A summary of the experimental de-

sign and results is provided in the section "Chronic Toxicity." The authors counted tumors observed in the respiratory tract and total number of tumors in organs outside the respiratory tract. There was no evidence of excess tumor formation in animals exposed only to hydrogen chloride compared with the control group. The combination of hydrogen chloride and formaldehyde did not affect the incidence of nasal cavity carcinogenesis compared with the incidence of nasal tumors observed in the formaldehyde-only exposure group. The conclusion was that hydrogen chloride did not promote the carcinogenicity of formaldehyde.

TOXICOKINETIC AND MECHANISTIC CONSIDERATIONS

Toxicokinetic studies of hydrogen chloride were not found in the literature. The high water solubility of hydrogen chloride indicates rapid adsorption of hydrogen chloride on mucous membranes after inhalation. Morris and Smith (1982) predicted that more than 99% of inhaled hydrogen fluoride would be absorbed by the upper respiratory tract in rats. Because hydrogen chloride, like hydrogen fluoride, has high water solubility and reactivity, it should also be highly absorbed in the upper respiratory tract of rats. Inhalation studies of hydrogen chloride in laboratory animals have shown tissue injury in the most anterior regions of the nasal cavity with much less or even negligible injury in the posterior areas of the nasal cavity or downstream in the trachea and lungs (Buckley et al. 1984; Stavert et al. 1991). The high water solubility and rapid dissolution of hydrogen chloride partly explain the low systemic toxicity observed after hydrogen chloride exposure (Machle et al. 1942; Toxicogenics 1984; Sellakumar et al. 1985). However, high concentrations of hydrogen chloride (for example, greater than 500 ppm) appear to saturate the absorption or buffering capacities of the nasal mucosa, and pulmonary damage—such as congestion, mild hemorrhage, and multifocal acute alveolitis—is observed more frequently (Burleigh-Flayer et al. 1985; Kaplan et al. 1993b). Tracheal injury was also observed in mouth-breathing rats exposed to hydrogen chloride at 1,300 ppm for 30 min, but no lower respiratory effects were observed in nose-breathing rats under the same exposure conditions (Stavert et al. 1991). Thus, humans may be more susceptible to lung effects when breathing through their mouths than when breathing through their noses under identical exposure conditions.

Once absorbed into the mucous layers and membranes, hydrogen chloride is not metabolized but dissociates into hydrogen ions and chloride ions (pK, -7 in aqueous medium). The hydrogen ions react with water to produce hydronium ions, which, as proton donors, react readily with organic molecules. That reaction is presumably responsible for cellular injury and, if severe enough, cell death. Fluid accumulates at the site of injury and explains why pulmonary edema and such other factors as vascular changes and interference in gaseous transfer (of oxygen in particular) are associated with the cause of animal death

(Machle et al. 1942; Darmer et al. 1974). The chloride ions derived from dissociation of hydrogen chloride are likely to be distributed throughout the body because they are normal electrolytes. In general, it is presumed that chloride ions generated from hydrogen chloride inhalation—even brief exposures at high concentrations—are not sufficient to perturb the body's electrolyte balance.

INHALATION EXPOSURE LEVELS FROM THE NATIONAL RESEARCH COUNCIL AND OTHER ORGANIZATIONS

A number of organizations have established or proposed acceptable exposure limits or guidelines for inhaled hydrogen chloride. Selected values are summarized in Table 3-3.

COMMITTEE RECOMMENDATIONS

The committee's recommendations for EEGL and CEGL values for hydrogen chloride are summarized in Table 3-4. The current U.S. Navy values are provided for comparison.

1-Hour EEGL

Biologic end points that were considered the most relevant for derivation of the 1-h EEGL were mild irritation of the eyes and mucosal surfaces and alterations in respiratory frequency at hydrogen chloride concentrations that produced reversible effects. Alteration in respiratory rate is a sensitive indicator of sensory and pulmonary irritation (ASTM International 2004). Chemicals that decrease respiratory frequency by 20-50% are considered moderate irritants (ASTM International 2004). An approximate 10% decrease in respiratory rate was observed in mice exposed to hydrogen chloride at 40 ppm for 10 min (Barrow et al. 1977). The RD_{50} values in mice and rats were 309 ppm (Barrow et al. 1977) and 560 ppm (Hartzell et al. 1985), respectively. Fifteen-minute exposures of baboons at 500 ppm (Kaplan et al. 1988) and 30-min exposures of rats at 200 ppm (Hartzell et al. 1985), of sedentary guinea pigs at 320 ppm (Burleigh-Flayer et al. 1985), and of exercising guinea pigs at 107 ppm (Malek and Alarie 1989) produced alterations in respiratory rate or mild irritation, which returned to normal after exposure. However, exercising guinea pigs exposed at 140 ppm or higher exhibited respiratory distress and incapacitation (Malek and Alarie 1989). The small superficial ulcerations in nasal respiratory epithelium of mice that Lucia et al. (1977) found after a 10-min exposure at 17 ppm were considered reversible lesions of insufficient concern for setting a 1-h EEGL.

TABLE 3-3 Selected Inhalation Exposure Levels for Hydrogen Chloride from the National Research Council and Other Agencies[a]

Organization	Type of Level	Exposure Level (ppm)	Reference
Occupational			
ACGIH	TLV-ceiling	2	ACGIH 2003
NIOSH	REL-ceiling	5	NIOSH 2005
OSHA	PEL-ceiling	5	29 CFR 1910.1000
Spacecraft			
NASA	SMAC		Lam and Wong 2000
	1-h	5	
	24-h	2.5	
	30-day	1	
	180-day	1	
Submarine			
NRC	EEGL		NRC 1987
	1-h	20	
	24-h	20	
	CEGL		NRC 1987
	90-day	0.5	
	SEAL 1 (10-day)	20	NRC 2002
	SEAL 2 (24-h)	35	

(Continued)

TABLE 3-3 Continued

Organization	Type of Level	Exposure Level (ppm)	Reference
General Public			
NAC/NRC	AEGL-1 (1-h)	1.8	NRC 2004
	AEGL-2 (1-h)	22	
	AEGL-1 (8-h)	1.8	
	AEGL-2 (8-h)	11	

[a]Comparability of EEGLs and CEGLs with occupational-exposure and public-health standards or guidance levels is discussed in Chapter 1 ("Comparison with Other Regulatory Standards or Guidance Levels").

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AEGL, acute exposure guideline level; CEGL, continuous exposure guidance level; EEGL, emergency exposure guidance level; NAC, National Advisory Committee; NASA, National Aeronautics and Space Administration; NIOSH, National Institute for Occupational Safety and Health; NRC, National Research Council; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; SEAL, submarine escape action level; SMAC, spacecraft maximum allowable concentration; TLV, Threshold Limit Value.

TABLE 3-4 Emergency and Continuous Exposure Guidance Levels for Hydrogen Chloride

Exposure Level	Current U.S. Navy Values (ppm)	Committee Recommended Values (ppm)
EEGL		
1-h	5	9
24-h	2	3
CEGL		
90-day	1	1

Abbreviations: CEGL, continuous exposure guidance level; EEGL, emergency exposure guidance level.

To derive a 1-h EEGL, the extensive data sets of respiratory-rate alterations and RD_{50} determinations in laboratory animals exposed to hydrogen chloride were used as predictive measures of hydrogen chloride irritancy in humans. Alarie (1981) has used the mouse RD_{50} value to derive 8-h Threshold Limit Values (TLVs) of dozens of chemical irritants empirically. Schaper (1993) developed an extensive database on 295 airborne materials with RD_{50} values and demonstrated a high correlation of TLVs with 0.03 times the RD_{50} (there were TLVs for 89 chemicals). For hydrogen chloride, the proposed TLV would be 9.3 ppm (0.03 times 309 ppm). Because the TLV is defined as a level of exposure that a typical worker can experience without an unreasonable risk of disease or injury, the committee recommends 9 ppm as the 1-h EEGL. Experimental studies in humans support that recommendation. Elkins (1959) concluded that exposures to hydrogen chloride at 5 ppm or higher were immediately irritating and exposures at over 10 ppm highly irritating, although some workers developed some tolerance. Henderson and Hagard (1943) reported that 50-100 ppm for 1 h was the maximum tolerable concentration and that 10 ppm for prolonged exposure was the maximum tolerable concentration.

24-Hour EEGL

There is no firm database for establishing a 24-h EEGL. To derive the 24-h EEGL, the committee considered two approaches: one based on sensory irritation and the other on histopathology of the nasal cavity. The first approach uses the empirically derived 8-h TLV of 9.3 ppm—a value that is considered to be preventive of sensory irritation in humans (described above)—and applies an uncertainty factor of 3 to account for extrapolation of 8-h responses to continuous 24-h exposures (9.3/3 = about 3 ppm). It is unclear whether the concentration-time relationship defined by ten Berge et al. (1986) applies for sensory irritation from hydrogen chloride, but in this case, the use of an uncertainty factor

of 3 gives the same result as applying that relationship (9 ppm for 8 h = 3 ppm for 24 h), assuming n = 1. The second approach uses the LOAEL from the 90-day inhalation toxicity study in rats and mice (Toxigenics 1984) and applies an uncertainty factor of 3 to account for interspecies differences (10/3 = about 3 ppm). Additional uncertainty factors for extrapolating a LOAEL to no-observed-adverse-effect level (NOAEL) or a 6-h exposure to a 24-h exposure were not applied because the lesions observed in the 90-day study (minimal to mild rhinitis in rats and minimal to mild intracytoplasmic eosinophilic globules in nasal epithelium in mice) were considered tolerable and reversible for a single 24-h exposure. Thus, the same value was derived with the two approaches, and 3 ppm is recommended as a 24-h EEGL.

90-Day CEGL

Biologic end points that were considered the most relevant for derivation of the 90-day CEGL were histopathologic changes in tissues of the respiratory tract after repeated hydrogen chloride exposure. Two long-term inhalation toxicity studies, a 90-day study in rats and mice (Toxigenics 1984) and a lifetime (128-week) study in rats (Sellakumar et al. 1985), concluded that minimal to mild alterations in the upper respiratory tract (nasal cavity) and middle respiratory tract (larynx to trachea) resulted from exposure to hydrogen chloride at 10 ppm. The lesions (such as rhinitis and tracheal hyperplasia) were considered neither tumorigenic nor life-threatening. With 10 ppm as a minimal-effect LOAEL, a 90-day CEGL of 1 ppm was derived as follows. An uncertainty factor of 3 was applied to obtain a NOAEL from the LOAEL. The lesions observed at 10 ppm were due to superficial irritation and were minimal in severity, so an uncertainty factor of 3 was used rather than the standard default of 10. An additional uncertainty factor of 3 was applied for interspecies extrapolation. The lesions observed in the 90-day study were consistent between species and strains of laboratory animals, so the default factor of 10 for interspecies extrapolation was reduced. As discussed in Chapter 1, the use of two uncertainty factors of 3 is rounded to 10, so the resulting 90-day CEGL value is 1 ppm (10/10). An additional adjustment for extrapolating from intermittent exposure (6 h/day 5 days/week) to continuous exposure (24 h/day 7 days/week) was not applied because the rhinitis observed in the 90-day study did not increase in severity given the findings in the 128-day study. Both studies appear to have performed thorough histopathologic evaluations of the animals' respiratory tract, so the duration of exposure to hydrogen chloride at low concentrations does not appear to be a critical factor in producing effects. Support that the committee's CEGL value is protective is the epidemiologic study by Kremer et al. (1995), in which workers exposed to hydrogen chloride aerosols at 2.1 mg/m^3, sulfur dioxide vapor at 0.3 mg/m^3, and sulfate aerosols at 0.5 mg/m^3 for several years, including peak exposure to hydrogen chloride vapor at up to 40 mg/m^3 (27 ppm) for some work operations, did not show airway hyperreactivity.

DATA ADEQUACY AND RESEARCH NEEDS

Information in the scientific literature suggests that concentration, not exposure duration, is responsible for irritant effects of chemical irritants. Well-designed inhalation toxicity studies are needed to demonstrate that that observation applies to hydrogen chloride. Little is known about the acid-base buffering capacity of mucous membranes and tissues of the respiratory tract. Because hydrogen chloride dissociates rapidly to hydronium ions on contact with tissue surfaces, studies designed to quantitate the acid-buffering capacity of mucosal surfaces and tissues of the nasal cavity may be of value for studying dosimetry and threshold effects of hydrogen chloride.

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4

Hydrogen Fluoride

This chapter summarizes the relevant epidemiologic and toxicologic studies of hydrogen fluoride. It presents selected chemical and physical properties, toxicokinetic and mechanistic data, and inhalation-exposure levels from the National Research Council and other agencies. The committee considered all that information in its evaluation of the U.S. Navy's 1-h, 24-h, and 90-day exposure guidance levels for hydrogen fluoride. The committee's recommendations for hydrogen fluoride exposure levels are provided at the end of this chapter with a discussion of the adequacy of the data for defining the levels and the research needed to fill the remaining data gaps.

PHYSICAL AND CHEMICAL PROPERTIES

Hydrogen fluoride is a corrosive, colorless gas that may fume in air (Budavari et al. 1989). Odor thresholds have been reported to range from 0.04 to 3 ppm (HSDB 2008). Like hydrogen chloride, hydrogen fluoride is highly soluble in water. *Hydrofluoric acid* is the term used to describe aqueous solutions of hydrogen fluoride. Selected physical and chemical properties are shown in Table 4-1.

OCCURRENCE AND USE

Hydrogen fluoride is used primarily to produce aluminum fluoride, synthetic cryolite, fluoropolymers, and chlorofluorocarbons (Lindahl and Mahmood 2005). It is also used in inorganic fluoride production, uranium enrichment, and fluorine production. Fluoride is found in some foods and beverages, particularly fish, seafood, gelatin, and tea; and many public water sources are fluoridated

TABLE 4-1 Physical and Chemical Properties of Hydrogen Fluoride

Synonyms	Anhydrous hydrofluoric acid
CAS registry number	7664-39-3
Molecular formula	HF
Molecular weight	20.01
Boiling point	19.51°C
Melting point	–83.55°C
Flash point	NA
Explosive limits	NA
Specific gravity	1.002 at 0°C/4°C
Vapor pressure	917 mmHg at 25°C
Solubility	Very soluble in water and alcohol; slightly soluble in ether; soluble in many organic solvents
Conversion factors	1 ppm = 0.82 mg/m^3; 1 mg/m^3 = 1.22 ppm

Abbreviation: NA, not available or not applicable.
Sources: Budavari et al. (1989) and HSDB (2008).

(ATSDR 2003). Ambient air concentrations of hydrogen fluoride are typically below the detection limit, although concentrations may be higher near industrial facilities that use or produce hydrogen fluoride (ATSDR 2003).

Hydrogen fluoride has been measured on board submarines. NRC (1988) listed hydrogen fluoride as a potential contaminant of submarine air and reported a concentration of 0.3 ppm. No information was provided on sampling protocol, location, operations, or duration. Trials conducted on three nuclear-powered attack submarines did not detect hydrogen fluoride; the level of detection was about 3 ppb (Hagar 2008). Whether the reported results are representative of the submarine fleet is not known; few details were provided about the conditions on the submarines when the samples were taken. No other exposure data were located. Hydrogen fluoride emissions aboard submarines are thought to arise from decomposition of halogenated hydrocarbons and refrigerants (Hagar 2008).

SUMMARY OF TOXICITY

Hydrogen fluoride and its aqueous solutions present an acute hazard by inhalation or dermal exposure. The primary target of airborne gaseous hydrogen fluoride is the respiratory tract; however, injury to distant organs may also occur because of absorption of substantial amounts of fluoride. Acute effects of hydrofluoric acid include damage to skin and lungs, including severe burns, and sys-

temic effects, such as cardiac arrhythmias and acute renal failure (see, for example, Sanz-Gallén et al. 2001; Björnhagen et al. 2003; Horton et al. 2004; Holstege et al. 2005; Mitsui et al. 2007; Vohra et al. 2008). Some of the systemic effects may be due to depletion of calcium and magnesium or hyperkalemia.

The critical effects of inhalation exposure to hydrogen fluoride are respiratory tract irritation and the induction of respiratory disease. Respiratory tract irritation is documented in animal models and has been observed in controlled human exposure studies. Marked sensory irritation can occur at exposures greater than 3 ppm for 1 h (Lund et al. 1997). Prolonged respiratory tract effects can occur after short-term exposure. To evaluate longer-term exposures or systemic effects, the total fluoride intake from all exposure routes (inhalation, dermal, and ingestion) must be considered (EPA 1988; NRC 2006). Chronic exposure to hydrogen fluoride (with particulate fluorides) in the aluminum industry is associated with increased risk of asthma (Taiwo et al. 2006).

The literature on the systemic toxicity of fluoride is voluminous and is not addressed in full detail here. NRC (2006) recently reviewed fluoride toxicity with an emphasis on chronic toxicity. Fluoride-induced effects include hormonal disturbances; renal damage; reproductive toxicity; skeletal changes, including fluorosis; and possible genotoxicity and cancer.

Effects in Humans

Accidental Exposures

Several case reports of death after acute accidental exposure to hydrogen fluoride are available and have been extensively reviewed by ATSDR (2003) and NRC (2004). Most of the reports stem from accidents involving spills of hydrofluoric acid. Because of its high volatility, inhalation exposure to hydrogen fluoride results from spills of hydrofluoric acid. The degree to which hydrofluoric acid-induced burns or dermal absorption of fluoride may have contributed to the death is not known. Nonetheless, the case reports indicate that lung injury, including pulmonary edema (with or without hemorrhage), is common after such accidents.

An informative case report describes the delayed and prolonged chemical pneumonitis that developed in a woman after use of large amounts of 8% hydrofluoric acid as a cleaner in an unventilated bathroom (Bennion and Franzblau 1997). Airborne hydrogen fluoride concentrations were unknown. Symptoms developed slowly in the days after the exposure and eventually necessitated oxygen therapy (100% O_2; 10 cm H_2O peak end-expiratory pressure) because of hypoxemia. Chest radiography indicated a lung infiltrate, and signs included diffuse rhonchi and wheezing in both lungs.

Another case report describes a woman who used 8-9% hydrofluoric acid as a cleaner in a ventilated bathroom (Franzblau and Sahakian 2003). It was estimated that hydrogen fluoride in the bathroom may have exceeded 170 ppm.

She developed breathing problems, such as persistent wheezing and difficulty taking a deep breath, over the 1-2 months after exposure. Examination at that time revealed a mild obstructive pattern. Several months after the exposure, she was diagnosed with reactive airways dysfunction syndrome (RADS); her intermittent wheezing on exertion persisted for at least 3 years.

An industrial accident in Texas in 1987 resulted in the release of 24,000 kg of hydrogen fluoride and about 3,000 kg of isobutane over a small community (population, 41,000; Wing et al. 1991). The airborne hydrogen fluoride concentration 1 h after the accident was reported to be 10 ppm; 2 h after the accident, concentrations were "minimal." The report indicates that air sampling was performed at those times but provides no information on the analytic methods used to determine hydrogen fluoride concentrations. A total of 939 people sought emergency care; common symptoms were eye irritation, throat irritation (burning), headache, and shortness of breath. Of those who sought care, 94 were hospitalized. Forced expiratory volume in 1 s (FEV_1) was less than 80% of predicted in one-third of the people who sought medical care and were not hospitalized compared with half the people who were hospitalized. A follow-up study revealed that respiratory symptoms persisted in some people for at least 2 years, although much reduced (Dayal et al. 1992). The degree to which psychologic factors influenced the symptoms is unknown, but it is thought that the symptoms could not be explained entirely on the basis of psychologic stress (Dayal et al. 1994).

In summary, respiratory tract injury appears to be the predominant response to accidental exposure to hydrogen fluoride. Respiratory tract effects include irritation, airway obstruction (as assessed with FEV_1), and airway inflammation. Upper airway symptoms may have occurred in some situations and gone unreported because they were overshadowed by the lower airway effects. There are suggestions that long-term respiratory tract effects may occur after exposure to hydrogen fluoride at high concentrations as indicated by the development of RADS in one subject and the presence of persistent respiratory symptoms in the general population after the release of hydrogen fluoride during an industrial accident. The studies indicate that the respiratory tract may be a critical target of hydrogen fluoride in the general population but do not provide information on concentration-response relationships.

Fluoride ion is rapidly and efficiently absorbed into the circulation after inhalation of hydrogen fluoride or airborne fluorides as indicated by increased blood or urinary fluoride concentrations (see, for example, Collings et al. 1951, 1952; Largent et al. 1951). Therefore, the possibility of systemic fluoride-induced injury after accidental exposure to hydrogen fluoride is important to consider. Little information is available on systemic effects after accidental inhalation exposure to fluoride, but accidental ingestion has been followed by itching, rash, gastrointestinal symptoms, and numbing or tingling of extremities or the face (reviewed by NRC 2006).

Experimental Studies

Upper Airway Irritation

There are several published controlled studies of short-term inhalation exposure to hydrogen fluoride in humans (Table 4-2). The exposure durations in the studies spanned from 1 min to 6 h/day for multiple days. All studies report upper airway irritation as the predominant symptom. The degree of upper airway irritation was reported as intolerable at 122 ppm for more than 1 min, marked at 61 ppm for several minutes, and mild at 32 ppm for several minutes (Machle et al. 1934).

Lund et al. (1997) described a 1-h exposure with exercise at low concentration (0.2-0.7 ppm), intermediate concentration (0.9-2.9 ppm), and high concentration (3.1-6.3 ppm). Exercise consisted of a fixed workload of 75 W on a bicycle ergometer for the last 15 min of exposure. There were no air-exposed control subjects, but baseline reporting of symptoms was conducted for all subjects before exposure. Subjects were men, 21-44 years old; persons with asthma or recent respiratory tract infection were excluded from the study, but the study group did include people with "hay fever." Symptoms, including upper airway (nose or throat) itching and soreness, were reported during exposure on a scale of 0-5 (1 was very mild, and 5 was severe). More detail was not provided on the scaling; the authors report ratings of 1-3 as representing a "low" degree of irritation and greater than 3 as representing a "high" degree of irritation. It seems reasonable to assume that *low* corresponds to mild irritation and *high* corresponds to moderate to marked irritation. In the low-concentration group, four of nine subjects reported mild upper airway irritation. In the intermediate-concentration group, six of seven reported mild irritation. In the high-concentration group, three of seven reported moderate to severe irritation, and the other four reported mild irritation. Thus, a clear concentration-response relationship was observed in the study. Only mild irritation was reported at concentrations as high as 2.9 ppm, whereas marked irritation was reported in some subjects at concentrations as low as 3.1 ppm. Thus, 3 ppm appears to reflect the demarcation between minimal and marked irritation, at least as determined by the small number of subjects in this study. In a later study with high concentration (4.0-4.8 ppm), six of 10 subjects reported mild irritation, and one of 10 reported marked irritation (Lund et al. 2002)—essentially the same response pattern observed in their earlier study (Lund et al. 1997). There were no air-exposed control subjects, but baseline reporting of symptoms was conducted for all subjects before exposure.

Largent (1961) performed a study with multiple 6-h exposures to hydrogen fluoride 5 days/week for a total of 10-50 exposures. Again, upper airway irritation was experienced. One subject exposed at 1.4 ppm reported no symptoms, and all five subjects exposed at 2.6-4.7 ppm reported the perception of

TABLE 4-2 Effects of Hydrogen Fluoride in Controlled Human Studies

Concentration (ppm)	Duration	Subjects and Effects	Reference
32, 61,122	1 to several min	Two healthy subjects, smoking status unknown Maximum tolerable level (1 min) at 122 ppm; marked conjunctival, nasal, and large airway irritation at 61 ppm (several minutes); mild conjunctival, nasal, and large airway irritation at 32 ppm (several minutes); sour taste detected at all concentrations	Machle et al. 1934
1.4, 2.6-4.7	6 h/day 5 days/week 10-50 days	Five healthy subject, smoking status unknown No reported airway irritation in one subject exposed at average of 1.4 ppm; slight cutaneous (facial), ocular, and nasal irritation in all subjects at average concentration of 2.6-4.7 ppm daily for a total of 10-50 days; cutaneous erythema frequent (requiring face-cream application); increased symptoms in one subject who developed an upper respiratory tract infection during the protocol	Largent 1961
0.2-6.3	1 h (with exercise)	Twenty healthy, nonsmoking men (21-44 years old); persons with airway infection or history of asthma excluded; three exposure groups (low, 0.2-0.7 ppm; middle, 0.9-2.9 ppm; high, 3.1-6.3 ppm); symptom scores reported as "low," presumably mild (1-3 on scale of 0-5), and "high," presumably moderate to marked (>3 on scale of 0-5). Mild upper airway irritation was reported in four of nine subjects in low-concentration group, six of seven in middle concentration group, four of seven in high-concentration group; moderate to severe upper airway irritation reported in three of seven in high-concentration group; mild lower airway irritation reported in two of seven and moderate to severe irritation in one of seven in high-concentration group; eye irritation (mild) reported in two subjects in each concentration group	Lund et al. 1997

(Continued)

TABLE 4-2 Continued

Concentration (ppm)	Duration	Subjects and Effects	Reference
0.2-6.3	1 h (with exercise)	Nineteen healthy, nonsmoking men (21-44 years old); persons with airway infection or history of asthma excluded; three exposure groups (low, 0.2-0.7 ppm; middle, 0.9-2.9 ppm; high, 3.1-6.3 ppm). Publication presumably provides BAL results in subjects described in Lund et al. (1997); BAL performed 24 h after exposure; percentage of lymphocytes increased in both bronchial and bronchoalveolar portions of BAL with no apparent concentration-response relationship; increases appeared to be present in middle- and high-concentration groups; no observed changes in any other cell type; myeloperoxidase increased in bronchial portion of BAL with no apparent concentration-response relationship	Lund et al. 1999
4.0-4.8	1 h (with exercise)	Ten healthy, nonsmoking men (21-44 years old); persons with airway infection or history of asthma excluded; all exposed at 4.0-4.8 ppm for 1 h with exercise; nasal irritation symptoms reported as "low," presumably mild (1-3 on scale of 0-5), and "high," presumably moderate to marked (>3 on a scale of 0-5). Mild irritation reported by six of 10 and marked irritation by one of 10 subjects; nasal lavage performed immediately and 90 min after exposure; lavage neutrophil count and lavage proteins (TNF-α, PGE2, LTB4, peptide LT) significantly increased; symptom score and lavage neutrophil counts correlated with each other	Lund et al. 2002
4.0-4.8	1 h (with exercise)	Ten healthy, nonsmoking men (21-44 years old); persons with airway infection or history of asthma excluded; all exposed at 4.0-4.8 ppm for 1 h with exercise; nasal symptomology not measured; BAL performed 2 h after exposure No increase observed in differential cell count or in numerous mediators (interleukins, myeloperoxidase, eicosanoids, others); several significantly decreased.	Lund et al. 2005

Abbreviations: BAL, bronchoalveolar lavage; LTB4, leukotriene B4; PGE2, prostaglandin E2; TNF-α, tumor-necrosis factor-alpha; peptide LT, peptide leukotriene.

slight irritation. One subject developed an "upper airway cold" during the protocol, at which time exposure at 3.4 ppm produced "considerable discomfort." All subjects completed the multiple-exposure regimen—an indication that the degree of irritation was not sufficient to cause withdrawal from the study. Although a quantitative scaling of symptoms was not reported, comparison of the data with the symptoms reported in the studies of Lund et al. (1997, 2002) suggests that repeated exposure to hydrogen fluoride does not result in exacerbation of the irritation response and may actually lead to some degree of habituation.

In summary, symptoms of upper airway irritation were uniformly reported in clinical studies. The threshold for mild irritation may be 0.5 ppm or less in some people. Given that the studies used small numbers of subjects, the database suggests that a significant fraction of subjects experience moderate to marked irritation at concentrations over 3 ppm but only mild irritation at lower concentrations.

Lower Airway Irritation

Lower airway irritation has been reported in human subjects exposed to hydrogen fluoride but is generally of less magnitude than upper airway irritation. In the intermediate-concentration group (0.9-2.9 ppm) of the study of Lund et al. (1997), one of seven subjects reported mild lower airway irritation (chest tightness and soreness, coughing, expectoration, or wheezing) during the 1-h exposure (compared with six of seven reporting mild upper airway irritation). In the high-concentration group (3.1-6.3 ppm), two of seven reported mild lower airway symptoms, and one of seven reported moderate to marked lower airway symptoms compared with three of seven reporting upper airway symptoms of this degree. A concentration-response relationship may be apparent, but the changes in the lower airway symptoms did not achieve statistical significance, and this led the study authors to conclude that lower airway symptoms were not reported to a significant degree in relation to exposure to hydrogen fluoride. The study design included forced expiration to assess lower airway physiologic changes. No consistent change was observed in forced vital capacity (FVC) or FEV_1. Thus, mild symptoms of lower airway irritation occur at exposures as high as 2.9 ppm, and more marked symptoms may occur in some people exposed at higher concentrations, but such changes occurred in the absence of alterations in airway function as assessed by forced expiration.

Airway Inflammation

Hydrogen fluoride exposure for 1 h results in airway inflammation as assessed by increases in inflammatory cells in nasal lavage or bronchoalveolar lavage (BAL) fluid. Exposure at 4.4 ppm for 1 h (range, 4.0-4.8) results in a significant increase in nasal lavage neutrophils and proinflammatory mediators,

including tumor-necrosis factor-alpha, prostaglandin E2, and leukotriene B4 (Lund et al. 2002). Although hydrogen fluoride clearly induced upper airway inflammation, the exposure was not debilitating, nor would any long-term effects be expected to result from a response of this nature. Exposure to hydrogen fluoride for 1 h also results in inflammatory cell changes in the lower airways as assessed by BAL (Lund et al. 1999). A significant correlation between increases in BAL lymphocyte numbers (but not neutrophil or eosinophil numbers) and increased exposure concentrations was observed 24 h after exposure (Lund et al. 1999, which involved the same subjects described in Lund et al. 1997). It is difficult to discern precisely the concentration-response relationships from the data presented, but apparently no alteration occurred in the low-concentration (0.2-0.7 ppm) group; increases in BAL lymphocyte number occurred only in the intermediate (0.9-2.9 ppm) and high (3.1-6.3 ppm) groups. The changes were observed 24 h but not 2 h after the 1-h exposure (Lund et al. 1999, 2005). Although lavage neutrophil numbers were not significantly increased, a slight increase in the myeloperoxidase content in the bronchial portion of the BAL fluid was observed; this suggests that subtle recruitment or activation of neutrophils occurred. The absence of an overt increase in neutrophils or overt symptoms suggests that the responses would not result in short-term or long-term health impairment.

Other Irritation Effects

Cutaneous irritation and ocular irritation have been reported in subjects exposed to hydrogen fluoride. In the study of Machle et al. (1934), two subjects exposed to hydrogen fluoride at 32 ppm or higher for several minutes reported cutaneous, ocular, and respiratory tract irritation. Ocular irritation was reported during 1-h exposures in the study of Lund et al. (1997), but the degree of ocular irritation was less than that of upper airway irritation. Largent (1961) used multiple 6-h exposures and found that cutaneous irritation was experienced at 2.6-4.7 ppm. Subjects applied cream to alleviate symptoms. Cutaneous erythema was common in the five subjects although reported to be without discomfort. One subject experienced peeling of the skin in the third week of exposure. It should be noted that the sour, pungent taste of hydrogen fluoride can be detected during exposure at above 3 ppm. Amoore and Hautala (1983) reported the odor threshold at below 1 ppm.

Systemic Effects

Exposure to hydrogen fluoride or other airborne fluorides may result in absorption of fluoride ion (see, for example, Collings et al. 1951, 1952; Largent et al. 1951; Waldbott and Lee 1978); thus, the potential for fluoride-induced systemic effects should be considered. For example, given a ventilation rate of

15 m^3/day (EPA 1997) for a 70-kg man and 100% deposition and absorption, a 1-h exposure to hydrogen fluoride at 3 ppm results in systemic absorption of 1.5 mg of fluoride (0.02 mg/kg).[1] Few experimental studies involving human exposure to hydrogen fluoride or inhaled fluorides are available; experimental studies and case reports involving ingestion of fluoride have reported antithyroid effects (0.03-0.14 mg/kg-day for 20-245 days; Galletti and Joyet 1958) and hypersensitivity or reduced tolerance to fluoride (0.02 mg/kg-day for short-term exposures; Grimbergen 1974; Waldbott 1956, 1958).

One study reported a threshold of hydrogen fluoride for the light-adaptive reflex[2] of 0.04 ppm (Sadilova et al. 1965) in three subjects exposed to hydrogen fluoride at 0.02, 0.04, or 0.07 ppm (exposure duration not available), but it is difficult to evaluate the underlying experimental work (Smith and Hodge 1979), and the toxicologic relevance of the response is unknown (ATSDR 2003). The absorbed doses at those exposures are likely to be so low that it is difficult to attribute the neurologic effect to absorbed fluoride itself.

Occupational and Epidemiologic Studies

A variety of occupational and epidemiologic studies of airborne and ingested fluoride have been conducted; many of them have been reviewed by NRC (2006) and ATSDR (2003). The following paragraphs discuss respiratory symptoms (asthma), renal damage, endocrine effects, increased risk of bone fracture, and bone and joint pain (skeletal fluorosis). In the workplace, exposure to hydrogen fluoride rarely occurs in the absence of exposure to other particulates (such as calcium fluoride [CaF_2] or sodium aluminum fluoride [Na_3AlF_6]) or gaseous fluoride-containing materials (such as tetrafluorosilane [SiF_4]); this confounds interpretation of the results with respect to the effects of hydrogen fluoride. That is particularly true of possible effects of systemic fluoride absorption because the source of the fluoride is not known with certainty.

Many studies of worker health in the aluminum industry have found an association between occupational exposure to fluoride in aluminum "potrooms" and respiratory disease or asthma (see, for example, Kaltreider et al. 1972; Soyseth and Kongerud 1992; Kongerud et al. 1994). Most studies, however, did not reveal potential etiologic agents. In aluminum potrooms, workers are exposed to particulate fluoride, gaseous fluoride (presumably hydrogen fluoride), sulfur dioxide, and other irritants. A recent study of the health of workers in the aluminum industry suggests that exposure to airborne fluorides is associated with an increased incidence of asthma (Taiwo et al. 2006). Analysis of records on

[1]The calculation is as follows: (15 m^3/day)(1 day/24 h)(3 ppm)(0.82 mg/m^3 per ppm)(19/20 mg fluoride per mg hydrogen fluoride) = 1.5 mg of fluoride for 1-h exposure, assuming 100% absorption.

[2]The light-adaptive reflex is defined as reflex changes in ocular sensitivity to light based on dark adaptation. It is measured as a marker of neurologic effects.

12,000 workers (about 10% of whom worked in potrooms) found an increased risk of asthma in workers exposed to gaseous fluoride at 0.27 ± 0.53 ppm (mean ± SD) for an average of 16 ± 10.8 years. The study included only people who had a new diagnosis of asthma after two or more asthma-free years in the workplace; thus, anyone who developed occupationally related asthma in the first 2 years of employment was excluded. The average age of the potroom workers was 43.7 ± 10.1 years. Using a multivariate generalized linear model relating the natural logarithm of predicted asthma rate, the authors concluded that asthma risk was significantly associated with exposure to hydrogen fluoride and current smoking but not to other contaminants in the workplace, such as particulate fluoride and sulfur dioxide. The relative risk for development of asthma was estimated by the model to be 1.18 per 0.1 mg/m^3 change in hydrogen fluoride (95% confidence interval [CI], 1.09-1.3), which corresponds to a relative risk of 1.18 per 0.12 ppm. Although documentation of an association does not indicate cause and effect, a 1-h exposure to hydrogen fluoride does cause increased BAL lymphocytes (Lund et al. 1999), and persistent respiratory symptoms were reported in the general community after exposure to hydrogen fluoride in an industrial accident (Wing et al. 1991). Those facts raise concern that the increased incidence of asthma in potroom workers may reflect a response to hydrogen fluoride. It is important to note that the presence of high dust concentrations and other irritants and occasional short-term (15-min) high-exposure excursions to hydrogen fluoride may have contributed to the response (Taiwo et al. 2006).

Waldbott and Lee (1978) reported a case of systemic fluoride toxicity from repeated exposures to hydrogen fluoride gas in the alkylation unit of an oil company. Estimated exposures over the worker's 10 years of employment were often above 3 ppm, on the basis of odor detection, and were thought to have been very high (25-200 ppm) during some procedures. Chronic symptoms included reduction in pulmonary function, gastrointestinal problems, and severe back and leg pains. Fluoride measured in bone 10 years after the maximal exposures was significantly above normal. Given a hydrogen fluoride concentration of 3 ppm, an 8-h workday, a ventilation rate of 15 m^3/day, and complete absorption, the worker's minimum systemic fluoride dose was 8 mg/day, averaged over the entire week, or about 0.08 mg/kg-day for his reported weight of 230 lb (105 kg).[3]

Derryberry et al. (1963) reported a significantly higher frequency of albuminuria in a group of workers exposed to airborne fluoride in a phosphate-fertilizer plant than in nonexposed controls (12.2% vs 4.5%) and suggested a relationship between fluoride excretion and renal function. Urinary fluoride excretion averaged 4.6 mg/L (range, 2.1-14.7 mg/L) in the exposed group and 1.15 mg/L (range, 0.15-3.2 mg/L) in the controls. Two studies of aluminum potroom workers did not yield similar findings (reviewed by Hodge and Smith 1977).

[3]The calculation is as follows: (15 m^3/day)(1 day/24 h)(3 ppm)(0.82 mg/m^3 per ppm)(19/20 mg fluoride per mg hydrogen fluoride)(8 h/day)(5/7) = 8 mg/day, assuming 100% absorption and dose averaged over the entire week.

Ando et al. (2001) attributed decreased glomerular filtration rates to chronic exposure to fluoride from coal combustion; both inhalation of airborne fluoride and ingestion of contaminated food were involved. A few other reports have linked ingestion of fluoride to renal damage (for example, increased concentrations of the renal enzymes *N*-acetyl-β-glucosaminidase and γ-glutamyl transpeptidase in children's urine; Liu et al. 2005; Xiong et al. 2007) or urolithiasis (Singh et al. 2001). NRC (2006) has also reviewed human renal effects of fluoride exposure and made recommendations for further research.

NRC (2006) concluded that fluoride interferes with normal endocrine function in humans. Reported effects include increased thyroid stimulating hormone; altered concentrations of thyroid hormones, calcitonin, or parathyroid hormone; secondary hyperparathyroidism; and impaired glucose tolerance (see Table 4-3). Thyroid effects were associated with estimated average or typical fluoride intakes as low as 0.05-0.1 mg/kg-day (0.01-0.03 mg/kg-day with iodine deficiency). Increased likelihood of impaired glucose tolerance was associated with intakes above 0.07 mg/kg-day, and increased parathyroid hormone concentrations and secondary hyperparathyroidism were found at fluoride intakes of at least 0.15 mg/kg-day. Adequacy of nutrition seems to play a role in many end points; effects are less likely, or require higher fluoride intakes, with improved nutrition. Most of the studies reviewed in NRC (2006) were cross-sectional and

TABLE 4-3 Summary of Selected Endocrine Effects Associated with Oral Fluoride Exposure in Humans

End Point	Estimated Fluoride NOAEL (mg/kg-day)	Estimated Fluoride LOAEL (mg/kg-day)	Key References
Altered thyroid function[a]	0.01-0.05	0.05-0.1	Bachinskii et al. 1985; Jooste et al. 1999; Susheela et al. 2005
Increased calcitonin concentrations	0.02-0.04	0.06	Teotia et al. 1978
Increased PTH concentrations or secondary hyperparathyroidism	0.02-0.06	0.15	Teotia et al. 1978
Impaired glucose tolerance	0.03	0.07	Trivedi et al. 1993

[a]Altered T4 or T3 concentrations, increased TSH concentrations, or increased goiter prevalence. Values shown are based on situations with adequate iodine intake. Iodine deficiency can decrease NOAEL and LOAEL.
Abbreviations: LOAEL, lowest observed-adverse-effect level; NOAEL, no-observed-adverse-effect level; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.
Source: NRC 2006.

did not evaluate individual exposures; case reports, clinical studies, and experimental studies were also included. Most of the epidemiologic studies have involved long-term or lifelong exposures.

On the basis of extensive review of epidemiologic, observational, and clinical studies, NRC (2006) concluded that lifetime exposure to fluoride at drinking-water concentrations of 4 mg/L and higher is likely to result in higher bone-fracture rates in the population than exposure at 1 mg/L (estimated average fluoride intakes from all sources, around 0.08 mg/kg-day vs 0.03 mg/kg-day). The evidence suggested an increased risk of bone fracture at 2 mg/L (estimated average fluoride intake from all sources, around 0.05 mg/kg-day), but NRC (2006) did not consider the available information to be conclusive. In general, the risk of fractures (especially hip fractures) increases with the concentration of fluoride in the bones—in effect, the bones become more brittle.

Skeletal fluorosis includes a variety of radiographic and clinical presentations, from increased skeletal density (stage I) to chronic joint pain, arthritic symptoms, calcification of ligaments, and osteosclerosis of cancellous bones (stage II) to excessive calcification in joints, ligaments, and vertebral bodies, muscle wasting, and neurologic deficits due to spinal-cord compression (stage III, or "crippling" skeletal fluorosis; NRC 2006). A number of reports describe skeletal fluorosis of various degrees in workers exposed to gaseous or particulate fluorides (see, for example, Roholm 1937; Franke and Auermann 1972; Schlegel 1974; Franke et al. 1975; Baud et al. 1978; Dominok et al. 1984). On the basis of data collected by Derryberry et al. (1963), the California Office of Environmental Health Hazard Assessment (OEHHA 2003) derived a lowest observed-adverse-effect level (LOAEL) and a no-observed-adverse-effect level (NOAEL) of fluoride of 1.89 and 1.07 mg/m^3, respectively, for increased bone density as observed radiographically (corresponding to hydrogen fluoride at 2.4 and 1.4 ppm in an occupational setting). Given a ventilation rate of 15 m^3/day and a 40-h workweek, those concentrations would correspond to average systemic fluoride intakes of 6.8 and 3.8 mg/day, or 0.1 and 0.05 mg/kg-day for a 70-kg man. The range of exposure durations at the time of examination was 7.1-24.8 years for people who had minimally increased bone density and 4.5-25.9 for people who had normal bone density (Derryberry et al. 1963, cited in OEHHA 2003). Bone fluoride concentrations in the ranges reported for stage II and stage III skeletal fluorosis will probably be reached by long-term (approaching lifetime) fluoride intakes of around 0.05 mg/kg-day (estimated from NRC 2006), but bone fluoride concentrations appear to be a marker, rather than a determinant, of the risk of skeletal fluorosis (NRC 2006). Franke et al. (1975) reported a lack of clear correlation among bone fluoride concentrations, radiologic changes, and symptoms; some workers with slight radiologic changes reported intense pain in the spine and large joints, and some with radiologically distinct fluorosis reported few complaints.

Effects in Animals

Acute Toxicity

A rich dataset on the acute lethality and toxicity of hydrogen fluoride in laboratory animals exists. The data have been extensively reviewed by NRC (2004) and ATSDR (2003). In general, brief (1-h or less) exposure at more than 100 ppm results in severe respiratory tract lesions consisting of necrosis or inflammation of the nasal passages and to a lesser extent, if at all, those lesions in the lower airways. Concentration-time relationships have been examined in short-term studies, and it has been uniformly concluded that the acute-lethality data on exposures of 30 min or less are best described by the relationship $C^n \times t = k$, where C = concentration, t = time, k = constant, and n = 2 (Rosenholtz et al. 1963; ten Berge et al. 1986; Alexeef et al. 1993; NRC 2004), indicating that concentration is more important than time relative to acute lethality. Dalbey et al. (1998) noted that the relationship held for 2-min and 10-min exposures but commented that it might not hold for 60-min exposures. Thus, uncertainty exists relative to concentration-time relationships for exposures of 60 min or more. Although the data are not directly applicable to establishment of guidance on longer exposure because they are from short-term studies that focused on lethality, they do strongly indicate that the respiratory tract is the primary target of hydrogen fluoride in brief high-concentration exposures.

The preponderance of nasal lesions in short-term exposure studies is no doubt due to the extensive removal or extraction of inspired hydrogen fluoride in the nasal cavity of rodents (Morris and Smith 1982). Rodents are obligate nose-breathers, so rodent toxicity studies may underestimate the lower airway injury that might result in mouth-breathing humans exposed to hydrogen fluoride. Pseudo-mouth-breathing in rats can be obtained by insertion of an oral-tracheal cannula. Two studies of rats have used that technique. Nose-breathing and pseudo-mouth-breathing rats were exposed to hydrogen fluoride at 1,300 ppm for 30 min with a 24-h follow-up in the study of Stavert et al. (1991). In nose-breathing rats, the study authors found that hydrogen fluoride induced a marked reduction in minute ventilation (due to reduced breathing frequency), a response indicative of nasal trigeminal sensory nerve activation (Alarie 1973). In contrast, they found that pseudo-mouth-breathing rats exhibited an initial increase followed by a progressive decrease in ventilation, a response typical of lower airway vagal sensory nerve activation (Alarie 1973). None of the nose-breathing rats died, but 25% of the pseudo-mouth-breathing animals died within 24 h after exposure. Severe nasal necrosis and inflammation occurred in the anterior portion of the nose in the nose-breathing animals, and no significant lower airway lesions were observed (Stavert et al. 1991). In contrast, moderate to severe necrosis and inflammation of the trachea and major bronchi, without epithelial damage to the smaller airways, occurred in the pseudo-mouth-breathing animals, and mild neutrophilic inflammation was observed in the alveoli. It is not known

whether the alveolar neutrophils represented alveolar damage, aspiration of airway neutrophils, or translocation during the airway fixation process.

Using a similar oral-tracheal cannulation method, Dalbey et al. (1998) examined the response of pseudo-mouth-breathing rats exposed to hydrogen fluoride for 2, 10, or 60 min with a 24-h follow-up. The aim of the study was to examine concentration-time relationships. The 60-min exposures were at 20 and 48 ppm (1,200 and 2,800 ppm-min, respectively) for pseudo-mouth-breathing animals and 34 ppm (2,040 ppm-min) for nose-breathing animals. The 2-min and 10-min groups in the study were exposed at about 1,200, about 2,800, about 9,500 and about 17,000 ppm-min. Breathing frequencies decreased dramatically in the nose-breathing animals exposed at 1,000 ppm or higher for short periods, indicative of nasal trigeminal nerve activation, but were not markedly altered in the pseudo-mouth-breathing animals. In the 60-min low-concentration groups, breathing frequencies and minute ventilation were increased over baseline in nose-breathing but not pseudo-mouth-breathing animals. Pulmonary-function tests, BAL, and histopathology were used to characterize the injuries after the nonlethal exposures; all measures indicated the induction of airway injury by hydrogen fluoride in the 2-min or 10-min exposures at 9,500 and 17,000 ppm-min. As in the study of Stavert et al. (1991), after exposures of 10 min or less, nasal lesions predominated in the nose-breathing animals and large tracheobronchial airway lesions in the pseudo-mouth-breathing animals. Hydrogen fluoride-induced effects were much less pronounced in the 60-min exposure groups. BAL protein and glucose-6-phosphate dehydrogenase were slightly increased in the 60-min 48-ppm group but not in the 60-min 20-ppm group. Pulmonary function (as assessed by FVC, FEV_1, and diffusing capacity) was unaffected, but a marginal increase in total lung capacity was noted. Histologic changes were not observed in the lower airways of pseudo-mouth-breathing animals after exposure at 20 or 48 ppm for 60 min. No nasal lesions were observed in nose-breathing rats after 60-min exposure at 34 ppm.

In summary, short-term animal experiments indicate that the respiratory tract is the primary target of hydrogen fluoride in these exposure scenarios. Nasal sensory nerve activation occurs during exposure in nasal-breathing animals. Injury occurs in the first airway that hydrogen fluoride comes into contact with: the nose in nose-breathing animals and the trachea in pseudo-mouth-breathing animals. At the same concentration-time product, injury is more severe in groups exposed at higher concentrations for shorter periods, indicating the predominant influence of exposure concentration. A NOAEL for a 60-min exposure was 34 ppm (the only concentration tested) in nose-breathing rats and 20 ppm in mouth-breathing rats.

Machle et al. (1934) exposed a small number of rabbits and guinea pigs to hydrogen fluoride at 29-9,784 ppm for 5 min to 41 h. Signs of irritation (coughing, sneezing, and mucoid conjunctival and nasal discharges) were observed at all exposures but were mild at 61 ppm and less. “Erosion of areas of the cornea and necrosis of the turbinates” were also observed frequently. Pulmonary hemorrhage, edema, and bronchitis were common in animals that died within 48 h of

exposure. Lesions were also observed in the liver and kidneys, but the extent to which they reflected changes that were secondary to the pulmonary effects or underlying disease in the control animals used is not clear. NOAEL or LOAEL values could not be determined from this study. The data in this study indicate that a $C^n \times t$ relationship exists for exposures of 4 min to 8 h with lethality as the end point, but the presentation of the data precludes precise estimation of n in the concentration-time relationship.

Morris (1979) performed a concentration-response study in which rats (six per group) were subjected to whole-body exposure to hydrogen fluoride at 13, 33, 88, 142, 181, or 218 ppm for 6 h and animals were killed 6 h after exposure (Table 4-4). Exposures at 181 or 218 ppm resulted in 100% mortality. Mucoid nasal discharges were apparent in the animals, and hemorrhagic lungs were observed at necropsy. Histopathologic examination of the lungs and kidneys was performed on surviving but not dying animals. An underlying degree of chronic peribronchial and perivascular lymphocytic inflammation was observed in control rats and rats exposed to hydrogen fluoride and was not related to exposure. No lung lesions related to exposure were observed in the animals exposed at 142 ppm or lower. The nasal cavity was not examined. Renal proximal tubular injury, as evidenced by nuclear pyknosis, was increased in a concentration-dependent manner; 88 ppm was the lowest concentration associated with injury. Blood urea nitrogen concentrations were also increased in a concentration-response manner; concentrations were significantly increased in animals exposed at 33 ppm or higher compared with control animals. Plasma ionic fluoride concentrations averaged 0.032, 0.57, 1.03, 2.72, and 5.73 μg/mL in rats exposed at 0, 13, 33, 88, and 142 ppm, respectively, and were significantly increased over control values in all exposed groups. Lung fluoride exceeded plasma fluoride by 2-3 fold, and this suggests that inspired hydrogen fluoride penetrated to the lungs in this exposure regimen. (That was not the case in animals exposed for 1 h.) The study documents increased systemic burdens of fluoride after hydrogen fluoride exposure and the presence of renal injury in animals exposed at 33 ppm or higher. Acute lethality, probably of respiratory tract origin, was observed, but the failure to include examination of nasal lesions precludes determination of a useful NOAEL.

Repeated Exposures and Subchronic Toxicity

Table 4-4 summarizes the results of studies of repeated exposure of animals. Stokinger (1949) exposed dogs, rabbits, guinea pigs, rats, and mice to hydrogen fluoride at 8.6 or 33 ppm 6 h/day, 6 days/week for 5 weeks. Subcutaneous hemorrhages around the eyes and feet were apparent in rats and mice, primarily at 33 ppm. Subcutaneous hemorrhages also occurred in the feet of rats at 8.6 ppm, although the lesions were less severe. At 33 ppm, there was 100% mortality in rats and mice and no deaths in the other species. No deaths were

TABLE 4-4 Effects of Hydrogen Fluoride in 6-Hour or Longer Animal Studies

Concentration (ppm)	Time	Species and Effects	Reference
13, 33, 88, 142, 181, 218	6 h	Rats. 100% mortality at 181 and 218 ppm, presumably due to nasal obstruction; histologic analysis not performed on dying animals; no histopathologic pulmonary lesions observed at 142 ppm or lower, renal tubular cell pyknosis observed at 88 ppm and higher, and blood urea nitrogen increased at 33 ppm and higher; nasal tissues not examined	Morris 1979
18.6	6-7 h/day, 5 days/week, 10 weeks	Rabbit, guinea pig, monkey. Lethal to two of three guinea pigs; necropsy performed 7-9 months after exposure protocol; bronchial (guinea pigs) and alveolar (guinea pigs, rabbits) lung lesions observed; no lung damage in monkeys, but renal injury observed in monkeys and rabbits; nasal tissues not examined	Machle and Kitzmiller 1935
8.6, 33	6 h/day, 5 days/week, total of 166 exposure-hours	Rat, mouse, guinea pig, rabbit, dog. 100% mortality at 33 pm in rats and mice; no deaths in other species; histopathologic analysis on dog, rabbit, and rat at 33 ppm, and moderate lung hemorrhage or edema observed in all three species; only gross necropsy performed on 8.6-ppm group, and no effect reported in rat and rabbit, but focal lung hemorrhage observed in one of five dogs; nasal tissues were not examined	Stokinger 1949
1, 10, 25, 65, 100	6 h/day, 5 days/week, 2 weeks	Male and female rat. 100% mortality in males at 65 ppm or greater, 100% mortality in females at over 25 ppm, no deaths at other concentrations; ocular opacity, skin lesions, nasal and ocular discharges observed at 25 ppm or greater; body weights were decreased at 10 ppm or higher	Placke et al. 1990
0.1, 1, 10	6 h/day, 5 days/week, 90 days	Male and female rat. 25% mortality in males, 5% mortality in females at 10 ppm; no observed histopathologic lesions in any exposure group	Placke and Griffin 1991

observed at 8.6 ppm. In the animals exposed at 33 ppm, pulmonary hemorrhage and edema of varied degree were noted in the dogs, rabbits, and rats (the only three species in which pathologic findings were examined). Renal cortical degeneration was observed in the rats. Only gross examination was performed on animals at 8.6 ppm. Localized hemorrhagic areas were noted in the lungs of one of five dogs but not the rats or rabbits. The lack of histopathologic examination of the nose and lungs in the 8.6-ppm groups makes it difficult to determine whether this concentration is a NOAEL or LOAEL; however, the observation by gross examination of localized hemorrhage in one of five dogs suggests that the LOAEL was exceeded.

Machle and Kitzmiller (1935) exposed four rabbits, three guinea pigs, and two monkeys to hydrogen fluoride at 18.6 ppm 6-7 h/day, 5 days/week for 10 weeks. Surviving animals were allowed to recover for 7-9 months before termination. Lesions were found in the lungs, liver, and kidneys of exposed animals. Two guinea pigs died during the exposure phase of the study; pathologic examination revealed pulmonary damage in both; pulmonary injury was also observed in the guinea pig that survived the recovery period. All four rabbits survived until termination, and all had alveolar damage (edema and cellular infiltration) and renal injury (tubular necrosis or degeneration). Both monkeys survived exposure and exhibited similar renal injury but not lung damage. The exposure concentration of 18.6 ppm clearly represented a frank-effect level as indicated by the deaths and by the tissue damage that was observed in all species.

Battelle Laboratories (Placke et al. 1990) performed a repeated-exposure inhalation study with five male and five female rats per group exposed to hydrogen fluoride 6 h/day, 5 days/week for a total of 10 exposures. Exposure concentrations were 0, 1, 10, 25, 65, and 100 ppm. Exposure at 65 or 100 ppm caused 100% mortality; 100% mortality also occurred in female rats in the 25-ppm group, but no male rats exposed at this concentration died. No deaths occurred in the 1-ppm and 10-ppm groups. Corneal opacity, skin lesions, and ocular and nasal discharges were observed in the animals exposed at 25 ppm or higher; these effects probably reflected the irritating properties of hydrogen fluoride. Histopathologic examination of tissues was not performed. Body weights were reduced in animals exposed at 10 ppm or higher. The authors concluded that 10 ppm was a LOAEL and 1 ppm a NOAEL.

Battelle Laboratories (Placke and Griffin 1991) performed a 90-day repeated-exposure inhalation study with groups of 20 male and 20 female rats exposed 6 h/day, 5 days/week for a total of 65 exposures (over 90 days). Exposure concentrations were 0, 0.1, 1, and 10 ppm. Mortality (25% in males and 5% in females) occurred in the 10-ppm group but no others. Complete histology, including four nasal sections per animal was performed on all animals with the protocol of Young (1981). No lesions were observed, even in the dying animals; a cause of death was not determined in the study. Rosenholtz et al. (1963) reported that nasal lesions induced by hydrogen fluoride are localized to the external nares and nasal vestibule. The most anterior nasal section in Young's protocol does not include the most anterior portions of the nose (squamous epi-

thelium-lined vestibule); thus, it is possible that the most likely sites of lesions in the noses of the rats in the Battelle study were not examined.

In summary, mortality and respiratory tract injury commonly result from single and repeated 6-h inhalations. Nasal lesions are probably present, but histologic examination of nasal tissues after repeated exposures has not been uniformly performed or, if performed, may have missed the affected area. Furthermore, renal damage is observed after single or repeated 6-h exposures, most likely because of fluoride absorption. The published studies fail to establish a clear NOAEL because effects were observed at all exposure concentrations. Repeated exposure at 8.6 ppm may yield a LOAEL based on pulmonary hemorrhage in one of five dogs, but the absence of histopathologic analysis makes this conclusion tenuous.

Additional experiments have shown subchronic effects of inhalation exposure to hydrogen fluoride. They involved continuous exposure (24 h/day) of albino rats to hydrogen fluoride at 0.01, 0.04, or 0.1 ppm for 5 months (Sadilova et al. 1965). The authors reported disturbances in conditioned reflexes and lengthened motor chronaxie of lower hind leg flexors in rats exposed at 0.04 ppm or higher and morphologic changes in nerve cells in the motor and sensory areas of the brains of animals exposed at 0.1 ppm. Others have concluded that it is not possible to evaluate the underlying experimental work fully (Smith and Hodge 1979). More important, the results seem highly unlikely to be related to the exposures. At a ventilation rate of 0.2 m^3/day (0.14 L/min), rats exposed at 0.04 and 0.1 ppm inhale a total of 6 and 20 μg of fluoride. Given that a rat consumes rodent chow at 10 g/100 g of body weight per day and that it typically contains fluoride at at least about 30 μg/g or more (de Lopez et al. 1976; Morris 1979), it is unlikely that the systemic fluoride burdens were significantly altered by the inhaled hydrogen fluoride.

NRC (2006) reviewed several subchronic animal studies of oral fluoride exposure. Bobek et al. (1976) found disturbed thyroid function in male rats given fluoride at 0.4-0.6 and 4-6 mg/kg-day in drinking water for 60 days; ATSDR (2003) derived a LOAEL of 0.5 mg/kg-day from the study. Hara (1980) described effects on thyroid function in rats at fluoride doses as low as 0.1 mg/kg-day for 54-58 days. Zhao et al. (1998) found increased thyroxine concentrations and reduced radioiodine uptake in mice with normal iodine intake at fluoride doses of 3 mg/kg-day for 100 days.[4] Rigalli et al. (1992, 1995) reported disturbed glucose tolerance in female rats at fluoride intakes of about 10 mg/kg-day for 90 or 100 days. It is important to note that rats and mice tend to require

[4]Estimated fluoride doses (here and later in the report) were calculated from information provided in the cited papers. In the absence of reported consumption rates, the committee used a water consumption rate of 0.1 L/kg of body weight or a food consumption rate of 0.1 kg of feed per kilogram of body weight, as appropriate.

fluoride intakes at least 5-20 times higher than humans do to yield similar physiologic concentrations or health effects (NRC 2006).

Chronic Toxicity

NRC (2006) reviewed a number of chronic animal studies for several end points, including endocrine, bone, and neurologic effects. Altered glucose metabolism occurred in rabbits at fluoride exposures of 7-10.5 mg/kg-day for 6 months (Turner et al. 1997), and altered thyroid metabolism occurred in rats at 3 mg/kg-day for 7 months (Guan et al. 1988). Several studies of Turner et al. (reviewed by NRC 2006) found decreased bone strength in rats and rabbits with long-term fluoride intake, corresponding to bone fluoride concentrations of 6,000-8,000 mg/kg. ATSDR (2003) derived a NOAEL of 0.15 mg/kg-day and a LOAEL of 0.5 mg/kg-day for decreased vertebral strength and bone mineralization in male rats given fluoride in drinking water for 16 or 48 weeks (Turner et al. 2001).

Reproductive Toxicity in Males

Ortiz-Pérez et al. (2003) reported altered serum hormone concentrations with normal semen measures in men occupationally exposed to fluoride in a factory that was producing hydrofluoric acid and aluminum fluoride. The observed effects included increased follicle-stimulating hormone (FSH) and decreased testosterone, inhibin B, and prolactin. Total fluoride exposures of the occupationally exposed men were estimated to be 3-27 mg/day from drinking water and occupational exposure compared with 2-13 mg/day in a group exposed to fluoride only from drinking water. The intakes correspond to fluoride doses of 0.03-0.2 mg/kg-day and 0.05-0.4 mg/kg-day for the low and high exposure groups, respectively, on the basis of 70-kg body weight (NRC 2006). The fluoride exposures of the two groups overlapped, and the occupational group had exposure to other chemicals besides fluoride.

Tokar and Savchenko (1977) also reported increased FSH and decreased testosterone in a study of 41 men (33-45 years old) who had fluorosis (apparently of occupational origin) compared with 19 control men who had no occupational contact with fluorine compounds. In men with at least 15 years of exposure to fluorine compounds, there was also an increased concentration of blood luteinizing hormone (LH). Full details of the study, including the magnitude of fluoride exposure and information about concurrent exposures, are not available in English.

Susheela and Jethanandani (1996) found a significant reduction in serum testosterone concentrations in skeletal-fluorosis patients (exposed to fluoride at 1.5-14.5 mg/L in drinking water) compared with controls (no skeletal fluorosis and exposed to fluoride at 0.1-0.9 mg/L in drinking water). Male relatives of the

skeletal-fluorosis patients who did not have skeletal fluorosis but drank the same water as the skeletal-fluorosis patients had intermediate concentrations of testosterone. If one assumed a 2-L/day water intake for 60-kg men,[5] fluoride doses would be about 0.05-0.5 mg/kg-day for the skeletal-fluorosis patients and their male relatives without fluorosis, and 0.003-0.03 mg/kg-day for the controls. Thus, with or without skeletal fluorosis, men with high fluoride intakes had reduced serum testosterone. The mean serum fluoride concentration associated with reduced testosterone was 0.24 mg/L in the men with skeletal fluorosis and 0.19 mg/L in the relatives without fluorosis but only 0.05 mg/L in the control group.

The studies by Susheela and Jethanandani (1996) and Ortiz-Pérez et al. (2003) suggest, but do not confirm, that fluoride intake can alter the reproductive-hormone environment. The dosage necessary to produce the effects cannot be established with certainty on the basis of those studies but would probably be at least 0.05 mg/kg-day, whereas exposure at below 0.03 mg/kg-day appears to be associated with a low risk of effects on male reproductive hormone status.

Several animal studies have also reported effects of fluoride exposure on male reproduction. Das Sarkar et al. (2006) reported decreases in testicular enzymes and low plasma concentrations of testosterone, FSH, and LH in rats exposed to sodium fluoride at 20 mg/kg-day (fluoride at 9 mg/kg-day) for 28 days. Administration of calcium and vitamin E reversed the effects to control values in that study. Araibi et al. (1989) reported significant decreases in serum testosterone, a 50% reduction in fertility, and a decrease in the percentage of seminiferous tubules containing spermatozoa in rats exposed to sodium fluoride (fluoride intake of 9 mg/kg-day) in their feed for 60 days. A decrease in diameter of the seminiferous tubules was observed at a fluoride intake of 4.5 mg/kg-day.

Abnormalities of spermatogenesis and decreased ability of epididymal spermatozoa to capacitate in vitro have been reported in mice given fluoride at 10 or 100 mg/L in drinking water (tap water with or without aluminum at 10 mg/L) for 3 months (Dvoráková-Hortová et al. 2008). Effects were not seen in mice that received fluoride alone at 1 mg/L but were seen when fluoride (1 mg/L) and aluminum (10 mg/L) were jointly administered. That finding is consistent with other reports that fluoride toxicity increases in the presence of aluminum (NRC 2006). The estimated fluoride intakes were 0.1, 1, and 10 mg/kg-day.

Immunotoxicity

NRC (2006) reviewed the available information on immune-system effects of fluoride. Both stimulatory and inhibitory effects have been reported. Mice exposed to fluoride at 5 or 10 mg/m^3 in air (4 h/day for 14 days, aerosols less

[5]Because the study was conducted in India, a smaller body size was assumed (NRC 2006).

than 10 μm in diameter) showed concentration-dependent suppression of pulmonary bactericidal activity against *Staphylococcus aureus* (Yamamoto et al. 2001). At 10 mg/m^3, there was a significant decrease in the number of alveolar macrophages in BAL fluid in mice not bacterially challenged. There was also a significant increase in polymorphonuclear leukocytes and lymphocytes at 10 mg/m^3 with a significant decrease in body weight and an increase in lung weight (attributed to microscopically observed edema). No significant pulmonary effect was seen at 2 mg/m^3 in comparison with the controls. The authors concluded that fluoride inhalation might reduce the ability to cope with bacterial infections. Unlike inspired hydrogen fluoride, aerosols penetrate to the alveoli, and this makes direct extrapolation of the study results difficult.

A study of the relationship between asthma and occupational fluoride exposure was discussed earlier in the chapter (see "Occupational and Epidemiologic Studies").

Genotoxicity

NRC (2006) concluded that the evidence of genotoxicity of fluoride was inconsistent. Fluoride does not appear to be a direct mutagen, but a number of mammalian in vitro systems have shown dose-dependent cytogenetic or cell-transformational effects of fluoride exposure. Several papers suggest an indirect mechanism, such as interaction with DNA synthesis or repair enzymes, rather than a direct interaction with DNA (Aardema et al. 1989; Aardema and Tsutsui 1995; Meng and Zhang 1997). Lasne et al. (1988) suggested a mechanism of promotion without excluding a genetic mechanism. Human cells also seem to be much more susceptible to chromosomal damage by fluoride than rodent cells (Kishi and Ishida 1993). Meng et al. (1995) and Meng and Zhang (1997) reported increased cytogenetic effects (sister-chromatid exchanges, chromosomal aberrations, and micronuclei in peripheral blood lymphocytes) in workers exposed to airborne fluoride, mostly as hydrogen fluoride and tetrafluorosilane, at concentrations of 0.5-0.8 mg/m^3.

Genotoxic effects in vitro have been reported at fluoride concentrations at or above about 5 mg/L, depending on the experimental system examined (Table 4-5). In nonfatal cases of acute hydrofluoric acid poisoning, urinary and serum fluoride concentrations as high as 110 and 42 mg/L, respectively, have been reported (Björnhagen et al. 2003; Vohra et al. 2008). Urinary fluoride concentrations as high as 44 mg/L have been reported after occupational fluoride exposures in excess of 3 mg/m^3 (Derryberry et al. 1963; summarized by OEHHA 2003). Thus, it is possible that renal and bladder epithelium could experience fluoride concentrations, from exposure to inhaled hydrogen fluoride, in a range at which genotoxic effects have been reported.

TABLE 4-5 Summary of Results of Positive Genotoxicity Studies of Fluoride

End Point	Reference
In vitro Systems	
Dose-dependent transformation of SHE cells after NaF at 75 and 100 µg/mL (F^- at 34 and 45 mg/L)	Lasne et al. 1988
Cell transformation (or promotion of cell transformation) after NaF at 25 µg/mL (F^- at 11.3 mg/L) in BALB/3T3 mouse embryo cells	Lasne et al. 1988
Dose-dependent increase in chromosomal aberrations in CHO cells exposed during G_2 to NaF at 25-100 µg/mL (F^- at 11-45 mg/L); no significant increases after NaF at or below 10 µg/mL (F^- at 4.5 mg/L)	Aardema et al. 1989
Chromosomal aberrations (clastogenicity) in cell lines from chimpanzees and men but not in other primates or in rodents; NaF at 1-6 mM (F^- at 19-114 mg/L)	Kishi and Ishida 1993
Chromosomal aberrations in CHO cells after NaF at or above 50 mg/L (F^- at 22.6 mg/L)	Aardema and Tsutsui 1995
Clastogenicity (increase in chromosomal aberrations) in cultured human diploid cells after F^- at 5 or 10 ppm (5 or 10 mg/L) for 2.5 h or continuously for 5-6 days	Oguro et al. 1995
Dose-dependent increases in chromosomal aberrations in rat vertebral body-derived cells after NaF at 0.5-1.0 mM (F^- at 9.5-19 mg/L) for 24-48 h	Mihashi and Tsutsui 1996
Small dose-dependent increase in chromosomal aberrations in cultured human lymphocytes after NaF at 10, 20, or 30 µg/mL (F^- at 4.5-13.5 mg/L); no increase in SCEs	Gadhia and Joseph 1997
DNA damage (ascertained with Comet assay) to human embryo hepatocyte cells after NaF at 40, 80, 160 µg/mL (F^- at 18, 36, 72 mg/L)	Wang et al. 2004
Cytoxicity in human primary cell cultures (skin fibroblasts) and permanent cell lines; IC_{10} of HF of 0.6-1.0 mM (F^- at 11.4-19 mg/L) or of NaF of 1.3-3.3 mM (F^- at 25-63 mg/L); NOAEC of HF of 0.08-0.24 mM (F^- at 1.5-4.6 mg/L) or of NaF of 0.09-0.32 mM (F^- at 1.7-6.1 mg/L)	Lestari et al. 2005
In vivo Studies in Humans	
Increased SCEs, micronuclei in 53 fluorosis patients with F^- at 4-15 mg/L in drinking water	Wu and Wu 1995
Increased SCEs, chromosomal aberrations, and micronuclei in peripheral blood lymphocytes from occupational exposures to F^- at 0.50-0.80 mg/m^3 (mostly as HF and SiF_4)	Meng et al. 1995; Meng and Zhang 1997

Abbreviations: CHO, Chinese hamster ovary; F^-, fluoride ion; G_2, phase G_2 of cell cycle; HF, hydrogen fluoride; IC_{10}, inhibitory concentration at 10%; NaF, sodium fluoride; NOAEC, no observable adverse effect concentration; SCE, sister-chromatid exchange; SHE, Syrian hamster embryo; SiF_4, tetrafluorosilane.

Carcinogenicity

NRC (2006) concluded that fluoride appears to have the potential to initiate or promote cancers, but the overall evidence from human and animal studies is mixed. Several occupational studies (Grandjean et al. 1992; Romundstad et al. 2000; Grandjean and Olsen 2004) are consistent with an association between exposure to inhaled fluoride and bladder cancer (reviewed by NRC 2006). Estimated fluoride concentrations at which the cohorts were exposed were 15-20 mg/m^3 (Grandjean et al. 1992; Grandjean and Olsen 2004) and 2.5 mg/m^3 or less (Romundstad et al. 2000). The U.S. Environmental Protection Agency has not classified fluoride with respect to carcinogenicity (EPA 1989). The International Agency for Research on Cancer lists inorganic fluorides in group 3, "not classifiable as to its carcinogenicity to humans," on the basis of reviews in 1982 and 1987 (IARC 1987, p. 208).

TOXICOKINETIC AND MECHANISTIC CONSIDERATIONS

Several lines of reasoning suggest that respiratory tract irritation by hydrogen fluoride results from local effects due to its acidic nature. The respiratory tract is not a target for fluoride ion (NTP 1990) and pulmonary immunotoxic effects of fluoride-containing dust typically require higher concentrations than that needed for local irritation. In contrast, the respiratory tract is known to be sensitive to acidic vapors. Aqueous soluble weak acids, such as acetic acid, are known sensory irritants in animals and humans (Morris et al. 2003; Shusterman et al. 2005), and the injury pattern in the nose after acute exposure to hydrogen fluoride (Rosenholtz et al. 1963; Dalbey et al. 1998) is identical with that after exposure to weak acids (Buckley et al. 1984). Thus, the acidic nature of hydrogen fluoride probably contributes substantially to its irritant properties. It should be noted, however, that biologically significant concentrations of hydrogen ion are not absorbed systemically during exposure to hydrogen fluoride at 3 ppm or lower—at a ventilation rate of 15 m^3/day, the total absorbed acid burden in the human is 1.3 µmol/min at that exposure concentration. Although that may be sufficient to induce acidification locally in the respiratory tract, it is not sufficient to result in significant systemic acidification.

Regional deposition patterns are critical in influencing respiratory tract injury due to inspired irritants (EPA 1994). Much evidence suggests that hydrogen fluoride is scrubbed efficiently in the first airways with which it comes into contact: the nose during nose-breathing and the trachea and bronchi during mouth-breathing. In humans, nasal irritation predominates over lower airway irritation, and this suggests a nasal site of action. In rats, short-term (1-h or less) exposure caused predominantly nasal injury with little if any lower airway injury in nose-breathing animals. In mouth-breathing animals, tracheal injury and bronchial injury occur indicating that these tissues are sensitive to injury when a sufficient amount of hydrogen fluoride reaches them (Stavert et al. 1991; Dalbey et al.

1998). That injury does not occur in distal airways of mouth-breathing animals suggests substantial scrubbing in the large airways.

Studies on nasal uptake efficiency during a 35-min protocol revealed greater than 99% uptake in the upper respiratory tract of the rat (Morris and Smith 1982). Complete scrubbing of water-soluble ionizable acids in the nasal passages is consistent with theoretical understanding of vapor uptake processes (Morris and Smith 1982; Morris 2006). Lung fluoride concentrations in rats exposed to hydrogen fluoride for 1 h are no higher than plasma fluoride concentrations (Morris 1979; Morris and Smith 1982); this suggests that substantial amounts of hydrogen fluoride do not penetrate to the lungs via the airstream during short-term exposure. In contrast, after 6-h exposure in rats, lung fluoride concentrations exceed plasma concentrations by 3-fold, and this suggests that penetration to the lower airways does occur in prolonged exposures (Morris 1979). That may reflect the gradual accumulation of fluoride in the lungs due to the persistent delivery of even a small percentage of the inspired hydrogen fluoride or enhanced penetration of the nose as exposure times lengthen and nasal lesions occur. Future experiments would be needed to resolve the issue, but the results suggest that the potential for lung injury may increase with exposure time.

Inhaled hydrogen fluoride is rapidly absorbed into the bloodstream, as indicated by increased plasma and tissue fluoride concentrations after exposure. Blood fluoride concentrations were increased in a concentration-dependent manner after 35-min isolated upper respiratory tract exposure to hydrogen fluoride and indicated that rapid and efficient absorption occurs in the nasal cavity (Morris and Smith 1982). Such absorption patterns in the nose are common (Black and Hounam 1968; Yokoyama et al. 1971). Increased systemic fluoride concentrations after exposure to hydrogen fluoride have been documented in the rat and dog (Morris and Smith 1982; Largent 1961). Plasma fluoride concentrations are significantly increased after 1-h exposure to hydrogen fluoride in the human; the peak plasma concentration occurs at the end or within 30 min of the end of exposure (Lund et al. 1997). In their entirety, the data indicate that inhaled hydrogen fluoride is rapidly absorbed in the respiratory tract. Particularly with respect to short-term exposures (35 min in rats and 60 min in humans), it is unlikely that significantly increased plasma concentrations would have been observed if fluoride deposition and absorption were not highly efficient. Although precise determinations are not possible, it is appropriate to assume that inhaled hydrogen fluoride is completely deposited and that the fluoride is completely and rapidly absorbed into the bloodstream during inhalation exposure (Morris and Smith 1982). A number of human studies have documented increased urinary fluoride concentrations or systemic fluoride effects due to inhalation of airborne hydrogen fluoride or particulate fluorides (see, for example, Roholm 1937; Collings et al. 1951; 1952; Largent et al. 1951; Derryberry et al. 1963; Franke and Auermann 1972; Schlegel 1974; Franke et al. 1975; Hodge and Smith 1977; Baud et al. 1978; Waldbott and Lee 1978; Grandjean and Thomsen 1983; Dominok et al. 1984; Grandjean et al. 1990; Rees et al. 1990).

The absorption, distribution, and excretion of fluoride have been reviewed by ATSDR (2003). In brief, fluoride is rapidly and efficiently absorbed from the gastrointestinal tract via passive diffusion. Absorption efficiencies can approach 99-100%. In that regard, gastrointestinal absorption appears to be similar to respiratory tract absorption. Absorbed fluoride ion does not accumulate in most soft tissues but does accumulate in bone. Fluoride is incorporated into bone by replacing the hydroxyl ion to form hydroxyfluroapatite. It has been estimated that about 60% of an intravenous dose of fluoride is sequestered in bone and the remainder eliminated in urine.

Fluoride exerts systemic effects on the body in a number of ways: enzyme inhibition, alteration of normal physiologic signaling mechanisms, interference with endocrine function, disruption of calcium balance, and increased brittleness of bones due to incorporation of fluoride into the apatite lattice structure (NRC 2006). NRC (2006) has described the pharmacokinetics of fluoride and various possible mechanisms of specific toxic effects. The presence of aluminum fluoride or beryllium fluoride complexes may cause increased toxicity or additional toxic effects. Some effects of fluoride are more likely in the presence of low calcium intake, low iodine intake, or generalized poor nutrition. Fluoride retention and hence toxicity may be increased in the presence of renal impairment (NRC 2006).

INHALATION EXPOSURE LEVELS FROM THE NATIONAL RESEARCH COUNCIL AND OTHER ORGANIZATIONS

A number of organizations have established or proposed acceptable exposure limits or guidelines for inhaled hydrogen fluoride. Selected values are summarized in Table 4-6.

COMMITTEE RECOMMENDATIONS

The committee's recommendations for EEGL and CEGL values for hydrogen fluoride are summarized in Table 4-7. The current U.S. Navy values are provided for comparison.

1-Hour EEGL

Nasal irritation appears to be the most sensitive response to hydrogen fluoride. Nasal sensory nerve activation has been shown to occur in the rat (as evidenced by decreased breathing frequencies) and the human (as evidenced by nasal tickling, soreness, and other symptoms). The controlled human

TABLE 4-6 Selected Inhalation Exposure Levels for Hydrogen Fluoride from the National Research Council and Other Organizations[a]

Organization	Type of Level	Exposure Level (ppm)	Reference
Occupational			
ACGIH	TLV-TWA (measured as fluoride)	0.5	ACGIH 2005
	TLV-Ceiling (measured as fluoride)	2	
NIOSH	REL-TWA	3	NIOSH 2005
	REL-ceiling (15-min)	6	
OSHA	PEL-TWA	3	29 CFR 1910.1000
General Public			
ATSDR	Acute MRL	0.02	ATSDR 2008
NAC/NRC	AEGL-1 (1-h)	1	NRC 2004
	AEGL-2 (1-h)	24	
	AEGL-1 (8-h)	1	
	AEGL-2 (8-h)	12	

[a]Comparability of EEGLs and CEGLs with occupational-exposure and public-health standards or guidance levels is discussed in Chapter 1 ("Comparison with Other Regulatory Standards or Guidance Levels").

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AEGL, acute exposure guideline level; ATSDR, Agency for Toxic Substances and Disease Registry; MRL, minimal risk level; NAC, National Advisory Committee; NIOSH, National Institute for Occupational Safety and Health; NRC, National Research Council; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; TLV, Threshold Limit Value; TWA, time-weighted average.

TABLE 4-7 Emergency and Continuous Exposure Guidance Levels for Hydrogen Fluoride

Exposure Level	Current U.S. Navy Values (ppm)	Committee Recommended Values (ppm)
EEGL		
1-h	2	3
24-h	1	1
CEGL		
90-day	0.1	0.04

Abbreviations: CEGL, continuous exposure guidance level; EEGL, emergency exposure guidance level.

experimental studies of Lund et al. (1997, 1999, 2002, 2005) provide the most reliable data for establishing a 1-h EEGL. The studies incorporated exercise in the exposure regimen, and the study groups included people with allergic rhinitis. In those studies, several subjects experienced moderate to marked irritation in response to hydrogen fluoride at exposure concentrations of 3.1 ppm or higher, whereas no subjects exposed to concentrations of 2.9 ppm or lower reported this degree of irritation. Therefore, the data suggest that marked irritation occurs at 3.0 ppm or higher. That conclusion is supported by the work of Largent (1961), who reported on one subject with a rhinovirus infection who experienced considerable discomfort at 3.4 ppm. Nasal inflammation as assessed by nasal lavage is induced by hydrogen fluoride at 4.0 ppm but is unlikely to have long-term health significance. Lower airway lymphocytic inflammation was observed after 1-h exposures to hydrogen fluoride at over 0.9 ppm; however, no significant alterations in pulmonary function (FEV_1 and FVC) were observed at this or higher exposure concentrations. No significant short-term or long-term health effects would be expected in connection with the lower airway lymphocytic inflammation. Animal studies indicate that the lower respiratory tract may be more sensitive to the effects of hydrogen fluoride than nasal tissues. However, Lund et al. included exercise and anticipated mouth-breathing, thus alleviating the concern that lower respiratory tract effects may not have been observed because of nose-breathing.

On the basis of the above data, 3 ppm was selected as the appropriate point of departure for derivation of a 1-h EEGL to minimize the possibility of marked sensory irritation. The level of irritation that may be experienced is not considered sufficient to impair the ability to perform essential tasks. An uncertainty factor for interindividual variability does not appear to be required inasmuch as the study group included potentially sensitive people, such as those with rhinitis resulting from hay fever. Thus, a 1-h EEGL of 3 ppm is recommended. That exposure level is probably above the odor threshold and may cause mild irritation but is unlikely to produce more severe irritation.

24-Hour EEGL

An extensive data base for establishment of a 24-h EEGL does not exist, so determining an appropriate point of departure for a 24-h EEGL is not straightforward. Considerable data exist on 1-h exposures of animals and humans, but extrapolation of 1-h data to 24 h is problematic. The rodent single-6-h exposure study of Morris (1979) did not include examination of the most sensitive target, the nasal passages. Animal-toxicity data from repeated exposures might provide insights into an appropriate 24-h EEGL, but most of those studies used lethal concentrations, so their results are unsuitable for this purpose. One study reported no deaths and focal pulmonary hemorrhage (by gross examination) in one of five dogs after multiple 6-h exposures at 8.6 ppm (Stokinger 1949). Although those data are not sufficient for risk-assessment purposes, they

suggest that severe life-threatening injury did not occur in the dog even with multiple exposures at that concentration.

The human subject study of Largent (1961) incorporated multiple daily 6-h exposures to hydrogen fluoride at 2.6-4.7 ppm. Subjects reported only slight nasal irritation, so the 1-h threshold value of 3.0 ppm for marked irritation might be appropriate for a 6-h exposure. Certainly, the multiple-exposure data suggest that increased sensitivity to the irritating effects of hydrogen fluoride does not occur. Although far from strong, the few animal data suggest that substantial respiratory tract damage is unlikely to result from a single 6-h exposure at that concentration. The most appropriate $C^n \times t$ function for extrapolation from 6 h to 24 h is not known inasmuch as there is considerable uncertainty regarding the $C^n \times t$ function. Therefore, rather than using a concentration-time adjustment based on a $C^n \times t$ function, the committee recommended that a database uncertainty factor of 3 be used.

Application of the uncertainty factor results in a 24-h EEGL of 1.0 ppm. Given a total ventilation of 15 m^3 in 24 h, an absorbed fluoride dose of 12 mg for a 70-kg man can be derived. That dose would most likely not produce systemic injury in a single exposure. Some people may experience nasal irritation at the 24-h EEGL. Some degree of a respiratory inflammatory response might also result, but it would not be expected to impair the ability to perform essential tasks nor would it be expected to be of long-term health consequence.

90-Day CEGL

Few data are available for establishment of a 90-day CEGL. Epidemiologic data on occupational exposure suggest that occupational exposure to hydrogen fluoride at an average of 0.27 ppm may be associated with an increased risk of asthma (Taiwo et al. 2006). Multivariate analysis provided a relative risk for hydrogen fluoride of 1.18 per 0.12 ppm (95% CL 1.09-1.3). It should be noted that the workers were exposed to multiple fluorides (particulate and gaseous) for many years, so precise evaluation of the effects of hydrogen fluoride is difficult. Nonetheless, acute exposure to hydrogen fluoride results in mild lower respiratory tract (for example, tracheobronchial) lymphocytic inflammation (at 0.9 ppm or higher for 1 h; Lund et al. 1999), a case report indicates the development of RADS after acute exposure to hydrogen fluoride (Franzblau and Sahakian 2003), and prolonged respiratory symptoms occurred in the general public after an accidental release of hydrogen fluoride (Dayal et al. 1992). Thus, on the basis of the weight of the evidence, it is difficult to discount the potential of a causal relationship between occupational exposure to hydrogen fluoride and asthma.

There are few animal data on subchronic or chronic respiratory effects of hydrogen fluoride. Severe effects, including ocular opacity and ocular and nasal fluid discharge, occur in rats exposed at 25 ppm for multiple days (Placke et al. 1990). In the Battelle subchronic 90-day inhalation study (Placke and Griffin

1991), 25% mortality was observed in male rats exposed to hydrogen fluoride at 10 ppm. Neither mortality nor histologic lesions were observed at 0.1 or 1 ppm for 90 days, but it is not clear that the critical regions of the nose were examined (Placke and Griffin 1991; Rosenholtz et al. 1963). On the basis of body-weight reductions, the study authors considered 1 ppm to represent a NOAEL. The subchronic animal exposure study of Stokinger (1949) included only a small number of animals, and complete histopathologic evaluation was not performed, so use of the results is problematic. In that study, one of five dogs exposed to hydrogen fluoride at 8.6 ppm 6 h/day, 5 days/week for 10 weeks exhibited focal pulmonary hemorrhage that was observable during necropsy, but no histologic examinations of the nose or lungs were included. Thus, the committee considered the animal studies as inadequate for establishing a CEGL.

If a human NOAEL were derived from the animal NOAEL of 1 ppm by applying an interspecies uncertainty factor of 3-10, the resulting value would not differ markedly from a NOAEL derived from occupational epidemiology in which a relative risk of asthma for hydrogen fluoride of 1.18 per 0.12 ppm was estimated. Given the weaknesses of the animal database and the weight that human data should receive for risk assessment, it is appropriate to base the 90-day CEGL on the human occupational epidemiologic data. Because the other agents in the workplace (such as particulate fluorides and sulfur dioxide) and the short-term high-exposure excursions may have contributed to the asthma risk in the workers, the relative risk for hydrogen fluoride of 1.18 per 0.12 ppm may overestimate the health risk. Therefore, 0.12 ppm is a reasonable point of departure for CEGL derivation. A concentration-time extrapolation of the data is problematic; workers in the study of Taiwo et al. (2006) were exposed 8 h/day, 5 days/week for at least 2 years compared with submariners' exposure 24 h/day for 90-day durations. The two scenarios may represent similar exposure concentrations on an annualized basis; therefore, a concentration-time extrapolation is not proposed. The worker population in the epidemiologic study most likely included people who had rhinitis or were otherwise sensitive, so an interindividual uncertainty factor is not suggested here. Although the occupational epidemiologic study of Taiwo et al. (2006) was well performed, uncertainties are associated with using this study, particularly the uncertainty introduced by excluding people who had a new diagnosis of asthma within 2 years of beginning work. On the basis of that uncertainty and the difficulty of extrapolating a typical 5 days/week occupational exposure to the submarine setting, a database uncertainty factor of 3 was applied. The resulting 90-d CEGL is 0.04 ppm. Sensory irritation is not expected at this exposure level on the basis of the 1-h and multiple 6-h human studies by Lund et al. (1997) and Largent (1961).

The proposed 90-d CEGL of 0.04 ppm most likely protects against systemic fluoride-induced toxicity if airborne hydrogen fluoride is the only important source of fluoride exposure. At a ventilation rate of 15 m^3/day, it corresponds to a total absorbed dose of 0.5 mg/day (0.007 mg/kg-day for a 70-kg person). However, for systemic effects, it is necessary to consider fluoride exposure from all sources (EPA 1988; NRC 2006). Furthermore, it is necessary to

consider effects that could occur within a 90-day exposure and long-term effects due to cumulative exposures, of which 90-day exposures on a submarine would be a part. Health end points that require long-term exposure or accumulation of fluoride include effects on bones (increased risk of fracture and of skeletal fluorosis). Other effects (such as endocrine effects) do not necessarily require accumulation or long-term exposure but may depend on current physiologic fluoride concentrations. In particular, subchronic thyroid effects have been reported in animals—an indication that altered concentrations of thyroid hormones do not necessarily require long exposure. Impaired glucose tolerance and male reproductive effects have also been reported in animals exposed to fluoride for 28-100 days.

Table 4-8 summarizes systemic fluoride effects and corresponding estimated intakes in humans. For most end points, systemic effects in generally healthy people have been reported in situations corresponding to estimated average chronic intakes of around 0.05 mg/kg-day or higher.

Long-term fluoride exposure would include exposure to airborne and ingested fluoride on board a submarine and on shore. Table 4-9 summarizes the estimated average fluoride intake (by source and total from all sources) based on information provided to the committee by the U.S. Navy (LCDR D. Martin, U.S. Navy, personal commun., July 8, 2008). The proposed 90-d CEGL of 0.04 ppm based on chronic respiratory effects would lead to a systemic fluoride intake of 0.5 mg/day (0.007 mg/kg-day) at an inhalation rate of 15 m^3/day (EPA 1997) and an average body weight of 70 kg. That value would correspond to an estimated average total systemic fluoride intake (from all sources) of 0.023 or 0.026 mg/kg-day for normal or high activity levels, respectively (Table 4-9). That estimated total daily fluoride intake is less than 0.05 mg/kg-day, the lowest dose associated with the potential for fluoride-induced systemic toxicity (Table 4-8). Persons who have fluoridated water on shore will have total systemic fluoride intakes on board a submarine that will be lower than those on shore.

TABLE 4-8 Summary of Systemic Effects in Humans Associated with Chronic Intake of Fluoride from All Sources

Effects	Estimated NOAEL (mg/kg-day)	Typical Fluoride Intake Associated with Effects (mg/kg-day)
Endocrine effects	0.01-0.03	0.05
Increased risk of bone fracture	NA	~0.05
Skeletal fluorosis (stage II)	NA	0.05
Reduced testosterone concentrations	<0.03	0.05

NA, not available.

TABLE 4-9 Estimated Fluoride Intakes (mg/kg-day) for Specified Exposure Situations[a]

Source of Fluoride Exposure	On Board Submarine	On Shore
Drinking water (normal activity)	0.0024[b]	Fluoridated source:[c] 0.0173 Nonfluoridated source:[c] 0.0024
Drinking water (high activity)[d]	0.005	Fluoridated source: 0.05 Nonfluoridated source: 0.005
Food and beverages[e]	0.0114	0.0114
Pesticides[f]	0.0007	0.0007
Toothpaste[g]	0.0014	0.0014
Air	0.007[h]	0.0006
Totals: Normal activity	0.023	Fluoridated source: 0.031 Nonfluoridated source: 0.017
High activity	0.026	Fluoridated source: 0.064 Nonfluoridated source: 0.019

[a]Based on NRC (2006) estimates for U.S. adults 20-49 years old unless otherwise indicated.
[b]Assumes that drinking water on submarine is primarily from reverse-osmosis unit. Purified water is expected to have low fluoride concentrations (<0.15 mg/L; NRC 2006).
[c]Drinking water on shore could be from fluoridated sources (around 1 mg/L) or nonfluoridated sources (defined as <0.7 mg/L; assumed here to be ≤0.5 mg/L). Two types of sources are considered separately.
[d]Assumes a drinking-water intake of 50 mL/kg of body weight per day (Table 2-4, NRC 2006) and fluoride concentrations of 1 mg/L (fluoridated source) or 0.1 mg/L (on board submarine or nonfluoridated source on shore).
[e]Food on board submarine includes fresh and frozen ingredients, canned soups and vegetables, and canned fruits and fruit juices. Commercial beverages (such as soft drinks and bottled tea) are available. Tea, coffee, and Kool-Aid are available. Tea is prepared from tea bags. This diet is considered comparable with average diet of adults in United States with respect to fluoride intake.
[f]Exposure to fluoride from pesticides is considered typical for adults in United States.
[g]Toothpaste use and inadvertent ingestion of toothpaste are considered typical for adults in United States.
[h]Based on proposed 90-d CEGL of 0.04 ppm, inhalation rate of 15 m^3/day, and average body weight of 70 kg.

DATA ADEQUACY AND RESEARCH NEEDS

NRC (2006) identified a number of research needs regarding fluoride toxicology for various health end points. In particular, nearly all human studies require improved characterization of fluoride exposure, including individual fluoride intake. There are very few subchronic or short-term studies of humans with any route of exposure. There have been occupational studies and studies of ex-

posures to airborne fluoride from coal combustion in China, but most of the literature on effects in humans comes from ingestion exposures, primarily to fluoride in drinking water. Although many health end points (such as effects on bones) require long-term exposure or accumulation of fluoride, others (such as endocrine effects, low tolerance or hypersensitivity, and asthma) do not. A critical research need for animal studies would be a 90-day continuous-inhalation bioassay for hydrogen fluoride. Studies that use multiple 90-day exposures that mimic the exposure of the submarine crew may be needed to examine fully the potential for the induction of asthma. A species appropriate for examination of induction of allergic airway disease and measures of airway function would be critical for such a study.

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5

Hydrogen Sulfide

This chapter summarizes the relevant epidemiologic and toxicologic studies of hydrogen sulfide. It presents selected chemical and physical properties, toxicokinetic and mechanistic data, and inhalation-exposure levels from the National Research Council and other agencies. The committee considered all that information in its evaluation of the U.S. Navy's 1-h, 24-h, and 90-day exposure guidance levels for hydrogen sulfide. The committee's recommendations for hydrogen sulfide exposure levels are provided at the end of this chapter with a discussion of the adequacy of the data for defining the levels and the research needed to fill the remaining data gaps.

PHYSICAL AND CHEMICAL PROPERTIES

Hydrogen sulfide is a colorless flammable gas with a characteristic odor of rotten eggs (Budavari et al. 1989; Weil et al. 2006). Studies indicate that the odor threshold varies. Ruth (1986) reported an odor threshold of 0.5-10 ppb; others have reported much higher values (ATSDR 2006). The irritating concentration is reported as 10 ppm (Ruth 1986), and olfactory fatigue and nerve paralysis are reported at 100 and 150 ppm, respectively. Selected physical and chemical properties are shown in Table 5-1.

OCCURRENCE AND USE

Hydrogen sulfide is a component of the natural sulfur cycle and is produced endogenously in mammals (Weil et al. 2006). It arises from bacterial reduction of sulfates and decomposition of proteins. Hydrogen sulfide is a

TABLE 5-1 Physical and Chemical Properties of Hydrogen Sulfide

Synonyms	Hydrosulfuric acid
CAS registry number	7783-06-4
Molecular formula	H_2S
Molecular weight	34.08
Boiling point	–60.33°C
Melting point	–85.49°C
Flash point	260°C
Explosive limits	Lower limit, 4.3% by volume; upper limit, 46% by volume
Specific gravity	1.19 (air = 1.00)
Vapor pressure	15,600 mmHg at 25°C
Solubility	0.398 g/100 g of water at 20°C; soluble in some polar organic solvents, such as methanol, acetone, glycerol, and ether
Conversion factors	1 ppm = 1.39 mg/m^3; 1 mg/m^3 = 0.72 ppm

Sources: Budavari et al. 1989; HSDB 2005.

byproduct of many industrial processes and is used to make inorganic sulfides that are used to make such products as dyes, pesticides, polymers, and pharmaceuticals (Weil et al. 2006).

The ambient air concentration resulting from natural sources is estimated as 0.11-0.33 ppb (ATSDR 2006). Hydrogen sulfide has been measured in the submarine atmosphere. Data collected on three nuclear-powered attack submarines indicate a range of 2-22 ppb (Hagar 2008). Whether the reported concentrations are representative of the submarine fleet is not known; few details were provided about the conditions on the submarines when the samples were taken. No other exposure data were located. Hydrogen sulfide emissions are thought to arise from the sanitary system (Hagar 2008).

SUMMARY OF TOXICITY

Occupational exposure to hydrogen sulfide occurs in the agricultural, gas, oil-refining, and other industries, and workers often notice the characteristic rotten-egg odor associated with exposure. Most people readily perceive hydrogen sulfide because the olfactory detection limit for it is so low (for example, 0.3 ppb or greater as reported by Hoshika et al. 1993). The toxic effects of hydrogen sulfide are characteristically dose-related and most notably involve the nervous, cardiovascular, and respiratory systems (ATSDR 2006). People exposed at low concentrations of hydrogen sulfide and other sulfur gases often report head-

aches, nausea, and other symptoms (Glass 1990; Shusterman 1992). Hydrogen sulfide is a contact irritant, causing inflammatory and irritant effects on the moist membranes of the eyes and respiratory tract; respiratory tract inflammation can result with exposure at about 50 ppm. Eye irritation is the most common complaint associated with single or repeated hydrogen sulfide exposure. There is agreement in the literature that effects on the eye predominate at concentrations above 50 ppm (Beauchamp et al. 1984; ACGIH 2005). Adverse effects on the human eye after exposure at 20 ppm or less are often associated with concomitant exposure to other chemicals or irritants that would reduce the threshold of corneal irritation (ACGIH 2005).

People acutely exposed to hydrogen sulfide at about 100 ppm commonly experience lacrimation, photophobia, corneal opacity, tachypnea, dyspnea, tracheobronchitis, nausea, vomiting, diarrhea, and cardiac arrhythmias (ATSDR 2006). Those changes generally resolve on evacuation to fresh air. However, people recovering from hydrogen sulfide exposure can have cough and a variety of effects on the sense of smell, including diminished function (hyposmia), altered sensation (dysosmia), and false odor recognition (phantosmia), for a few days to weeks. In humans, inhalation of hydrogen sulfide at as low as 100-250 ppm for only a few minutes can result in incoordination, memory and motor dysfunction, and anosmia (so-called olfactory paralysis). Symptoms become more severe with longer exposure and sometimes lead to pulmonary edema. Exposure at much higher concentrations (about 500 ppm) may result in coma, which is often rapidly reversed when the victim is evacuated, or persistent headaches, equilibrium loss, and memory loss.

Laboratory studies generally indicate that toxic effects observed in animals exposed to hydrogen sulfide at high concentrations are identical with those observed in humans who exhibit acute toxicity of the gas. Compilations of the concentrations of hydrogen sulfide that produce serious systemic toxic effects and death in humans and laboratory animals indicate that species differences in toxicity are not significant (ATSDR 2006). Concentrations that produce effects in the respiratory, cardiovascular, and nervous systems are similar in rats and mice and humans, varying by a factor of less than 10. The mechanism of action to produce serious effects appears to be the same in all species because cellular respiration and energy production controlled by cytochrome oxidase in the mitochondria are inhibited by hydrogen sulfide in all species tested. That mechanism is consistent with effects observed in multiple organ systems in laboratory animals given acute, high exposures. Laboratory investigations have identified olfactory lesions in the nasal cavity of the rat after both acute high-concentration and subchronic low-concentration exposures to hydrogen sulfide.

As a direct-acting metabolic poison, hydrogen sulfide most profoundly affects organs that are critically dependent on oxidative metabolism, such as the brain and heart (ATSDR 2006). Like cyanide, hydrogen sulfide blocks the respiratory chain primarily by inhibiting cytochrome c oxidase.

Available data on animals suggest that hydrogen sulfide does not cause significant effects on fertility (ATSDR 2006). No studies of the carcinogenic

potential of hydrogen sulfide were available for review. There are few studies on the genotoxic potential of hydrogen sulfide, but test results show no indication of toxicity.

Effects in Humans

Accidental Exposures

Hydrogen sulfide is associated with fatal exposures in the workplace. According to U.S. Occupational Safety and Health Administration records, there were 80 fatalities in 57 hydrogen sulfide incidents from 1984 to 1994 (Fuller and Suruda 2000). Exposure concentrations and durations in those accidents were generally poorly defined.

Most fatalities occur in confined spaces (such as sewers, animal processing plants, and manure tanks) and result from respiratory failure, noncardiogenic pulmonary edema, coma, and cyanosis (Adelson and Sunshine 1966, cited in ATSDR 2006; Winek et al. 1968, cited in ATSDR 2006; Arnold et al. 1985). Pulmonary edema is not uniformly seen in fatal hydrogen sulfide poisoning cases, and recovery from coma can be relatively rapid on evacuation of the person to fresh air and application of artificial respiration and oxygen. Some people exposed at about 1,000 ppm develop vagal-mediated apnea and hydrogen sulfide-induced central respiratory arrest (Almeida and Guidotti 1999), and increased blood sulfide concentrations are occasionally detected after exposure at high concentrations.

Many people exposed to hydrogen sulfide at 500 ppm or higher become unconscious rapidly and then appear to recover. This syndrome is often referred to as knockdown and may result in long-term neurologic deficits, including incoordination, memory and motor dysfunction, personality changes, hallucinations, and anosmia. The clinical effects are consistent with organic brain disease resulting from hypoxia and may occasionally persist for several years after the initial hydrogen sulfide exposure (Arnold et al. 1985; Tvedt et al. 1991a; Tvedt et al. 1991b, cited in NRC 2002 and ATSDR 2006; Reiffenstein et al. 1992; Kilburn and Warshaw 1995). Vapor concentrations of about 500 ppm or higher are often fatal within minutes (Reiffenstein et al. 1992).

Signs and symptoms observed after acute exposure at 100-500 ppm include ocular and respiratory tract irritation, nausea, vomiting, diarrhea, headaches, loss of equilibrium, memory loss, olfactory paralysis, loss of consciousness, tremors, and convulsions (ATSDR 2006). Ocular effects include tearing, burning, and irritation of the cornea and conjunctivae (Lambert et al. 2006). The symptoms generally resolve without intervention after cessation of exposure (ATSDR 2006). The case reports below illustrate the effects of accidental exposure to hydrogen sulfide.

While drilling a pit to lay the foundation for a municipal sewage pumping station, 37 workers (24-50 years old) were accidentally exposed to hydrogen

sulfide at an undetermined concentration (Snyder et al. 1995). Signs and symptoms included headache, dizziness, breathlessness, cough, burning and discomfort in the chest, throat and eye irritation, nausea, and vomiting. Most of the workers recovered uneventfully, but one worker died and another remained in a coma for 5 days. The comatose patient was aggressively treated with hyperbaric oxygen. He was discharged from the hospital on day 16 with slow speech, impaired attention span, easy distractibility, isolated retrograde amnesia, decreased ability to communicate, impaired visual memory, and poor acquisition, retention, and recall of new information. His condition was unchanged at 12 and 18 months after exposure. In another case report, six patients were examined 5-10 years after accidental exposures to hydrogen sulfide at an unknown concentration (Tvedt et al. 1991a; Tvedt et al. 1991b, cited in ATSDR 2006). The patients had been unconscious for 5-20 min in the hydrogen sulfide atmospheres. Despite rapid evacuation, neurologic symptoms persisted, including impaired vision, memory loss, decreased motor function, tremors, ataxia, abnormal learning and retention, and slight cerebral cortical atrophy. One patient was severely demented on long-term follow-up.

Numerous other reports of permanent or persistent neurologic effects of exposure to hydrogen sulfide have been published (Wasch et al. 1989; Kilburn 1993, cited in ATSDR 2006; Kilburn and Warshaw 1995; Kilburn 1997). The reports imply that exposure to hydrogen sulfide at relatively high concentrations can cause severe health effects, but as with most case studies, there is a lack of definitive exposure data.

Experimental Studies

Bhambhani and co-workers (Bhambhani and Singh 1991; Bhambhani et al. 1994, 1996a,b, 1997) performed a series of experiments to examine the dose-related effects of low-concentration exposures to hydrogen sulfide in exercising volunteers. Exercise increased the exposure to hydrogen sulfide by raising the respiratory rate, thereby approximating the exposure situation of an exercising worker. In the first series of experiments, 16 healthy male volunteers undertook increasing increments of bicycle exercise while inhaling hydrogen sulfide at 0 (control), 0.5, 2.0, or 5.0 ppm on separate occasions; multiple physiologic measurements were made (Bhambhani and Singh 1991). The subjects inhaled the hydrogen sulfide vapor through their mouths while their noses were plugged with an external clip, so the study does not provide useful information concerning the ocular or nasal toxicity of hydrogen sulfide. The results indicated that there were no significant changes in the cardiorespiratory and metabolic process at any exposure concentration and at any exercise level. Heart rate and expired ventilation rate were unaffected. Oxygen uptake increased slightly, carbon dioxide output decreased slightly, and during exposure to hydrogen sulfide at 5.0 ppm there was a significant increase in blood lactate. The results suggested that anaerobic metabolism is increased by the presence of the sulfide, but whether

that is due to inhibition of cytochrome oxidase cannot be determined from the results.

In a second series of experiments, 13 male and 12 female healthy volunteers were exposed to hydrogen sulfide at 0 ppm (control) and 5.0 ppm while exercising for 30 min (Bhambhani et al. 1994, 1996a). The 5.0-ppm exposure did not change arterial blood gases, hemoglobin oxygen saturation, or cardiovascular and metabolic responses. Citrate synthetase, a marker of aerobic metabolism, was the only enzyme that showed a statistically significant decrease in activity. Lactate dehydrogenase and cytochrome oxidase were not altered in muscle tissue taken by biopsy. The results confirmed those from the previous study except that lactate concentrations in blood were slightly higher, but not statistically significantly different, in the 5.0-ppm group. Thus, healthy exercising men and women showed little response to hydrogen sulfide at 5 ppm.

Another study showed that healthy people (nine men and 10 women) exposed to hydrogen sulfide at 10 ppm for 15 min while exercising showed no changes from control values in a series of respiratory measurements (Bhambhani et al. 1996b). A final study in this series (Bhambhani et al. 1997) used 28 healthy volunteers (15 men and 13 women) exposed to hydrogen sulfide at 0 ppm (control) or 10 ppm while exercising for 30 min. Increased muscle lactate in men and women, decreased muscle cytochrome oxidase in men, and increased muscle cytochrome oxidase in women were found, although most changes were not statistically significant.

The controlled studies presented above were limited in a number of ways. The exercising volunteers were protected from exposure to their noses and eyes, so they could not smell the gas and were not subject to eye irritation, both sensitive outcomes of hydrogen sulfide exposure. In addition, the volunteers were not previously exposed to hydrogen sulfide at the concentrations used in the experiments.

Jappinen et al. (1990) exposed a group of 10 mildly asthmatic subjects (three men, a mean of 40.7 years old, and seven women, a mean of 44.1 years old) to hydrogen sulfide at 2 ppm for 30 min in a closed chamber. All subjects experienced unpleasant odor at the start of the exposure but rapidly became accustomed to it. Three of the 10 subjects experienced headache after exposure was completed. There were no changes in forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and forced expiratory flow (FEF) as a result of exposure. Calculated airway resistance was slightly decreased in two and increased in eight subjects with no significant change in mean values. Specific airway conductance was decreased in six and increased in four subjects. There was over a 30% change in airway resistance and specific airway conductance in two subjects, indicating bronchial obstruction. No adverse symptoms were noted.

Fiedler and colleagues (2008) exposed 74 healthy subjects (35 women and 39 men, a mean of 24.7 ± 4.2 years old) to hydrogen sulfide at 0.05, 0.5, or 5 ppm. On the basis of self-reporting, 47% (35) of the subjects were Asian, 35% (26) Caucasian, 8% (six) Hispanic, 7% (five) black, and 3% (two) other. Criteria

that resulted in exclusion of subjects included neurologic disease or brain injury, substantial current or previous exposure to other neurotoxicants, stroke or cardiovascular disease, serious pulmonary disease (such as asthma), hepatic or renal disease, serious gastrointestinal disorders (such as colitis), major psychiatric conditions, pregnancy, lactation, or use of specified medications (such as anxiolytics, antidepressants, and beta blockers). Selected subjects completed a medical history and physical examination that included spirometry, electrocardiography, blood counts and routine chemistry measures, and visual-acuity testing. For each exposure session, subjects completed ratings and tests before exposure (baseline) and during the final hour of the 2-h exposure period. Subjects used analogue scales to rate pleasantness, intensity, and irritation of the hydrogen sulfide odor and to evaluate environmental qualities. Symptoms were rated on a ratio scale from 0 (barely detectable or no sensation) to 100 (strongest imaginable). Other tests included evaluation of postural sway, visual-acuity and visual-contrast sensitivity, simple reaction time and continuous-performance test, the finger-tapping test, the symbol-digit substitution test, and the auditory verbal learning test. Increased concentrations of hydrogen sulfide resulted in increased ratings of odor intensity, irritation, and unpleasantness. Total symptom severity, including eye irritation, was not significantly increased in any exposure condition, but anxiety symptoms were significantly greater in people exposed to hydrogen sulfide at 5 ppm than in people exposed at 0.05 ppm. "No dose-response effect was observed for sensory or cognitive measures. Verbal learning was compromised during each exposure condition." The authors concluded that "although some symptoms increased with exposure, the magnitude of the changes was relatively minor. Increased anxiety was significantly related to ratings of irritation due to odor. Whether the effect on verbal learning represents a threshold effect of hydrogen sulfide or an effect due to fatigue could not be determined."

Occupational and Epidemiologic Studies

A number of community and occupational studies have examined the effects of exposure to hydrogen sulfide. Because hydrogen sulfide has an objectionable odor that is apparent at concentrations below 10 ppb, it is readily recognized in ambient air and is often considered a "nuisance odor." Thus, low concentrations of hydrogen sulfide can cause concern, particularly from the perspective of community exposure. For example, in the early 1980s, community concerns in Alberta, Canada, related to exposure to natural gas contaminated with hydrogen sulfide (that is, sour gas) resulted in a large cross-sectional survey (Dales et al. 1989; Spitzer et al. 1989) to determine whether there was a higher incidence of health effects in a community living close to a sour-gas facility than in an unexposed community. The results of the investigation were generally unremarkable, although some possible effects on the respiratory system were reported (Dales et al. 1989). No air measurements were taken, so no

direct correlations between health effects and air concentrations of hydrogen sulfide were possible (Spitzer et al. 1989).

Data reported from studies of communities experiencing low exposures to hydrogen sulfide and other contaminants from nearby industrial or natural sources could provide an indication of a threshold for adverse health effects. The study results are equivocal because of the mixture of pollutants in the air, which usually includes organic sulfides, sulfur dioxide, and particles. In two communities in Finland that were exposed to pulp-mill emissions, self-reported respiratory symptoms (wheezing and shortness of breath) and eye irritation or conjunctivitis were more frequent than in a community that was not exposed (Jaakkola et al. 1990). Children in the exposed communities did not appear to be more sensitive to the effects of exposure than adults (Marttila et al. 1994). Information obtained from questionnaires in a later study in which exposure concentrations were measured indicated that average 24-h exposures to hydrogen sulfide at less than 0.007 ppm (range, 0-0.059 ppm) did not have significant respiratory or ocular effects, but respiratory symptoms were observed above 0.007 ppm (Marttila et al. 1995). Those studies cannot be given great weight in identifying a threshold exposure for hydrogen sulfide toxicity because, as previously mentioned, other air pollutants undoubtedly contributed to the reported effects. At best, the information suggests that hydrogen sulfide may contribute to respiratory symptoms when mixed with other air pollutants originating in pulp production.

Viscose-rayon workers (123 men) repeatedly exposed to hydrogen sulfide or carbon disulfide participated in a health survey that included questions on eye effects (Vanhoorne et al. 1995). Their responses to a questionnaire were compared with those of a reference group of 67 workers who were not exposed to either chemical. Workplace hydrogen sulfide exposure was determined by personal sampling devices and ranged from 0.14 to 6.4 ppm. The frequency of exposure is unknown, but participating workers had been employed for at least a year. Workers exposed to hydrogen sulfide at 3.6 ppm or less did not have significantly more ocular complaints than the unexposed workers. Workers exposed to hydrogen sulfide at 6.4 ppm did have significantly more eye complaints, including pain, burning, irritation, hazy sight, and photophobia.

Jappinen et al. (1990) studied a cohort of 26 male pulp-mill workers (mean age, 40.3 years; range, 22-60 years) to assess the possible effects of daily hydrogen sulfide exposure on respiratory function. Most of the exposures were at 2-7 ppm, with a range of 1-11 ppm. Bronchial responsiveness, FVC, and FEV_1 were measured at the end of a work day that followed at least 1 day off from work. No significant changes in respiratory function or bronchial responsiveness were observed after hydrogen sulfide exposure compared with control values.

In another study, 21 swine confinement-facility workers were tested with spirometry immediately before and after a 4-h work period (Donham et al. 1984). They had statistically significant ($p < 0.05$) reductions in pulmonary flow rates: a mean FEF of 3.3-11.9% after the 4-h work period. The work environment was sampled for particles and gases during the exposure period, and there

was suggestive evidence of a concentration-response relationship between carbon dioxide and hydrogen sulfide exposure concentrations and lung-function decrements. However, the monitoring data were not presented in the study report.

Barthelemy (1939), using work-area sampling and wet-chemistry analytic methods, reported hydrogen sulfide concentrations of about 30 ppm in the presence of carbon disulfide and acid particles in a rayon-production facility. It was reported that coexposure to carbon disulfide and acid particles reduced the threshold for hydrogen sulfide-induced ocular irritation. Exposure to hydrogen sulfide at about 30 ppm under the mixed exposure conditions caused "quite a number" of workers to develop severe eye irritation sufficient to prevent their ability to work in the facility. Six years of monthly air-monitoring data and worker-complaint records showed that the number of reported conjunctivitis cases increased from zero in December 1932 to 332 by December 1933 (when the plant's ventilation system failed). Ocular effects included intense photophobia, eyelid spasm, excessive tearing, intense congestion, pain, blurred vision, and sluggish pupil reaction. Typical hydrogen sulfide concentrations at the facility when it was operating without eye complaints were 9-18 ppm. Barthelemy concluded that maintaining hydrogen sulfide concentrations below 20 ppm (even in the presence of carbon disulfide at about 30 ppm) eliminated reports of eye irritation. Other investigators have reported that the incidence of eye irritation is "materially increased" at hydrogen sulfide concentrations of 20 ppm or slightly higher (Carson 1963). A hydrogen sulfide concentration of 20 ppm appears to be a threshold for obvious effects on the eye.

Table 5-2 summarizes the common clinical signs observed in experimental and occupational studies.

Effects in Animals

Acute Toxicity

ATSDR (2006) reported similar findings on acute toxicity in rats, mice, and rabbits. Zwart et al. (1990) reported that the hydrogen sulfide concentration that was lethal to 50% (LC_{50}) of rats and mice was 684 and 677 ppm, respectively, after a 50-min exposure. MacEwen and Vernot (1972) reported LC_{50}s in rats and mice of 712 and 634 ppm after a 1-h exposure. The similarity in response among mammalian species is typical for contact irritants.

Sprague-Dawley, Long Evans, and Fischer-344 rats were exposed to hydrogen sulfide in whole-body exposure chambers for 2, 4, and 6 h (72 males and 84 females at 2-h and 6-h intervals, 72 of each sex at 4 h) (Prior et al. 1988). The resulting LC_{50}s for 2-, 4-, and 6-h exposures were 587, 501, and 335 ppm, respectively. Six exposure concentrations were used in the 6-h study, and eight each in the 2- and 4-h studies. All deaths were attributed to severe pulmonary

TABLE 5-2 Hydrogen Sulfide-Induced Effects Observed in People

Cohort	Hydrogen Sulfide Concentration (ppm)	Effect	Reference
Experimental: 10 asthmatics, 30 min	2	No clinical symptoms or statistically significant changes; headache in three of 10 subjects; airway resistance slightly decreased in two and increased in eight; specific airway conductance decreased in six and increased in four; over 30% change in airway resistance and specific airway conductance in two of 10 subjects	Jappinen et al. 1990
Occupational: 26 pulp-mill workers, end of workday after at least 1 day off	2-7 (range, 1-11)	No significant changes in respiratory function or bronchial responsiveness	Jappinen et al. 1990
Experimental: 16 men, various periods up to 16 min	0.5, 2.0, 5.0	NOAEL, 2 ppm for oxygen uptake, carbon dioxide output, and blood lactate during exercise	Bhambhani and Singh 1991
Occupational: 123 male, viscose-rayon workers, exposure to hydrogen sulfide or carbon disulfide daily, at least 1 year	0.14-6.4	NOAEL, 3.6 ppm, LOAEL, 6.4 ppm for eye complaints of pain, burning, irritation, hazy sight, and photophobia.	Vanhoorne et al. 1995
Occupational: unspecified number of rayon-industry workers exposed to hydrogen sulfide and carbon disulfide	9-30 (work-area samples over period of 6 years)	Concentrations below 20 ppm deemed not to be a problem; substantial ocular effects at 30 ppm: intense photophobia, lid spasm, excessive tearing, intense congestion, pain, blurred vision, sluggish pupil reaction	Barthelemy 1939

Abbreviations: LOAEL, lowest observed-adverse-effect level; NOAEL, no-adverse-adverse-effect level.

edema. Groups of five male and five female Wistar rats were exposed to hydrogen sulfide at various concentrations for 10, 30, or 50 min (Arts et al. 1989, cited in NRC 2002; Zwart et al. 1990). The 10-min LC_{50} was 835 ppm, and the 30- and 50-min LC_{50}s were 727 and 684 ppm, respectively (see Table 5-3)

Brenneman et al. (2002) exposed groups of 10-week-old Sprague-Dawley rats (five rats per concentration per exposure time) to hydrogen sulfide at 0, 30, 80, 200, or 400 ppm 3 h/day for 1 or 5 consecutive days. A concentration of 30 ppm for a single day or 5 days was the no-observed-adverse-effect level (NOAEL) for nasal lesions. The most prominent nasal lesion was olfactory mucosal necrosis. Repair of that lesion was complete at 6 weeks after exposure (Brenneman et al. 2002). The primary differences observed in effects between exposure durations of 1 and 5 days were that animals exposed for 5 days had a higher lesion incidence (100%) and more extensive injury of the nasal cavity. Brenneman and co-workers also reported transient metaplasia in the nasal respiratory mucosa after exposure at 80 ppm or higher. That lesion is not seen after subchronic hydrogen sulfide exposure, and this finding suggests that the regenerated respiratory epithelium becomes resistant to further injury. No pulmonary lesions were observed even at the highest concentration tested. The lowest observed-adverse-effect level (LOAEL) in the study was 80 ppm for the reversible olfactory mucosa lesion.

Lopez et al. (1989) showed that the gross and histologic evidence of pulmonary edema caused by 5-min exposure to hydrogen sulfide at a lethal concentration (1,662 ppm) was a direct effect because intraperitoneal injections of 30 mg/kg did not affect the airways or lungs. Brenneman et al. (2000a) exposed 10-week-old male CD rats that had undergone unilateral nasal occlusion to hydrogen sulfide at 400 ppm for 3 h. A day after the exposure, rats developed olfactory neuronal loss on the side of the open nostril. That lesion was absent on the side that had the occluded nostril; this suggests that the observed injury was the result of a direct effect rather than of systemic delivery of the gas.

TABLE 5-3 Summary of Rat and Mouse LC_{50}s

Exposure Duration	LC_{50} (ppm)		Reference
	Rat	Mouse	
10 min	835	1,160	Zwart et al. 1990
30 min	727	799	Zwart et al. 1990
50 min	684	677	Zwart et al. 1990
1 h	712	634	MacEwen and Vernot 1972
2 h	587		Prior et al. 1988
4 h	501		Prior et al. 1988
4 h	444		Tansy et al. 1981
6 h	335		Prior et al. 1988

Lopez et al. (1988) exposed Fischer-344 rats to hydrogen sulfide at 0, 10, 200, or 400 ppm for 4 h. Animals were killed 1, 18, or 44 h after exposure. The authors found olfactory mucosal necrosis in the rats exposed at 400 ppm. Olfactory lesions were not seen after exposure at 10 or 200 ppm. The authors also reported lesions in the respiratory mucosa after exposure at 400 ppm; the lesions consisted of necrosis with ulceration 1 h after exposure and early regeneration with inflammation 18 h after exposure.

Numerous studies suggest that hydrogen sulfide can affect brain neurochemistry, physiology, and behavior in rodents. Several studies are repeated-exposure studies and are included here for completeness. Higuchi and Fukamachi (1977) evaluated conditioned-avoidance responses in well-trained Wistar rats during a 1-h inhalation exposure to hydrogen sulfide at 100-500 ppm. Rats exposed at greater than 200 ppm displayed inhibited discriminated avoidance responses immediately after the exposure. Avoidance responses returned to normal within 1 or 24 h after exposure at 200 or 500 ppm, respectively. Similarly, moderate exposure to hydrogen sulfide (125 ppm) can interfere with the ability of rats to learn a baited radial-arm maze task (Partlo et al. 2001).

Struve et al. (2001) exposed male Sprague-Dawley rats to hydrogen sulfide 3 h/day for 5 days. Groups of 10 rats each received whole-body exposure at 0, 30, or 80 ppm. Groups of 20 rats each received nose-only exposure at 0, 30, 80, 200, or 400 ppm. Motor activity and water-maze (spatial-learning) performance were evaluated. No treatment-related effects were observed in whole-body exposure groups. One of 20 rats died after exposure at 400 ppm. Hydrogen sulfide exposure produced statistically significant changes in the water-maze test (NOAEL, 200 ppm; LOAEL, 400 ppm) and motor activity (NOAEL, 30 ppm; LOAEL, 80 ppm) in the nose-only exposure groups.

Neonatal rats exposed to hydrogen sulfide at 75 ppm 7 h/day, beginning on postnatal day (PND) 5 and ending on PND 21, develop increased cerebellar serotonin and norepinephrine concentrations (Hannah and Roth 1991; Skrajny et al. 1992). Hannah and Roth (1991) exposed Sprague-Dawley rats to hydrogen sulfide at 0, 20, or 50 ppm 7 h/day from gestation day (GD) 5 through PND 21. The mean Purkinje cell terminal path length was significantly higher in animals exposed at 20 and 50 ppm than in controls; however, the biologic significance of this finding is unclear because no concentration-response relationship was observed. In a similar experiment, Hannah et al. (1989) exposed pregnant rats from GD 5 through PND 21 to hydrogen sulfide at 75 ppm 7 h/day. Brain concentrations of aspartate, γ-aminobutyric acid, glutamate, and taurine were significantly decreased, but no follow-up studies were conducted to determine whether the changes affected behavioral or structural development. In a repeated-exposure study, groups of five male Sprague-Dawley rats were exposed to hydrogen sulfide at 0 ppm (nitrogen air mixture) or 25, 50, 75, or 100 ppm 3 h/day for 5 days (Skrajny et al. 1996). The rats had hippocampal electrodes implanted in the dentate gyrus or CA1 region to determine the effects of hydrogen sulfide on electroencephalographic (EEG) activity in the hippocampus and neocortex. Exposure to hydrogen sulfide at 100 ppm resulted in increased hippocampal theta activity

but did not change the basic behavior-EEG correlation. Total hippocampal theta activity increased in a cumulative manner in both the dentate gyrus and CA1 regions during exposure at 25 ppm or higher. The increase was significant ($p < 0.05$) after exposure on days 3, 4, and 5 and did not return to control values during the 24-h period between exposures. Complete recovery of the animals exposed at 100 ppm took about 2 weeks.

Li and co-workers (2008) exposed anesthetized, paralyzed, and mechanically ventilated piglets to hydrogen sulfide at 20, 40, 60, and 80 ppm over 6 h (exposure at each concentration for 1.5 h). A control group of four piglets were exposed to air for 6 h. Blood lactate concentrations did not change significantly in exposed piglets; this suggested a lack of a metabolic effect on aerobic respiration. The findings are inconsistent with the increased blood lactate concentrations reported in humans exposed to hydrogen sulfide at 5 ppm for up to 16 min (Bhambhani and Singh 1991).

Repeated Exposures and Subchronic Toxicity

Curtis et al. (1975) exposed three immature pigs continuously (24 h/day) to hydrogen sulfide at 0 or 8.5 ppm for 17 days. Pigs were subjected to a complete gross examination at necropsy and histologic examination of tissues from the respiratory tract, eyes, and viscera. The pigs weighed an average of 13.2 kg at the beginning of the study and gained an average of 0.53 kg/day. The results indicate that the exposure concentration was a NOAEL.

Brenneman et al. (2000b) exposed groups of 12 male Sprague-Dawley rats to hydrogen sulfide at 0, 10, 30, or 80 ppm 6 h/day, 7 days/week for 10 weeks. Multifocal, bilaterally symmetric olfactory neuron loss and basal cell hyperplasia, limited to the olfactory mucosa, were observed in rats exposed at 30 ppm or higher. Lesions were observed in the dorsal medial meatus and dorsal and medial areas of the ethmoid recess. Exposure to hydrogen sulfide at 80 ppm induced more severe and more frequent olfactory mucosal injury than exposure at 30 ppm. No treatment-related effects were noted at 10 ppm, which was the NOAEL for lesions in the olfactory mucosa.

In a subchronic study, groups of 10 male and 10 female Fischer-344 rats, B6C3F1 mice, and Sprague-Dawley rats were exposed to hydrogen sulfide at 0, 10, 30, or 80 ppm 6 h/day, 5 days/week for 90 days (Dorman et al. 2004). Exposure at 80 ppm was associated with reduced feed consumption for the first week in rats and throughout the study in mice. Male Fischer-344 rats, female Sprague-Dawley rats, and female B6C3F1 mice exposed at 80 ppm had lower terminal body weights and lower body weight gain than air-exposed controls. No treatment-related gross pathologic, hematologic, or serum-chemistry effects were observed. Rhinitis (100% incidence) was observed in mice exposed at 80 ppm. A concentration-related increase in incidence of olfactory neuronal loss occurred at 30 ppm or higher in both sexes of the mice and the Fischer-344 rats; in the Sprague-Dawley rats, lesions were observed only at 80 ppm. Bronchiolar epithe-

lial hypertrophy and hyperplasia were evident in male and female Sprague-Dawley rats at 30 ppm or higher and in male Fischer-344 rats at 80 ppm. Overall, a NOAEL of 10 ppm was demonstrated for the bronchiolar lesions.

Partlo et al. (2001) exposed groups of 16-24 Sprague-Dawley rats repeatedly to hydrogen sulfide at 125 ppm 4 h/day, 5 days/week for 5 or 11 weeks. A 16-arm maze was used to evaluate learning and memory. Exposure to hydrogen sulfide for 5 weeks had no effect on a previously learned task nor did exposure affect acquisition of a new task in an 11-week training session that coincided with daily exposure. However, the exposed rats' ability to find all the reinforcements before the end of each trial period in the 11 weeks was impaired, and this suggested an effect on performance rate. When the learning task was changed by reversing the locations of reinforcement, hydrogen sulfide exposure had a detrimental effect on the rats' ability to learn the new complex task; they required more arm entries than the controls to locate the reinforcements.

Chronic Toxicity

No chronic experimental studies of animals exposed to hydrogen sulfide were found.

Reproductive Toxicity in Males

Dorman et al. (2000) exposed groups of 12 male and 12 female Sprague-Dawley rats to hydrogen sulfide at 0, 10, 30, or 80 ppm 6 h/day, 7 days/week for 2 weeks before breeding. Exposures continued during a 2-week mating period and then on GD 0-19. Exposure of the dams and pups (eight rats per litter after culling) resumed from PND 5 to PND 18. Adult male rats were exposed on 70 consecutive days. Offspring were evaluated on the basis of motor activity, passive avoidance, a functional observational battery, acoustic startle response, and neuropathology. A significant ($p < 0.05$) decrease in food consumption was observed in parental males only in the 80-ppm group during the first week of exposure. There were no deaths and no treatment-related adverse clinical signs in parental males or females. There were no significant effects on reproductive performance of the parental rats as assessed by the number of females with live pups, average gestation length, and average number of implants per pregnant female. No treatment-related effects in pups were noted in growth, development, or behavioral tests. No other effects were noted at any concentration.

Immunotoxicity

No studies evaluating the immunotoxicity of animals exposed to hydrogen sulfide were located. However, hydrogen sulfide is recognized as a proinflam-

matory mediator. For example, increased hydrogen sulfide generation and up-regulation of cystathionine γ-lyase activity have been observed in animal models of hindpaw edema, acute pancreatitis, endotoxemia, and sepsis, whereas inhibition of hydrogen sulfide formation can reduce the severity of pancreatitis and sepsis (Zhang et al., 2007).

Genotoxicity

Few studies of the genotoxic potential of hydrogen sulfide are available. Hydrogen sulfide was negative in an Ames reverse-mutation assay in *Salmonella typhimurium* strains TA97, TA98, and TA100 with and without hepatic S9 from male Sprague-Dawley rat or Syrian hamster liver (ATSDR 2006). Attene-Ramos et al. (2006) examined the genotoxicity of sulfide (as sodium sulfide) with single-cell gel electrophoresis (SCGE; comet assay) in Chinese hamster ovary and HT29-Cl.16E cells. They found that sulfide was not genotoxic in the standard SCGE assay. However, in a modified SCGE assay in which DNA repair was inhibited, a marked sulfide-induced genotoxic effect was observed. A sulfide concentration as low as 250 μmol/L caused a significant increase in genomic DNA damage. No other genotoxicity studies were located.

Carcinogenicity

No carcinogenicity study of hydrogen sulfide was located.

TOXICOKINETIC AND MECHANISTIC CONSIDERATIONS

Sulfide is present as an endogenous substance in normal mammalian tissues (Mitchell et al. 1993; Kage et al. 1998, cited in ATSDR 2006; Boehning and Snyder 2003). Normal tissues contain relatively high concentrations (in the parts per million range) of endogenous sulfide ion (HS^-). Hydrogen sulfide has been measured in rat brain at 1-2 ppm, and background concentrations in the lung range from 50 to 140 ppm (Dorman et al. 2002). Volatile sulfur compounds are produced by oral bacteria (Persson et al. 1990); hydrogen sulfide and methyl mercaptan are the main components found in mouth air. Humans with severe halitosis may have oral cavity hydrogen sulfide concentrations that exceed 10 ng/mL (0.7 ppm; Tsai et al. 2008). Endogenous sulfide also arises from bacterial activity in the lower bowel (NRC 1979). There is some evidence that hydrogen sulfide participates in normal nerve transmission (Kimura 2000). Hydrogen sulfide added at physiologic concentrations facilitates the induction of long-term potentiation in the hippocampus and is accompanied by increases in cAMP, which indirectly activates postsynaptic *N*-methyl-D-aspartate receptors for glutamate (Boehning and Snyder 2003). Thus, like nitric oxide and carbon monox-

ide, hydrogen sulfide has been identified as a putative gaseous biologic molecule and neurotransmitter (Szabó 2007). Functioning as a metabolite or as a nerve transmitter, it has been shown to mediate an array of biologic effects, including cytotoxic effects to cytoprotective actions.

Hydrogen sulfide is formed from cysteine by cystathionine β-synthetase and cystathionine γ-lyase. The production of sulfide is closely associated with the catabolism of cysteine and methionine and with gluthathione metabolism (Wang 2002; Fiorucci et al. 2006). In tissue homogenates, sulfide is produced at 1-10 pmol/s-mg of protein (Doeller et al. 2005). That results in low micromolar extracellular concentrations of sulfide.

The major metabolic and excretory pathway of hydrogen sulfide involves oxidation to sulfate (Beauchamp et al. 1984). The exact mechanism of the oxidation is unknown, but both enzymatic (sulfide oxidase) and nonenzymatic catalytic systems have been proposed. Glutathione stimulates mitochondrial oxidation of thiosulfate to sulfite in vitro, and a sulfite intermediate may be converted to sulfate by sulfite oxidase. After oxidation, hydrogen sulfide is excreted as free sulfate or as a conjugated sulfate in the urine (Beauchamp et al. 1984).

Two other metabolic pathways for hydrogen sulfide have been identified: methylation of hydrogen sulfide to produce methanethiol and dimethylsulfide and reaction of hydrogen sulfide with metalloenzymes or disulfide-containing enzymes (Beauchamp et al. 1984). Data suggest that thiol *S*-methyltransferase catalyzes the methylation of hydrogen sulfide to yield less toxic methanethiol and dimethylsulfide (Beauchamp et al. 1984).

Hydrogen sulfide may also reduce disulfide bridges in proteins, and this reaction is probably responsible for hydrogen sulfide-induced inhibition of succinic dehydrogenase. Oxidized glutathione (but not reduced glutathione) is protective against hydrogen sulfide poisoning. The protection is probably due to the scavenging of hydrosulfide by the oxidized glutathione-disulfide linkage, which prevents the reaction of the sulfide with other enzymatic sites (Beauchamp et al. 1984).

Dorman et al. (2002) evaluated the relationship between the concentration of sulfide and cytochrome oxidase activity in target tissues after acute inhalation exposure to hydrogen sulfide at sublethal concentrations. Specifically, they exposed groups of six male CD rats to hydrogen sulfide at 0, 10, 30, 80, 200, or 400 ppm for 3 h and examined hindbrain, lung, liver, and nasal cytochrome oxidase activity and sulfide concentrations immediately after exposure. Lung sulfide and sulfide-metabolite concentrations were also analyzed at 0, 1.5, 3, 3.25, 3.5, 4, 5, and 7 h after the start of exposure to hydrogen sulfide at 400 ppm. Lung sulfide concentrations increased during exposure and returned to baseline values within 15 min after exposure at 400 ppm, and lung sulfide-metabolite concentrations were transiently increased immediately after the end of exposure. Decreased cytochrome oxidase activities were noted in the olfactory epithelium at 30 ppm or greater. Increased olfactory epithelial sulfide concentrations were noted after exposure at 400 ppm. No effects on hindbrain or nasal respiratory epithelial sulfide concentrations were noted. Hepatic sulfide concentrations were

increased at 200 ppm or higher, and, surprisingly, hepatic cytochrome oxidase activity was increased in all treatment groups. The authors concluded that sulfide concentrations in the brain, lung, or nose are unlikely to increase after a single 3-h exposure to hydrogen sulfide at 30 ppm or lower.

Nasal extraction of hydrogen sulfide was measured in the isolated upper respiratory tracts of male Sprague-Dawley CD (Crl:CD[SD]BR) rats (Schroeter et al. 2006). Extraction was measured for constant unidirectional inspiratory flow at 75, 150, and 300 mL/min, which corresponded to 50, 100, and 200% of the predicted minute volume of the adult male CD rat. Nominal exposures to hydrogen sulfide at 10, 80, and 200 ppm were used. The concentration of hydrogen sulfide entering and leaving the upper respiratory tract was measured about every 8 min through the end of the 120-min exposure. Extraction was calculated as [(inlet concentration – exit concentration)/inlet concentration] and expressed as percent. Time-averaged extraction values were calculated as the average of the 15 samples for each animal. Time-averaged nasal extraction depended on the concentration of inspired hydrogen sulfide and the rate of airflow through the nasal cavity and ranged from 32% for a 10-ppm exposure at 75 mL/min to 7% for a 200-ppm exposure at 300 mL/min.

Hydrogen sulfide is a contact irritant and causes inflammatory and irritant effects on the moist membranes of the eyes and respiratory tract (Beauchamp et al. 1984). Eye irritation is the most common complaint associated with single or repeated exposure to hydrogen sulfide (Barthelemy 1939; Ahlborg 1951, cited in ATSDR 2006; Carson 1963).

The clinical picture resulting from acute lethal exposure to hydrogen sulfide (500-1,000 ppm) is almost identical with that of hydrogen cyanide poisoning. The symptoms are typically those of respiratory insufficiency accompanied by a period of hyperpnea followed by respiratory failure, noncardiogenic pulmonary edema, coma, and cyanosis (ATSDR 2006). In many cases, people lose consciousness after only one or two breaths of hydrogen sulfide (knockdown). A direct irritating effect on mucous membranes gives hydrogen sulfide a greater tendency than cyanide exposure to produce conjunctivitis and pulmonary edema.

Studies by Smith et al. (1977) and Khan et al. (1990) showed that under physiologic conditions, hydrogen sulfide acts to block the respiratory chain primarily by inhibiting cytochrome c oxidase and that the undissociated species (H_2S) is a more potent inhibitor than the anionic species (HS^-). Hydrogen sulfide blocks cytochrome c oxidase-dependent reduction of oxygen to water and thus impairs oxidative phosphorylation. Tissues with high oxygen demand (such as cardiac muscle and brain) are particularly sensitive to sulfide inhibition of electron transport, which is the same mechanism as has been shown for cyanide, and, as with cyanide poisoning, the presence of methemoglobin restores the activity of the cytochrome c oxidase enzyme system (ATSDR 2006). The enzyme blockage not only has a direct potent toxic effect but appears to cause indirectly hyperpnea through stimulation of the carotid and aortic body chemosensors by blocking the availability of oxygen (Ammann 1986).

Animal studies confirm that the olfactory system is especially sensitive to hydrogen sulfide inhalation. Acute, repeated exposure of rats to hydrogen sulfide at moderately high concentrations (80 ppm or higher) resulted in nasal lesions characterized by respiratory epithelial metaplasia and full-thickness necrosis of the olfactory mucosa (Brenneman et al. 2002). The mechanism by which hydrogen sulfide inhalation damages the nasal epithelium and results in adverse clinical signs is poorly understood. Direct inhibition of cellular enzymes is one mechanism of hydrogen sulfide toxicity (Beauchamp et al. 1984). As mentioned earlier, hydrogen sulfide-induced inhibition of cytochrome oxidase is believed to disrupt the electron-transport chain and impair oxidative metabolism. Although nasal cytochrome oxidase is a sensitive marker of hydrogen sulfide exposure, there is an incomplete correlation between hydrogen sulfide-induced nasal lesions and cytochrome oxidase inhibition (Dorman et al. 2002).

An alternative mechanism by which hydrogen sulfide inhalation could cause nasal lesions is dissociation of hydrogen sulfide that results in the release of free protons, which could alter intracellular pH and cause cytotoxicity. Roberts et al. (2006) treated nasal respiratory and olfactory epithelial cell isolates and explants from naïve rats with the pH-sensitive intracellular chromophore SNARF-1 and exposed them to air or hydrogen sulfide at 10, 80, 200, or 400 ppm for 90 min. "Intracellular pH was measured with flow cytometry or confocal microscopy…A modest but statistically significant decrease in intracellular pH occurred after exposure of respiratory and olfactory epithelium to hydrogen sulfide at 400 ppm." However, decreased cytochrome oxidase activity was observed after exposure at over 10 ppm, so changes in intracellular pH might play a secondary role in hydrogen sulfide-induced nasal injury.

Injury to and regeneration of the nasal respiratory mucosa occurred in animals exposed to hydrogen sulfide 6 h/day for 7 days/week, and this suggests that the regenerated respiratory epithelium becomes resistant to further injury (Brenneman et al. 2002). To understand that response, Roberts et al. (2008) exposed 10-week-old male Sprague-Dawley rats nose-only to air or hydrogen sulfide at 200 ppm 3 h/day for 1 day or 5 consecutive days. "Nasal respiratory epithelial cells at the site of injury and regeneration were laser-capture microdissected, and gene-expression profiles were generated at 3, 6, and 24 h after the initial 3-h exposure and 24 h after the fifth exposure with the Affymetrix Rat Genome 230 2.0 microarray. Gene-ontology enrichment analysis showed that exposure to hydrogen sulfide altered gene expression associated with a variety of biologic processes, including cell-cycle regulation, protein kinase regulation, and cytoskeletal organization and biogenesis."

Moulin et al. (2002) showed that the predicted regional flux of hydrogen sulfide correlates with the distribution of nasal olfactory lesions in the rat. In follow-up studies, Schroeter et al. (2006) used the olfactory-lesion incidence data from Brenneman et al. (2000b) to show a good correlation with hydrogen sulfide nasal-tissue dose predictions of an anatomically accurate computational fluid-dynamics model. An anatomic human model was used to estimate human nasal-tissue doses. The maximum 99th percentile flux value in the human model

was used to estimate a human NOAEL of 5 ppm with the EPA (1994) inhalation reference concentration method.

INHALATION EXPOSURE LEVELS FROM THE NATIONAL RESEARCH COUNCIL AND OTHER ORGANIZATIONS

A number of organizations have established or proposed acceptable exposure limits or guidelines for inhaled hydrogen sulfide. Table 5-4 summarizes selected values.

COMMITTEE RECOMMENDATIONS

The committee's recommendations for EEGL and CEGL values for hydrogen sulfide are summarized in Table 5-5. The current U.S. Navy values are provided for comparison.

1-Hour EEGL

The proposed 1-h EEGL of 10 ppm is intended to prevent severe eye irritation and is based on a weight-of-evidence approach. That EEGL is consistent with a recent critical review of the available human and animal toxicology data (Lambert et al. 2006). As reviewed by Lambert and co-workers (2006), Nesswetha (1969) studied etiologic factors in 6,500 cases of keratitis superficialis punctata (spinner's eye) that were attributed to occupational exposure to hydrogen sulfide. Mild eye irritation occurred after 6-7 h of exposure at 10 ppm, and similar symptoms developed after 4-5 h at 14 ppm. On the basis of the data, the committee notes that it is unlikely that eye irritation worsens with time.

Additional epidemiologic studies support the 1-h EEGL. Barthelemy (1939) reported that typical concentrations of hydrogen sulfide that were not associated with eye complaints ranged from 9 to 18 ppm. He concluded that hydrogen sulfide concentrations below 20 ppm "seemed not to be a problem," although other investigators have reported a "material increase" in eye-irritation incidence at 20 ppm or slightly higher (Carson 1963). A hydrogen sulfide concentration of 20 ppm appears to be a threshold for adverse effects on the eye sufficient to impair the ability of workers to perform their jobs.

Human chamber studies provide additional support of the 1-h EEGL (Bhambhani and Singh 1991; Bhambhani et al. 1994, 1996a,b, 1997; Fiedler et al. 2008). Taken together, the results of those studies do not indicate changes in healthy adults that signal the initiation of a toxic response to hydrogen sulfide exposure at up to 10 ppm. The magnitude of the few exposure-related changes

TABLE 5-4 Selected Inhalation Exposure Levels for Hydrogen Sulfide from National Research Council and Other Agencies[a]

Organization	Type of Level	Exposure Level (ppm)	Reference
Occupational			
ACGIH	TLV-TWA	10	ACGIH 2005
	TLV-STEL	15	
NIOSH	REL-ceiling (10 min)	10	NIOSH 2005
OSHA	PEL-ceiling	20	29 CFR 1910.1000
	PEL-ceiling (10 min max peak)[b]	50	
Submarine			
NRC	EEGL		NRC 1985
	10-min	50	
	24-h	10	
	CEGL		
	90-day	1	
	SEAL 1 (10-day)	15	NRC 2002
	SEAL 2 (24-h)	30	
General Public			
ATSDR	Acute MRL	0.07	ATSDR 2008
	Intermediate MRL	0.02	
NAC/NRC	AEGL-1 (1-h)	0.51	EPA 2002
	AEGL-2 (1-h)	27	
	AEGL-1 (8-h)	0.33	
	AEGL-2 (8-h)	17	

[a]Comparability of EEGLs and CEGLs with occupational-exposure and public-health standards or guidance levels is discussed in Chapter 1 ("Comparison with Other Regulatory Standards or Guidance Levels").
[b]Acceptable maximum peak is relevant only for one 10-min exposure if no other measured hydrogen sulfide exposures have occurred.
Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AEGL, acute exposure guideline level; ATSDR, Agency for Toxic Substances and Disease Registry; CEGL, continuous exposure guidance level; EEGL, emergency exposure guidance level; MRL, minimal risk level; NAC, National Advisory Committee; NIOSH, National Institute for Occupational Safety and Health; NRC, National Research Council; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; SEAL, submarine escape action level; STEL, short-term exposure limit; TLV, Threshold Limit Value; TWA, time-weighted average.

TABLE 5-5 Emergency and Continuous Exposure Guidance Levels for Hydrogen Sulfide

Exposure Level	Current U.S. Navy Values (ppm)	Committee Recommended Values (ppm)
EEGL		
1-h	10	10
24-h	3	2.8
CEGL		
90-day	1	0.8

Abbreviations: CEGL, continuous exposure guidance level; EEGL, emergency exposure guidance level.

that were observed, the sporadic occurrence of the changes, and the lack of a functional change in the cardiorespiratory system are not consistent with a conclusion that the effects constituted a toxic response.

Studies in animals further support the recommended 1-h EEGL. Brenneman et al. (2002) exposed groups of 10-week-old Sprague-Dawley rats (five rats per concentration per exposure period) to hydrogen sulfide at 0, 30, 80, 200, or 400 ppm 3 h/day for 1 day or 5 consecutive days. The nasal lesions were characterized by necrosis of the olfactory mucosa, which was largely repaired within about 6 weeks after exposure. The primary differences observed in effects between the 1-day and 5-day exposure groups were the higher incidence of and more extensive lesions seen in the nasal cavity of rats exposed for 5 consecutive days. No pulmonary lesions were observed even at the highest concentration tested. The LOAEL of hydrogen sulfide in the study was 80 ppm for the reversible olfactory mucosa lesion. The NOAEL for nasal lesions was 30 ppm for a single day or 5 days.

24-Hour EEGL

The basis of the 24-h EEGL was the study by Curtis et al. (1975). They exposed three immature pigs in a whole-body inhalation chamber to hydrogen sulfide at 8.5 ppm continuously (24 h/day) for 17 days. Pigs were subjected to a complete gross examination at necropsy, and a histologic examination was conducted on tissues from the respiratory tract, eye, and viscera. The results indicate that 8.5 ppm was a NOAEL. Application of an interspecies uncertainty factor of 3 yields a 24-h EEGL of 2.8 ppm. An interspecies uncertainty factor of 3 was considered appropriate because hydrogen sulfide is a contact irritant with a dose-response relationship that is similar among species.

The 24-h EEGL is supported by the study reported by Vanhoorne et al. (1995). Viscose-rayon workers (123 men), repeatedly exposed to hydrogen sulfide and/or carbon disulfide, participated in a health survey that included ques-

tions on eye complaints. Their responses to the questionnaire were compared with those of a reference group of 67 workers not exposed to either chemical. Personal exposure to hydrogen sulfide in the workplace was measured with personal sampling devices and ranged from 0.14 to 6.4 ppm. The published study did not report the frequency of exposure but only stated that participating workers had been employed for at least 1 year. Job descriptions in a previous report indicated that the hydrogen sulfide exposures occurred daily but were unclear as to the duration of exposure during the workday (Vanhoorne et al. 1991). Workers exposed to hydrogen sulfide at 3.6 ppm or lower did not have significantly more eye complaints than the unexposed workers. Workers exposed at higher concentrations averaging 6.4 ppm did have significantly more hydrogen sulfide-related complaints. The most frequent complaints about the eye were pain, burning, irritation, hazy sight, and photophobia. The findings suggest a 3.6 ppm NOAEL for repeated hydrogen sulfide exposure.

The 24-h EEGL is also supported by the available epidemiologic data. For example, Jappinen et al. (1990) studied a cohort of 26 male pulp-mill workers (mean age, 40.3; range, 22-60 years) to assess the possible effects of daily hydrogen sulfide exposure (at 10 ppm or lower) on respiratory function. Bronchial responsiveness, FVC, and FEV_1 were measured after at least 1 day off work and at the end of a workday. No significant changes in respiratory function or bronchial responsiveness were observed after hydrogen sulfide exposure compared with the control values.

90-Day CEGL

The study by Dorman et al. (2004) was used to develop the 90-day CEGL. Groups of 10 male and 10 female Fischer-344 rats, B6C3F1 mice, or Sprague-Dawley rats were exposed to hydrogen sulfide at 0, 10, 30, or 80 ppm 6 h/day, 5 days/week for 90 days. Exposure at 80 ppm was associated with reduced feed consumption for the first week in rats and throughout the study in mice. Decreased body-weight gain was observed in high-concentration male Fischer-344 rats, female Sprague-Dawley rats, and mice. No treatment-related effects were observed with regard to gross pathology, hematology, or serum chemistry. All the mice exposed at 80 ppm developed rhinitis. Histologic examination of the nose showed an exposure-related increased incidence of olfactory neuronal loss that occurred after exposure at 30 ppm or higher in both sexes of all experimental groups except that the lesion in Sprague-Dawley rats was seen only at 80 ppm. In the lung, bronchiolar epithelial hypertrophy and hyperplasia were evident in male and female Sprague-Dawley rats at 30 ppm or greater. The experimental NOAEL for nasal lesions was 10 ppm, which was used as the basis of the 90-day CEGL.

The inhalation study performed by Brenneman et al. (2000b) using rats exposed to hydrogen sulfide in a whole-body chamber (6 h/day, 7 days/week for 10 weeks) is also supportive of the committee's recommended value. In that

experiment, the NOAEL for lesions in the olfactory mucosa was 10 ppm. Hydrogen sulfide at 30 ppm was the LOAEL, and 80 ppm caused a marked increase in nasal lesions. Later studies have shown that the nasal mucosa is a very sensitive tissue and yield one of the lowest NOAELs (10 ppm) for hydrogen sulfide inhalation exposure (Dorman et al. 2004).

The 10-ppm value was time-scaled to account for a continuous (24-h/day) exposure (one-fourth of the 6-h/day NOAEL of 10 ppm, or 2.5 ppm). An interspecies uncertainty factor of 3 was used for animal-to-human extrapolation. An interspecies uncertainty factor of 10 was considered unnecessary because the nasal mucosa is so sensitive, as noted above. In addition, hydrogen sulfide is a contact irritant with a dose-response relationship that is similar among species. A 90-day CEGL of 0.8 ppm was derived.

Further support of the committee's recommended value is derived from studies performed by Schroeter et al. (2006). A pharmacokinetic-driven computational fluid dynamics (CFD) model was used to compare regions of high predicted hydrogen sulfide flux in rat nasal passages with the distribution of hydrogen sulfide-induced olfactory lesions in a subchronic inhalation study of Brenneman et al. (2000). Because the model yields a quantitative flux measure, the minimum flux value associated with olfactory lesions in rats could be estimated. That modeling approach was then used to predict hydrogen sulfide flux in human nasal passages by scaling the kinetic parameters and implementing a similar boundary condition in a human nasal-airflow model (Subramaniam et al. 1998). Olfactory fluxes predicted from the human CFD model were used to derive a NOAEL(human-equivalent concentration [HEC]) for hydrogen sulfide. The NOAEL(HEC) value was estimated to be 5 ppm.

DATA ADEQUACY AND RESEARCH NEEDS

Although there is an extensive literature on the health effects of hydrogen sulfide, questions remain about its possible effects and about concentrations at which effects may occur. Those questions apply particularly in connection with the end points of neurologic, respiratory, behavioral and developmental effects. At airborne concentrations above 20 ppm, the direct irritation effects of hydrogen sulfide are increasingly apparent. Acute respiratory effects are widely assumed to occur after even brief exposures at concentrations above 200 ppm, and acute neurotoxic responses occur at concentrations above 500 ppm. Questions now exist as to whether longer-term neurotoxic and respiratory or pulmonary deficits may occur after short-term high-concentration exposures. There are also concerns about human health effects in the low-exposure region, especially after chronic low-concentration exposure.

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6

Propylene Glycol Dinitrate

This chapter summarizes the relevant epidemiologic and toxicologic studies of propylene glycol dinitrate (PGDN). It presents selected chemical and physical properties, toxicokinetic and mechanistic data, and inhalation-exposure levels from the National Research Council and other agencies. The committee considered all that information in its evaluation of the U.S. Navy's 1-h, 24-h, and 90-day exposure guidance levels for PGDN. The committee's recommendations for PGDN exposure levels are provided at the end of this chapter with a discussion of the adequacy of the data for defining the levels and the research needed to fill the remaining data gaps.

PHYSICAL AND CHEMICAL PROPERTIES

When freshly prepared, PGDN is a colorless liquid that has "a disagreeable odor" (ACGIH 1991). Pure PGDN is unstable and has properties that are similar to those of ethylene glycol dinitrate, which is flammable, explosive, and shock-sensitive (ACGIH 1991). PGDN is mixed with 2-nitrodiphenylamine as a stabilizer and di-*n*-butyl sebacate as a desensitizer in Otto fuel II, which has been commonly used in toxicity studies of PGDN (Gaworski et al. 1985). Ruth (1986) reported an odor threshold ranging from 0.18 to 0.23 ppm. Stewart et al. (1974) reported the human odor threshold for PGDN as 0.2 ppm with olfactory fatigue occurring in as little as 5 min. Selected physical and chemical properties are shown in Table 6-1.

OCCURRENCE AND USE

PGDN is the primary component (about 76%) of Otto fuel II, which is used as a torpedo propellant (ATSDR 1995; NSWC 1995). Although the vapor

TABLE 6-1 Physical and Chemical Properties of Propylene Glycol Dinitrate

Synonyms	1,2-propylene glycol dinitrate, 1,2-propanediol dinitrate, isopropylene nitrate, propylene dinitrate, propylene nitrate, propane-1,2-diyl dinitrate
CAS registry number	6423-43-4
Molecular formula	$C_3H_6N_2O_6$
Molecular weight	166.09
Boiling point	92°C at 10 mmHg (decomposes above 121°C)
Melting point	–27.7°C
Flash point	NA
Explosive limits	NA
Specific gravity	NA
Vapor pressure	0.07 mmHg at 22°C
Solubility	0.13 g/100 mL of water
Conversion factors	1 ppm = 6.79 mg/m^3; 1 mg/m^3 = 0.15 ppm

Abbreviation: NA, not available or not applicable.
Sources: ACGIH (1991) and HSDB (2005).

pressure of PGDN is relatively low, it is the most volatile component of that fuel (NRC 2002). ATSDR (1995) noted that exposure could occur during torpedo-maintenance operations, manufacturing, or transport. However, exposure would not be expected to be substantial because PGDN has a low vapor pressure. Air concentrations of PGDN at four U.S. Navy torpedo facilities were reported to range from 0 to 0.22 ppm (ATSDR 1995). No exposure data on PGDN on submarines were located.

SUMMARY OF TOXICITY

The animal and human toxicity information on PGDN and Otto fuel II have been reviewed by Forman (1988), ACGIH (1991), ATSDR (1995), and NRC (1982, 2002).

PGDN is a systemic toxicant with effects on red blood cells, liver, kidneys, the cardiovascular system, and the central nervous system (CNS) in laboratory animals (Jones et al. 1972; NRC 2002). It is rapidly and completely metabolized in vivo within 24 h and eliminated primarily in urine as inorganic nitrate.

Monkeys exposed to PGDN at 70-100 ppm for 6 h exhibited signs of acute toxicity, including semiconsciousness and clonic convulsions, but no deaths. Rats exposed to a PGDN mist at 1,350 mg/m^3 for 4 h exhibited no overt signs of

intoxication; however, methemoglobin concentrations were 23.5% (Jones et al. 1972). The visual evoked response (VER) showed a significant increase in C-wave amplitude in monkeys exposed to PGDN at 2 ppm for 4 h (Mattsson et al. 1981). However, monkeys exposed at 2-33 ppm for 4 h and continuously at 39 ppm (Jones et al. 1972) did not change trained avoidance behavior. In a study with four animals species (squirrel monkeys, beagles, Sprague-Dawley-derived rats, and Hartley-derived guinea pigs) exposed to PGDN at 0, 10, 16, or 35 ppm continuously (24 h/day) for 90 days, hematologic changes were seen in dogs, and fatty livers were reported in multiple species at 10 ppm (Jones et al. 1972). There were no treatment-related increases in tumors in beagles exposed at 0 or 0.2 ppm for 14 months or in rats and mice exposed at 0, 0.2, or 36 ppm for 12 months (Gaworski et al. 1985); however, the studies are of limited value because the exposure durations were relatively short in relationship to the animals' life-spans, and the exposures may not have been maximized. Methemoglobinemia was observed in rats exposed to PGDN at 36 ppm after only 3 days of exposure and continued until the experiment was terminated. In addition, methemoglobinemia and hematologic changes were observed in dogs after 2 weeks of exposure to PGDN at 0.2 ppm. In a battery of mutagenicity and genotoxicity studies, PGDN produced positive results only in a study with L5178Y mouse lymphoma cells, in which it induced mutations at cytotoxic concentrations (Litton Bionetics 1979, cited in NRC 2002).

In humans exposed to PGDN, vasodilation results mainly in mild to severe frontal headaches; dizziness, loss of balance, nasal congestion, eye irritation, palpitations, and chest pain have also been reported (Stewart et al. 1974; Horvath et al. 1981). In contrast with studies in experimental animals, methemoglobinemia has not been reported in humans as a result of exposure to PGDN (Stewart et al. 1974). That finding may be related partly to the observation that in the presence of PGDN human erythrocytes appear less susceptible to forming methemoglobin than erythrocytes from sensitive test species, especially dogs. It may also be related to the fairly high concentrations (about 35 ppm) needed to produce the effect even in sensitive species; such concentrations would clearly be intolerable to humans because of headaches and sensory symptoms. Changes in VER similar to those observed in monkeys have been observed in humans exposed to PGDN at 0.2-1.5 ppm (Stewart et al. 1974). The VER changes have been interpreted as subclinical disruptions of the extraocular motor system. The VER changes were not reflected in decreased cognitive abilities in humans exposed to PGDN at 1.5 ppm except during periods of severe headache (Stewart et al. 1974). An increase in hospitalization for cardiac morbidity has been reported in workers exposed chronically to Otto fuel II during maintenance operations (Forman et al. 1987); however, no deaths of PGDN-exposed workers due to cardiac end points have been reported, and a cause-effect relationship between occupational exposure to PGDN and cardiac morbidity is uncertain because of the paucity of available data.

Effects in Humans

Accidental Exposures

Although PGDN is a potent vasodilator, reports of significant effects other than headache due to accidental exposure are rare. Human toxicity data on PGDN commonly involve exposure to Otto fuel II. The potential for fire and explosion plays a role in how PGDN and Otto fuel II are handled and consequently in the PGDN exposures that occur in the workplace. Humans exposed to Otto fuel II have experienced a number of effects, including headache, loss of balance, poor eye-hand coordination, eye irritation, nasal congestion, nausea, dizziness, and difficulty in breathing; the most common effect reported is headache (ATSDR 1995).

Sudden deaths due to circulatory failure have been associated with chronic exposure to nitrated esters, such as nitroglycerin and ethylene glycol dinitrate, an analogue of PGDN, in workers in the explosives industry (NRC 2002). The sudden deaths were attributed to compensatory vasospasm that may produce coronary insufficiency on withdrawal from nitrate ester exposure (NRC 2002). No similar cardiovascular deaths have been reported in U.S. Navy personnel during maintenance work on torpedoes, an activity in which accidental exposures to PGDN might be expected to occur (Horvath et al. 1981; Forman et al. 1987).

Experimental Studies

In the only available human experimental study, Stewart et al. (1974) exposed human volunteers to Otto fuel II in a controlled-environment chamber. The PGDN exposure concentrations were 0, 0.03, 0.1, 0.2 (0.21-0.26), 0.35 (0.33-0.37), 0.5, or 1.5 (1.2-1.5) ppm. Exposures lasted 1-8 h. The Otto fuel II vapor was 99% pure PGDN as measured with infrared analysis. The volunteers were 17 healthy men (22-25 years old) except for one of the exposures that involved two men (45 and 51 years old) and one woman (24 years old) who were members of the research staff. Most of the exposures used three subjects; the range was two to nine. The volunteers underwent a training program in the chamber. The experiments were intended to be double blind to control for bias; however, when the odor of PGDN was detectable, the subjects and the research staff were aware of its presence. The exposures at 0.2 ppm were repeated daily for 5 days. Observations of the volunteers included subjective evaluations (such as for headache and eye irritation) and observation for physiologic and CNS responses under medical supervision (VER, audiometry, clinical neurologic evaluation, electroencephalography (EEG), electrocardiography (EKG), pulse rate, pulse rhythm, pulmonary function, hematology, clinical chemistry, Marquette time-estimation test, and Flanagan arithmetic, coordination and inspection

tests). The volunteers were under close medical surveillance for 16 h after exposure.

At 0.03 ppm, one volunteer reported a mild frontal headache after a 1-h exposure; the headache cleared within 1 h. The same person consistently reported a headache during control exposures. No headaches were reported by three volunteers exposed to PGDN at 0.03 ppm for 8 h.

At 0.1 ppm, the person who reported a headache at 0.03 ppm reported a mild frontal headache after a 3-h exposure; a second person reported a headache after a 6-h exposure, and it lasted several hours after exposure. Two volunteers exposed at 0.1 ppm for 8 h reported no headaches. Black coffee was given immediately after exposure to volunteers with headaches and typically ameliorated the headaches.

The lowest concentration at which the odor of PGDN was detected was 0.2 ppm; it was detected at this concentration by four of nine subjects. The ability to detect the odor disappeared within 5 min. Headaches were mild in two of three volunteers during a 2-h exposure. Of the nine volunteers who were exposed at 0.2 ppm for 8 h, three were exposed for 8 h on two occasions, and seven developed headaches of varying intensity. During the 8-h exposures, there were five incidents of mild headache and six of severe headache; one subject reported eye irritation. The VER was minimally altered in most subjects but with no consistent pattern of response. No abnormalities were detected in test performance or physiologic end points at this concentration. Volunteers who were repeatedly exposed at 0.2-0.3 ppm over a 5-day period developed tolerance of the induction of headache; only mild headaches were reported by three of nine subjects on days 2 and 3, by none on day 4, and by one of nine on day 5. However; the alteration in VER that was observed in subjects exposed for 8 h on 1 day was cumulative in subjects exposed 8 h/day for 5 days; on each day, the baseline values were higher than on the day before.

At 0.35 ppm, the three subjects exposed for 2 h developed mild headaches. After an 8-h exposure at 0.35 ppm, one volunteer developed a mild headache, and two developed severe headaches. One subject in the 2-h group developed slight eye irritation that persisted throughout the exposure period but resolved 5 min after exposure. The odor of PGDN was detected by four of nine volunteers but not after 5 min of exposure. The wave form of the VER was altered, particularly in three subjects exposed for 8 h, producing an increase in the peak-to-peak amplitude of the 3-4-5 wave complexes. The authors interpreted the changes as consistent with the VER changes produced by CNS depression.

At 0.5 ppm, one of three volunteers developed a mild headache during a 1-h exposure; at 2 h, two volunteers reported mild headaches, and one reported a severe headache. By 7.3 h, all three volunteers reported severe headaches. Three members of the research staff exposed at that concentration for 1.25 h developed mild headaches. After exposure for 6.25 h, balance was impaired in two of three volunteers (heel-to-toe test with eyes closed); at 8 h, all three had abnormal modified Romberg tests (postural stability with eyes closed) and abnormal heel-to-toe tests with their eyes closed. One subject could not perform a normal heel-

to-toe test with his eyes open. The authors compared the equilibrium disturbance with ethanol intoxication. The three volunteers with "abnormal neurologic findings also showed a narrowing of their pulse pressure due to a rise in diastolic pressure." The mean increase in diastolic pressure was 12 mmHg and was not accompanied by alterations in heart rate or cardiac rhythm. Headaches were increasingly severe and throbbing in all three volunteers during exposure, and one of the three subjects reported dizziness and nausea after 6 h of exposure. VER changes at 0.5 ppm were similar to those observed at 0.35 ppm.

At 1.5 ppm, the odor of PGDN was immediately apparent to the subjects as they entered the exposure chamber. The intensity of the odor was graded from mild to strong. None of the subjects could detect it after 20 min. Three of eight subjects reported mild eye irritation within 5 min of exposure; all subjects reported eye irritation within 40 min of exposure. Conjunctivitis or excessive lacrimation did not accompany reports of irritation, and the irritation resolved within 5-8 min after exposure. All the volunteers developed severe frontal headaches after 30-90 min of exposure, which caused all exposures to be terminated after 3 h. The headaches after a 3-h exposure were described as nearly incapacitating. The headaches persisted for 1-7.5 h in the absence of continued exposure. As in early exposure scenarios, black coffee consumed after exposure ameliorated the headaches in some subjects. Of the cognitive-coordination tests, only the Flanagan coordination test was considered abnormal while the subjects were experiencing severe headaches. The VER in all volunteers showed a dramatic increase (10-70%) in amplitude in the peak-to-peak voltage of the 3-4-5 complex after 45-90 min of exposure. There was a shift to control values after 160-180 min of exposure, but VER patterns were still altered for 48 h after a 3-h exposure to PGDN.

None of the exposures resulted in changes in hematology, blood nitrate, methemoglobin, clinical chemistry, urinalysis, serum electrolytes, EEG, pulse rate and sinus rhythm, pulmonary function, visual and auditory acuity, EKG during exercise, or time-estimation tests. Only one of the cognitive tests (Flanagan coordination test) was affected by exposure, and the change occurred only in the four subjects exposed at 1.5 ppm while they were experiencing severe headaches.

Occupational and Epidemiologic Studies

Sudden deaths due to circulatory failure have been reported in workers exposed chronically to nitrated esters, such as nitroglycerin and ethylene glycol dinitrate, an analogue of PGDN (Carmichael and Lieben 1963). Sudden deaths in the explosives industry were attributed to compensatory vasospasm that may produce coronary insufficiency on withdrawal from nitrate ester exposure. No deaths attributable to cardiovascular effects were reported in U.S. Navy personnel involved in torpedo-maintenance work, as discussed below.

Horvath et al. (1981) evaluated the neurophysiologic effects—according to medical and occupational history, neuro-ophthalmologic examination, quantitative tests of oculomotor function (saccades or synchronized eye tracking movements), and ataxia—of chronic exposure to PGDN in a population of 87 workers employed in U.S. Navy torpedo-maintenance facilities for an average period of 47.4 months (range, 1-132 months). A control group of 21 workers was used for comparison. A major difference between the exposed and control groups was that the exposed group regularly consumed over twice as much alcohol as the controls. Exposed workers reported symptoms of frequent or occasional headaches (65% of respondents), nasal congestion (31%), eye irritation (26%), and dizziness (13%). Palpitations, dyspnea, chest pain, and loss of balance were reported by small percentages of workers. Results of the tests indicated no evidence of chronic neurotoxicity either in the study population compared with an unexposed control group in the same plant or in a subgroup of 28 workers with the longest exposure to PGDN.

Horvath et al. (1981) also evaluated the acute effects in a subgroup of 29 chronically exposed workers by comparing test values before and after completion of a torpedo-maintenance procedure that lasted 30-60 min. During that time, PGDN concentrations based on multiple grab samples taken in the work area averaged 0.06 ppm (range, 0-0.22 ppm; 88% of values 0.1 ppm or less, 50% of values 0.05 ppm or less, and one sample above 0.2 ppm; Horvath et al. 1981, cited in NRC 2002). There were no decrements in the ataxia tests, and the mean score in one test was increased after exposure. The mean saccade velocity (speed of eye movement) was significantly decreased (by 37.3 deg/s), and the mean saccade delay time (time by which initiation of eye movement in response to a stimulus is delayed) was significantly increased (by 6.4 ms). There were no changes in saccade accuracy or ocular smooth pursuit index. The changes in the saccade test results did not correlate with peak PGDN concentrations measured during the maintenance procedure. The workers involved in the procedure did not complain of headaches or nasal congestion, although one person involved in a spill developed a headache.

Forman et al. (1987) and an earlier report of their work by Helmkamp et al. (1984) evaluated cardiac morbidity in U.S. Navy personnel potentially exposed to PGDN while engaged in torpedo-maintenance work. Cardiovascular events in this group were compared with events in unexposed groups of torpedomen and fire-control technicians. The potentially exposed group consisted of 1,352 men with a yearly average of 822; hospitalization records were available for 1970-1979. The group of unexposed torpedomen consisted of 14,336 people over the 10-year period with a yearly average of 4,906, and the group of unexposed fire-control technicians consisted of 29,129 people with a yearly average of 11,198. Measured concentrations of PGDN included those of the Horvath et al. (1981) study and surveys in the same period in which 8-h time-weighted averages were below 0.05 ppm. Cardiac morbidity included myocardial infarction, angina pectoris, and cardiac arrhythmia, and these were used to calculate relative risk and age-adjusted incidences. There were higher incidences of hospitali-

zation for myocardial infarction and angina pectoris but not cardiac arrhythmia in the potentially exposed group than in either unexposed group. Relative risk was significant for myocardial infarction and angina pectoris compared with the fire-control-technician group but not compared with the torpedomen control group. When incidences of myocardial infarction and angina pectoris were combined, the relative risk was significant compared with the unexposed torpedomen group and the unexposed fire-control-technician group. Cardiovascular deaths occurred in the unexposed groups but not in the group potentially exposed to PGDN. There were few hospitalizations in the study and only four for myocardial infarction and two for angina pectoris in the potentially exposed group over the 10-year period.

Effects in Animals

Acute Toxicity

Rats treated with lethal oral or subcutaneous doses of PGDN were prostrate, anoxic, and cold and had signs of methemoglobinemia and respiratory depression (Clark and Litchfield 1969). At high oral or parenteral doses, deaths from anoxia due to almost complete conversion of hemoglobin to methemoglobin have been observed (ACGIH 1991). Death consistent with anoxia occurred up to 48 h after PGDN administration (Clark and Litchfield 1969). PGDN is a potent vasodilator in animals, inducing a maximal fall in blood pressure usually 30 min after injection (ACGIH 1991). Oral doses of PGDN that were lethal to half the animals ranged from 250 to 1,190 mg/kg in rats (NRC 2002).

Jones et al. (1972) reported deaths in preliminary, range-finding studies in which single animals were exposed to PGDN that was chemically stabilized. An unspecified number of squirrel monkeys exposed to PGDN at about 70-100 ppm for 6 h developed vomiting, pallor, coldness of the extremities, semiconsciousness, and clonic convulsions (Jones et al. 1972). The clinical signs disappeared within 30-45 min after removal from the exposure chambers.

Six rats (strain unknown) that were exposed to PGDN as a mist at 1,350 mg/m^3 for 4 h did not show adverse clinical signs during the exposure or within 14 days after it, although the mean methemoglobin concentration immediately after exposure was 23.5% (Jones et al. 1972).

The potential for PGDN to impair motor activity in animals was investigated as a model of human responses by injecting PGDN into the cerebrospinal fluid of rats (Bogo et al. 1987). Groups of 13-14 anesthetized male Sprague-Dawley rats that had been trained on the accelerod (used to test motor performance) were given injections of saline (control) or 5 or 10 μL of PGDN (0.01 or 0.02 μL/kg; about 0.007 or 0.014 μg/kg) directly into the cisterna magna of the brain. Motor performance was tested 12 min after injection, hourly for 6 h, and at 24 h in rats that had not been grossly traumatized by the injection procedure. No change in motor performance was observed in rats given 5 μL of PGDN

compared with the control group. A significant decrease in motor performance was observed during the first 2 h in rats given 10 μL. The authors suggested that the study confirmed the reported effects of PGDN on human motor performance.

Two male rhesus monkeys trained in free operant avoidance tests were exposed to PGDN at 2-33 ppm and observed for successful completion of the avoidance test and VER (Mattsson et al. 1981). The test used a multiple-avoidance schedule to evaluate performance: the monkeys were subjected to a series of discrete, cued-avoidance trials for 10 min, allowed to rest for 3 min, and then subjected to a 10-min session of free operant avoidance. For the VER, the A-B-C complex, comparable with the 3-4-5 complexes in the Stewart et al. (1974) study, was measured in response to flashes from a strobe light. The monkeys were tested individually, each at several concentrations at 1-week intervals. One monkey was exposed at 2 ppm three times and also at 7 and 20 ppm. The other monkey was exposed at 3, 10, and 33 ppm. Exposure duration was 4 h. Halothane at one-tenth the concentration that produces anesthesia in monkeys served as a reference depressant. Free operant behavior was not affected by any PGDN concentration, but the VER was significantly ($p < 0.05$) altered by exposure to PGDN. The C wave increased by 20% in amplitude at 2 ppm and decreased by 25% at higher concentrations; there were no changes in amplitude of the A and B waves or in the latency of the waveforms. No changes occurred in one of three trials at 2 ppm and in the trial at 10 ppm. During the course of the training, Mattsson et al. found that the C wave could be increased or decreased by 30-40% by changing the environment or the tension of the operant-response lever; therefore, the authors suggested that the changes observed during the exposures might have been caused by the irritating or distracting properties of the vapor. Halothane produced significant increases in the A, B, and C waves and slowed the latency of the B and C waves but did not change free operant avoidance behavior.

Repeated Exposures and Subchronic Toxicity

Inhalation exposure of eight male Sprague-Dawley-derived rats to PGDN at about 10 ppm 7 h/day, 5 days/week for a total of 30 exposures did not result in death or adverse clinical signs (Jones et al. 1972). Weight gain, hematologic values, and histopathologic examinations of heart, lungs, liver, spleen, and kidneys did not reveal adverse effects immediately after exposure (four rats) or 2 weeks later (four additional rats).

Jones et al. (1972) exposed four species of animals—nine male Squirrel monkeys, two male beagles, 15 male and 15 female Sprague-Dawley-derived rats, and 15 male and 15 female Hartley-derived guinea pigs per exposure concentration—to PGDN at 10, 16, or 35 ppm continuously (24 h/day) for 90 days. Equal numbers of control animals were exposed in a similar manner to uncontaminated air in parallel with each exposure concentration. Total leukocytes,

hemoglobin, and microhematocrit were determined before and at the conclusion of exposures. Necropsies were conducted after the last exposures, and tissue sections—heart, lungs, spleen, liver, and kidneys from all species; brain and spinal cord from dogs and monkeys; and adrenal glands from dogs—were examined microscopically. Selected biochemical measures, serum nitrate, and methemoglobin (including samples taken each week from two animals of each species exposed at the highest concentration) were also evaluated.

- At 35 ppm, one monkey died on day 31, possibly because of a complication of an abdominal filarial parasitic *Dipetalonema* infection (although other monkeys showed similar parasite infestation). The remaining monkeys did not show abnormal clinical signs during the exposures. Body-weight gains of surviving animals were normal. Fatty infiltration of the liver was present in monkeys exposed at 10 ppm. Heavy iron-positive deposits, commonly associated with mononuclear-cell infiltrates and focal necrosis, were present in the liver, spleen, and kidneys at 35 ppm. Monkeys exposed at 16 and 35 ppm also had increased serum urea nitrogen and decreased serum alkaline phosphatase. Monkeys exposed at 35 ppm developed methemoglobinemia (methemoglobin concentration, 17%) by day 14, but this declined to about control values by day 42.
- All dogs gained weight at a normal rate. At 35 ppm, hemoglobin and hematocrit were decreased by 63% and 37% in the two dogs. Hemosiderin deposits were observed in the livers of dogs in the 10-ppm group. Hemosiderin deposits and fatty changes were reported in the livers of the 16-ppm group. Heavy hemosiderin deposits and focal necrosis were observed in the livers of dogs in the 35-ppm group. At 35 ppm, iron-positive deposits were observed in the spleen and kidneys. Methemoglobinemia reached 23% on day 14 at 35 ppm; it declined thereafter but did not return to control values.
- Fatty infiltration was observed in the livers of some of the rats exposed at 10 ppm but not at higher concentrations. Female rats, but not male rats, exposed at 35 ppm showed focal necrosis of the liver and acute renal tubular necrosis. Methemoglobin concentrations of two rats exposed at 35 ppm increased to 9.9 and 12.8% on day 14 but decreased with continued exposure (on day 42 methemoglobin concentrations were 2.3 and 7.3 %).
- Fatty infiltration was observed in the livers of some of the guinea pigs exposed at 10 ppm. Guinea pigs exposed at 16 ppm consistently showed foci of pulmonary hemorrhage, and vacuolar changes occurred in the livers of all guinea pigs exposed at 35 ppm. Methemoglobin concentrations increased in two guinea pigs in the 35-ppm group, reaching 4.8 and 9.3 % on day 42.

Three trained male squirrel monkeys were exposed to PGDN continuously for 90 day at 39 ppm (Jones et al. 1972). A fourth trained monkey was exposed to filtered room air under the same conditions and served as the control. The animals were removed from the exposure chambers for a 2-h period once a week

to perform visual-discrimination or visual-acuity threshold tests. The only sign or change in the monkeys during exposure was mydriasis, which increased from slight to moderate. There were no changes in avoidance behavior in the monkeys as determined by the visual tests, and body weight was unaffected by the PGDN exposure.

Pairs of rhesus monkeys were exposed to ambient air or PGDN vapors 23 h/day for 125 days at concentrations that were increased incrementally from 0.3 to 4.2 ppm (Mattsson et al. 1981). Cued or free operant avoidance testing conducted daily showed no effects on either type of avoidance performance. There was no disruption of the ability of the monkeys to discriminate between the two avoidance schedules. The monkeys were tested for a further 16-day period after PGDN exposure and then necropsied. Samples of lungs, liver, spleen, kidneys, and lymph nodes were collected for microscopic analysis; however, no significant gross or microscopic lesions were identified in the samples.

Chronic Toxicity

A 1-year inhalation study (6 h/day, 5 days/week) was conducted to evaluate the carcinogenic potential of Otto fuel II at 0, 0.2, or 36 ppm on the basis of analysis for PGDN (Gaworski et al. 1985). Analysis indicated that the average material composition of the Otto fuel II tested was 74.3 ± 1.2% PGDN, 1.9 ± 0.6% 2-nitrodiphenylamine, and 23.8 ± 1.2% di-*n*-butyl sebacate with a trace contaminant (*o*-chloronitrobenzene) from the manufacture of 2-nitrodiphenylamine. Dogs (three male and three female beagles per group), rats (75 male and 75 female F344 rats per group), and mice (75 male and 75 female C57BL/6 mice per group) were exposed at 0.2 ppm, and 100 male and 100 female rats and mice were exposed at 36 ppm. Dogs were exposed to Otto fuel II for 14 months, and rodents for 12 months. Ten male and 10 female rodents from each exposure group were necropsied after the 1-year exposure, and the remaining animals were held for a 1-year observation period before being necropsied.

Dogs appeared to be the most sensitive species tested, with measurable reductions in red blood cells, hematocrit, and hemoglobin (Gaworski et al. 1985). Decreases in hematocrit and hemoglobin in dogs were evident after only 2 weeks of exposure at 0.2 ppm, and a decrease in red-cell count after 4 weeks of exposure. Reticulocyte counts were also decreased in spite of the reduction in red-cell measures. After a 60-day recovery period, the red-cell changes improved, although reticulocyte counts did not increase. Heinz bodies were not observed in red cells of the dogs. A mild increase in methemoglobin was observed in dogs exposed at 0.2 ppm and rats exposed at 36 ppm. No other significant effects were noted in rats exposed at either concentration. Microscopic examination of tissues collected from dogs, rats, and mice exposed to Otto fuel II did not suggest any significant exposure-related nonneoplastic changes.

Reproductive Toxicity in Males

Litton Bionetics (1979) reported that Otto fuel II was not active in a dominant lethal assay conducted in male mice. No lesions in the reproductive tract of male dogs, rats, or mice were identified in a 1-year inhalation bioassay conducted with Otto fuel II (Gaworski et al. 1985). See the section "Chronic Toxicity" above for details.

Immunotoxicity

No study specifically directed at the immunotoxicity of PGDN has been reported.

Genotoxicity

The genotoxicity of Otto fuel II was evaluated in a series of assays conducted by Litton Bionetics (1979). Otto fuel II was not mutagenic in microbial assays with five strains of *Salmonella typhimurium* or in *Saccharomyces cerevisiae* D4, with or without metabolic activation. It was positive for induction of mutations at the TK locus in L5178Y mouse lymphoma cells at concentrations that were cytotoxic. Otto fuel II did not induce sister-chromatid exchanges in L5178T mouse lymphoma cells, with or without metabolic activation. In a bone marrow cytogenetic analysis in mice in which Otto fuel II was administered acutely and repeatedly (five doses), chromosomal aberrations were not increased compared with the control, but the presence of ring chromosomes suggested weak activity. Otto fuel II was not positive in a dominant lethal assay in mice.

Carcinogenicity

Two-year carcinogenicity studies of PGDN have not been conducted; however, as discussed above in the section "Chronic Toxicity," 1-year inhalation studies with a 1-year follow-up have been conducted with Otto fuel II. In the 1-year inhalation study (6 h/day, 5 days/week), dogs were exposed to PGDN at 0 or 0.2 ppm for 14 months (three males and three females in each of the control and exposed groups), and F-344 rats and C57BL/6 mice were exposed at 0, 0.2, or 36 ppm for 12 months (100 males and 100 females in each of the control and high-concentration groups and 75 of each sex in the low-concentration group) (Gaworski et al 1985). Osteosarcomas were reported in one of the 55 male rats exposed at 0.2 ppm (1.8%) and two of the 85 exposed at 36 ppm (2.4%), and an osteoma was reported in one of the 61 female rats exposed at 0.2 ppm (1.6%). Although bone tumors are considered rare in rats, the low incidence of bone tumors did not fit a dose-response pattern particularly in light of the large differ-

ence in exposure concentrations. Consequently, the bone tumors were not considered to be related to exposure to PGDN as a component of Otto fuel II. No significant tumor incidence was observed in mice exposed to PGDN.

TOXICOKINETIC AND MECHANISTIC CONSIDERATIONS

After exposures of human volunteers to Otto fuel II (99% PGDN vapor) at 1.5 ppm for 1-3 h, the blood concentration of PGDN was less than 5 ppb, the analytic limit of detection (Stewart et al. 1974). A 1-h exposure to Otto fuel II at 1.5 ppm resulted in PGDN at 20-35 ppb in expired breath; no PGDN was detected in breath 15 min after exposure. Those few data suggest that PGDN is likely to be cleared from the blood via exhalation soon after exposure ceases even though headaches persist for longer periods.

PGDN was not detected in the plasma of rhesus monkeys during inhalation exposures at 0.3 ppm for 14 days or after an additional 56 days of exposure at 0.8 ppm (Mattsson et al. 1981). During a later exposure for 20 days at 1.6 ppm, plasma PGDN was about 35 μg/mL. During a final 14-day exposure at 4.2 ppm, plasma PGDN was about 170 μg/mL. PGDN is rapidly cleared from the blood; within 24 h of termination of exposure, it was not detectable.

Dermal absorption of PGDN is also possible because mortality, increased methemoglobin, and increased urinary nitrogen concentrations have been reported in rabbits after repeated applications to skin at 4 g/kg (Jones et al. 1972). About 10% of topically applied PGDN is estimated to be absorbed through the intact skin of rats by 30 min after application (Clark and Litchfield 1969).

According to Kylin et al. (1966, cited in NRC 2002), metabolism of PGDN is rapid and follows first-order kinetics. It is metabolized in the liver and red blood cells. Mononitrates and inorganic nitrate are produced, and the inorganic nitrate is eliminated in urine.

Clark and Litchfield (1969) studied the metabolism of PGDN in vitro and in vivo in Alderley Park rats. PGDN, mononitrates, inorganic nitrite, and inorganic nitrate were detected at various times during both experiments. For the in vivo study, rats received subcutaneous injections of PGDN at 65 mg/kg. PGDN peaked within 30 min of injection and declined to become undetectable by 8-12 h. The primary metabolite detected in the blood was propylene glycol 2-mononitrate, which was metabolized further to inorganic nitrate (56% of administered dose as measured in urine). Excretion was considered complete by 24 h because metabolites were not detected above control values after that point. For the in vitro study, rat blood was incubated with PGDN at 50 μg/mL. At 1 h, 50% of PGDN had been metabolized; 50% of the remainder was metabolized in the next hour. At 3 h, the primary metabolites were propylene glycol 2-mononitrate and inorganic nitrate; small amounts of unmetabolized PGDN, propylene glycol 1-mononitrate, and inorganic nitrite were present. The time courses of in vivo and in vitro metabolism of PGDN were similar.

The proposed metabolism of PGDN involves the reduction of a nitrate group to yield an unstable organic nitrite-nitrate intermediate followed by hydrolysis to yield the mononitrate and inorganic nitrite and oxidation of the latter in the blood to inorganic nitrate, which is excreted in urine (NRC 2002).

At relatively low concentrations, PGDN or its metabolites produce effects on red blood cells, the vasculature, and the CNS in some species of experimental animals. Except in the dog, effects on red blood cells are seen at high exposure concentrations. There are species differences in susceptibility to methemoglobin formation (Wyman et al. 1985). In a series of in vitro assays using blood, hemolysates, and partially purified hemoglobin solutions, formation of methemoglobin was greatest in the dog and less in the guinea pig, followed by the rat; the human was either the least sensitive or as sensitive as the rat. The primary determinant of methemoglobin formation appeared to be the structure of each species' hemoglobin and not the reactivity of blood enzymes. With chronic inhalation exposure to PGDN at 33 ppm, dogs and monkeys were more susceptible to formation of methemoglobin than rats and guinea pigs, the dog being the most susceptible and reaching a peak of about 20% during the second week of continuous inhalation exposure (Jones et al. 1972). In a 1-year inhalation exposure of dogs to PGDN at 0.2 ppm and rats at 36 ppm, similar low concentrations of methemoglobin were induced (Gaworski et al. 1985). After exposure of humans to Otto fuel II, PGDN-induced methemoglobin was not observed in subjects exposed at up to 1.5 ppm for a few hours (Stewart et al. 1974).

PGDN has effects on both the cardiovascular system and the CNS. The most commonly encountered symptom of human exposure to PGDN is headache due to dilation of cerebral blood vessels. Nitrate and nitrite esters are vasodilators and result in rapid lowering of systolic and, to a smaller extent, diastolic blood pressure with compensatory tachycardia. Administration of nitrites produces dilation of meningeal blood vessels (via relaxation of vascular smooth muscle), which is the basis of the transient pulsating headache (Nickerson 1975). Headache of presumed vascular origin is a frequent complaint after administration of therapeutic doses of the structurally similar nitrate triester nitroglycerin for angina. Dilation of the dural arteries is the probable cause of headaches and nasal congestion experienced by torpedo-maintenance workers in the study of Horvath et al. (1981).

Vascular effects after exposure to PGDN have been attributed to the formation of nitric oxide, which is produced either directly from the nitroester or liberated by decomposition of intermediates (Feelisch and Noack 1987). In animal studies, intravenous administration of PGDN has resulted in changes that initially decrease and then increase cerebral blood flow (Godin et al. 1995). Peripheral vasodilation after parenteral administration of PGDN can precipitate a rapid fall in systolic blood pressure (Clark and Litchfield 1969; Godin et al. 1995). However, no drop in blood pressure was observed in rats during a 30- to 45-min exposure to a saturated PGDN vapor generated from Otto fuel II (Godin et al. 1993) or in human volunteers who inhaled PGDN at 0.5 ppm for 7.3 h

(Stewart et al. 1974). Rather, a mean increase in diastolic blood pressure of 12 mmHg was associated with severe and throbbing headaches in human volunteers (Stewart et al. 1974). A drop in blood pressure and decreasing cardiac stroke volume can result in brain ischemia, causing the dizziness and weakness reported by one subject after exposure at 0.5 ppm for 6 h (Stewart et al. 1974) and by occupationally exposed workers (Horvath et al. 1981). Although no deaths or cardiac problems have been reported after exposures to PGDN, workers in the explosives industry have reportedly had cardiovascular events after repeated occupational exposures and depression of systolic and diastolic blood pressure after acute exposures (Carmichael and Lieben 1963). Continued exposure to nitrate esters at low concentrations can narrow the pulse-pressure differential between systole and diastole because of a progressive rise in diastolic blood pressure. When combined with high pulse rate, which occurs after cessation of exposure to nitrate esters, that may contribute to acute myocardial ischemia.

Another mechanistic consideration is that PGDN also acts as a CNS depressant in humans and results in changes in the VER, disturbances in postural balance, and changes in oculomotor performance (Stewart et al. 1974; Horvath et al. 1981). The PGDN concentrations in those studies did not greatly influence cognitive functions, and higher concentrations of PGDN had little or no effect on monkeys trained in avoidance tests (Jones et al. 1972; Mattsson et al. 1981). The mechanism of CNS depression induced by PGDN exposure is poorly understood but may be the same as that of CNS depression induced by volatile anesthetics, such as halothane (Mattsson et al. 1981). Susceptibility of humans to CNS depressants, such as volatile anesthetics, varies by no more than a factor of 2 as indicated by the concentration that produces immobility in 50% of patients (Kennedy and Longnecker 1996, cited in NRC 2002; Marshall and Longnecker 1996, cited in NRC 2002).

NRC (2002) concluded that the adult human population did not appear to be overly susceptible to PGDN on the basis of a literature review. Although laboratory animals are susceptible to methemoglobinemia at high PGDN concentrations, occupational and human experimental studies show that humans are not similarly affected. Those findings are supported by the in vitro studies in which human hemoglobin was shown to be generally less sensitive to formation of methemoglobin on PGDN exposure than that of other animal species. Although one might assume that humans vary widely in their susceptibility to the induction of headaches, Stewart et al. (1974) showed that the concentrations of PGDN at which mild headaches were induced in various subjects were relatively similar for an 8-h exposure (0.1 ppm for the most susceptible person vs 0.21-0.26 ppm for about half the subjects). Severe headaches were induced in all subjects at 1.5 ppm between 30 and 90 min. The data supported a linear relationship between concentration and time for headache induction (that is, n = 1 for the function $C^n \times t = k$, where C = concentration, t = time, and k = constant).

INHALATION EXPOSURE LEVELS FROM THE NATIONAL RESEARCH COUNCIL AND OTHER ORGANIZATIONS

A number of organizations have established or proposed acceptable exposure limits or guidelines for inhaled PGDN. Table 6-2 summarizes selected values.

COMMITTEE RECOMMENDATIONS

The committee's recommendations for EEGL and CEGL values for PGDN are summarized in Table 6-3. The current U.S. Navy values are provided for comparison.

1-Hour EEGL

Human experimental studies were used as the basis of the 1-h EEGL. Acute effects due to exposure to PGDN during maintenance of torpedos that contain Otto fuel II were evaluated in chronically exposed workers by comparing test values before and after completion of a torpedo maintenance procedure that lasted 30-60 min (Horvath et al 1981). None of the effects reported during the study was interpreted as indicating significant impairment during exposure to Otto fuel II. Stewart et al. (1974) exposed primarily young male volunteers to PGDN vapors at various concentrations for 1 h or longer. Three of six volunteers or research staff members who were exposed to PGDN at 0.5 ppm for 1-1.25 h developed mild headache but had no other adverse effects. At 1.5 ppm, eight subjects reported mild eye irritation within 40 min of exposure, which resolved on cessation of exposure. All the volunteers developed severe frontal headaches after only 30-90 min of exposure, so all exposures were terminated after 3 h, at which time the headaches were described as nearly incapacitating. The headaches persisted for 1-7.5 h in the absence of continued exposure. Only the Flanagan coordination test was considered abnormal while the subjects were experiencing severe headaches. The VER in all volunteers showed a dramatic increase (of 10-70%) in amplitude in the peak-to-peak voltage of the 3-4-5 complex after 45-90 min of exposure; the amplitude shifted toward normal after cessation of exposure but was still altered 48 h after exposure.

Those data indicate a threshold after a 1-h exposure to PGDN at 0.5-1.5 ppm for the induction of severe headaches that can be incapacitating and impair function. The available data and the small group used in the study of Stewart et al. (1974) do not allow a more precise definition of the threshold. On the basis of those human data, a point of departure for development of a 1-h EEGL is 0.5 ppm. Exposure at that concentration should avoid induction of severe headaches in naval personnel. Although one of three volunteers developed a mild headache

TABLE 6-2 Selected Inhalation Exposure Levels for Propylene Glycol Dinitrate from the National Research Council and Other Agencies[a]

Organization	Type of Level	Exposure Level (ppm)	Reference
Occupational			
ACGIH	TLV-TWA	0.05	ACGIH 1991
NIOSH	REL-TWA, skin	0.05	NIOSH 2005
General public			
ATSDR	Acute MRL	0.003	ATSDR 2008
	Chronic MRL	0.00004	
NAC/NRC	AEGL-1 (1-h)	0.17	NRC 2002
	AEGL-2 (1-h)	1	
	AEGL-1 (8-h)	0.03	
	AEGL-2 (8-h)	0.13	

[a]Comparability of EEGLs and CEGLs with occupational-exposure and public-health standards or guidance levels is discussed in Chapter 1 ("Comparison with Other Regulatory Standards or Guidance Levels").
Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AEGL, acute exposure guideline level; ATSDR, Agency for Toxic Substances and Disease Registry; MRL, minimal risk level; NAC, National Advisory Committee; NIOSH, National Institute for Occupational Safety and Health; NRC, National Research Council; REL, recommended exposure limit; TLV, Threshold Limit Value; TWA, time-weighted average.

TABLE 6-3 Emergency and Continuous Exposure Guidance Levels for Propylene Glycol Dinitrate

Exposure Level	Current U.S. Navy Values (ppm)	Committee Recommended Values (ppm)
EEGL		
1-h	0.15	0.2
24-h	0.02	0.02
CEGL		
90-day	0.01	0.004

Abbreviations: CEGL, continuous exposure guidance level; EEGL, emergency exposure guidance level.

during a 1-h exposure at 0.5 ppm, the headache was not considered sufficient to impair function. No interspecies or intraspecies uncertainty factors need to be applied because the data are from human exposures and the proposed 1-h EEGL is below the concentration expected to induce severe headaches in 1 h. However,

because so few data on acute human exposures to PGDN are available, an uncertainty factor of 3 is considered appropriate in determining a 1-h EEGL value. Thus, the recommended 1-h EEGL is 0.2 ppm.

24-Hour EEGL

During exposures of healthy male volunteers to PGDN at 0.03 or 0.1 ppm for up to 8 h, mild headaches or no headaches were reported (Stewart et al. 1974). Exposure to PGDN at 0.2 ppm for 8 h resulted in reports of headaches in seven of nine volunteers. According to the data of Stewart et al. (1974), the concentration-time product is about 0.5 ppm-h for mild headaches induced by PGDN and about 1.6 ppm-h for severe headaches (NRC 2002). The concentration-time relationship derived from Stewart et al. (1974) is linear. Thus, the threshold for mild headaches after a 24-h exposure to PGDN is calculated to be 0.02 ppm and for severe headache is 0.07 ppm. Because severe headaches are considered to be incapacitating, a 24-h EEGL of 0.02 ppm is proposed for PGDN. No interspecies or intraspecies uncertainty factors need to be applied because the data are from human exposures and the proposed 24-h EEGL is below the concentration expected to induce severe headaches in 24 h.

90-Day CEGL

The committee considered animal and human data in deriving a 90-day CEGL. In a 1-year inhalation study (6 h/day, 5 days/week) with Otto fuel II, dogs were exposed to PGDN at 0 or 0.2 ppm for 14 months, and F-344 rats and C57BL/6 mice were exposed at 0, 0.2, or 36 ppm for 12 months (Gaworski et al. 1985). Dogs developed changes in red-blood-cell measures (decreased hematocrit and hemoglobin) that were evident after only 2 weeks of exposure and decreased red-blood-cell count after 4 weeks of exposure. Reticulocyte counts were also decreased in spite of the reduction in red-cell measures. After a 60-day recovery period, the changes in red blood cells improved, although reticulocyte counts did not increase. A mild increase in methemoglobin was observed in dogs exposed at 0.2 ppm and rats exposed at 36 ppm. No other significant effects were noted in rats or mice exposed at either concentration. Microscopic examination of tissues collected from dogs, rats, and mice did not suggest any significant exposure-related changes.

No comparable data on human exposures are available for analysis. However, as discussed above, humans exposed to PGDN at 0.1 ppm reported mild headaches and at 0.2 ppm severe headaches (Stewart et al. 1974). Some tolerance of induction of headaches developed with repeated exposure at 0.2 ppm. Changes in VER were duration-related, and this indicates a cumulative effect at 0.2 ppm. Human exposure at 0.5 ppm for 8 h resulted in nausea, dizziness, and

more markedly altered VER. The results are supported by an occupational study of humans (Horvath et al. 1981) and studies of monkeys (Mattsson et al. 1981).

The 1-year dog and acute human studies indicate lowest observed-adverse-effect levels (LOAELs) of PGDN of 0.2 ppm and 0.1 ppm, respectively, and a human acute NOAEL for mild headache of 0.03 ppm (Stewart et al. 1974). Of the species tested for hematologic effects in an in vitro study (Wyman et al. 1985), a 90-day continuous-exposure study (Jones et al. 1972), and a 1-year exposure study (Gaworski et 1985), the dog was the most sensitive for development of red-blood-cell effects due to PGDN exposure. A 90-day CEGL based on hematologic effects in dogs is probably conservative in that in vitro studies indicate that human red blood cells are less sensitive to PGDN than those of the other species tested; however, comparable subchronic-exposure data on humans are not available.

Therefore, in the absence of a NOAEL for subchronic effects of PGDN exposure, a point of departure of 0.2 ppm for development of a 90-day CEGL is proposed on the basis of hematologic effects in dogs exposed 6 h/day, 5 days/week. A value of 10 is used to extrapolate the LOAEL to a NOAEL, and the resulting value is then time-scaled from 6 h/day, 5 days/week to 24 h/day, 7 days/week: (0.2 ppm/10)(6/24)(5/7) = 0.02 ppm × 0.18 = 0.004 ppm. Thus, the recommended 90-day CEGL is 0.004 ppm. No interspecies adjustment factor is considered necessary because the dog is the species most sensitive to hematologic effects of PGDN. And no intraspecies adjustment factor is considered necessary because the available data do not indicate a significant degree of variability among young men exposed to PGDN.

DATA ADEQUACY AND RESEARCH NEEDS

Although there have been short-term human exposure studies and 90-day and chronic animal toxicity studies of PGDN, the short-term and subchronic effects of PGDN are somewhat uncertain. The human data are limited to a study in which volunteers were briefly exposed to PGDN vapors (Stewart et al. 1974). The animal data on PGDN are from inhalation studies (Gaworski et al. 1985; Jones et al. 1972; Mattsson et al. 1981) that did not identify NOAELs for hematologic and male reproductive effects. Acute human PGDN-exposure studies that use more modern imaging techniques for cerebral blood flow and neurologic function are recommended. Depending on the results of the acute human studies, animal inhalation studies to determine NOAELs for neurologic, hematologic, and reproductive effects are recommended.

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Appendix A

Biographic Information on the Committee on Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants

DAVID DORMAN *(Chair)* is associate dean for research and graduate studies in the College of Veterinary Medicine at North Carolina State University. The primary objective of his research is to provide a refined understanding of chemically induced neurotoxicity in laboratory animals that will lead to improved assessment of potential neurotoxicity in humans. Dr. Dorman's research interests include neurotoxicology, nasal toxicology, and pharmacokinetics. He served as a member of the National Research Council Committee on Animal Models for Testing Interventions Against Aerosolized Bioterrorism Agents and the previous Committee on Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants. He received his DVM from Colorado State University. He completed a combined PhD and residency program in toxicology at the University of Illinois at Urbana-Champaign and is a diplomate of the American Board of Veterinary Toxicology and the American Board of Toxicology.

REBECCA BASCOM is a professor of medicine at the Milton S. Hershey Medical Center at Pennsylvania State University. Her expertise includes lung diseases and inhalation toxicology. Dr. Bascom leads the analysis team that is evaluating the cardiorespiratory health effects on New York City police officers exposed during the 9/11 terrorist attack. She has served on three National Research Council committees: the Committee on the Evaluation of the Department of Defense Comprehensive Clinical Evaluation Protocol, the Committee on Occupational Safety and Health in Research Animal Facilities, and the Committee

on Health Effects of Indoor Allergens. Dr. Bascom earned her MD from the University of Oregon Health Sciences Center.

DAROL DODD is a senior research toxicologist and director of the Division of Toxicology and Preclinical Studies at the Hamner Institutes for Health Sciences. From 1990 to 2006, he was the program manager of the Toxic Hazards Research Unit under contract to the Air Force at Wright-Patterson Air Force Base, Ohio. His current primary responsibilities are to lead and coordinate applied toxicology research projects and to support marketing efforts for new business opportunities. His specific expertise is inhalation toxicology. He has more than 25 years of experience in toxicology and health-hazard assessments and is author or co-author of more than 200 scientific journal articles, book chapters, technical reports, and abstracts. He serves on editorial boards of toxicology journals and science committees. Dr. Dodd received his PhD in pharmacology and toxicology from the University of Kansas and is a diplomate of the American Board of Toxicology.

WANDA HASCHEK-HOCK is a veterinary pathologist and professor of comparative pathology at the University of Illinois College of Veterinary Medicine. She has over 30 years of experience in comparative, respiratory, and toxicologic pathology and has over 100 scientific peer-reviewed publications in pathology and toxicology. She has served on editorial boards of toxicology journals and numerous science committees and received the Society of Toxicologic Pathology's Achievement Award in 2007. Her research has focused on the pathophysiology of chemicals and natural environmental toxins with a recent focus on mycotoxins and food safety. Dr. Haschek-Hock received her BVSc (equivalent to a DVM) from the University of Sydney and her PhD from Cornell University. She is a diplomate of the American College of Veterinary Pathologists and the American Board of Toxicology.

JAMES LOCKEY is a professor of environmental health and internal medicine (Pulmonary Division) at the University of Cincinnati College of Medicine. His clinical interests include pulmonary disease, internal medicine, and occupational medicine, but his main research interests are in occupational pulmonary disease. He has been an investigator on a number of human research studies on pulmonary effects of occupational exposure to vermiculite contaminated with asbestiform minerals, on reproductive effects of occupational exposure to solvents, on respiratory morbidity and mortality in workers exposed to refractory ceramic fiber, on obstructive lung disease and diacetyl exposure associated with microwave-popcorn production, and on the relationship of diesel-exhaust exposure and the risk of allergic rhinitis and asthma in young children. He has also served as a member of the National Research Council Subcommittee on Manufactured Vitreous Fibers. Dr. Lockey earned his MD from Temple University.

JOHN MORRIS is the head of the Department of Pharmaceutical Sciences and a professor of pharmacology and toxicology at the University of Connecticut. His professional interests include inhalation toxicology, air pollutants and asthma, risk assessment, and physiologically based pharmacokinetic modeling. He has served on an asbestos committee for the Connecticut Academy of Science and Engineering and was chair of the Connecticut Hazardous Air Pollutant Advisory Panel. Dr. Morris has also served on the editorial boards of *Fundamental and Applied Toxicology, Inhalation Toxicology*, and *Toxicological Sciences*. He earned a PhD in toxicology at the University of Rochester.

JOHN O'DONOGHUE is an adjunct associate professor of environmental medicine at the University of Rochester School of Medicine and Dentistry. He was the director of the Health and Environment Laboratories and vice president for health, safety, and environment at Eastman Kodak Company until his retirement in 2004. His research interests include neurotoxicology and toxicologic pathology. Dr. O'Donoghue has served on several National Research Council committees, including the Committee on Toxicology, the Subcommittee on Toxicological Hazard and Risk Assessment, and the previous Committee on Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants. He received his VMD and PhD from the University of Pennsylvania and is a diplomate of the American Board of Toxicology.

ANDREW SALMON is a senior toxicologist and chief of the Air Toxicology and Risk Assessment Section at the California Environmental Protection Agency (Cal/EPA). Previously, he was a staff toxicologist in the Reproductive and Cancer Hazard Assessment Section of Cal/EPA and a consultant toxicologist with the California Public Health Foundation. He heads a group of toxicologists in Cal/EPA responsible for public-health risk assessments of toxic air contaminants. Dr. Salmon is a member of a number of professional organizations, including the Society of Toxicology, the Society for Risk Analysis, the British Toxicology Society, and the Royal Society of Chemistry. Dr. Salmon earned a PhD in biochemistry from Oxford University, UK.

KATHLEEN THIESSEN is a senior scientist at SENES Oak Ridge, Inc., Center for Risk Analysis. She has extensive experience in evaluating exposures, doses, and risks to human health from environmental contaminants and in the use of uncertainty analysis for environmental and health risk assessment. Dr. Thiessen has led working groups on dose reconstruction and urban remediation for the International Atomic Energy Agency's Biosphere Modelling and Assessment Programme and the Environmental Modelling for Radiation Safety Programme. She has also served as a member of the National Research Council Committee on Toxicologic Risk of Fluoride in Drinking Water. She received her PhD in genetics from the University of Tennessee-Oak Ridge Graduate School of Biomedical Sciences.

JOYCE TSUJI is a principal scientist and director of the Center for Toxicology and Mechanistic Biology in the Health Sciences Practice of Exponent, Inc. She is a board-certified toxicologist and a fellow of the Academy of Toxicological Sciences. She specializes in assessing health and environmental risks associated with chemicals in the environment or from consumer products. She has designed and implemented programs involving exposure assessment, biomonitoring, health education, and exposure intervention for populations with food-chain or environmental exposures. Dr. Tsuji has been recognized as an expert in risk assessment and toxicology in the United States and internationally on assignments for private clients, the U.S. Environmental Protection Agency, the U.S. Department of Justice, the Australian Environmental Protection Agency, and the states of New Jersey and Washington. She is currently serving on the National Research Council Committee on Toxicology and the Standing Committee on Risk Analysis Issues and Reviews, and she has previously served on the Committee on Spacecraft Exposure Guidelines, the Committee on Submarine Escape Action Levels, the first Committee on Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, and the Committee on Copper in Drinking Water. Dr. Tsuji received her PhD from the Department of Zoology with an emphasis in physiology and ecology at the University of Washington.

Appendix B

Statement of Task

A committee of the National Research Council (NRC) will review the U.S. Navy's current and proposed 1-hour and 24-hour emergency exposure guidance levels (EEGLs) and 90-day continuous exposure guidance levels (CEGLs) for selected submarine contaminants. The committee will develop EEGLs and CEGLs for those selected chemicals that do not have existing or proposed levels, where possible. Data gaps will be identified, and recommendations will be made for future research.

Glossary

ACGIH (American Conference of Governmental Industrial Hygienists). ACGIH is a member-based organization and community of professionals that advances worker health and safety through education and the development and dissemination of scientific and technical knowledge. ACGIH publishes exposure guidance values called Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs). Exposures at or below TLVs or BEIs do not create an unreasonable risk of disease or injury. TLVs and BEIs are designed for use by industrial hygienists in making decisions regarding safe levels of exposure to various chemical substances and physical agents found in the workplace.[1]

Acute exposure. An exposure lasting 24 hours or less.[2]

Acute exposure guideline levels (AEGLs). AEGLs "represent threshold exposure limits for the general public and are applicable to emergency exposures ranging from 10 min to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. AEGL-1 is the airborne concentration (expressed as ppm (parts per million) or mg/m^3 (milligrams per cubic meter)) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure. AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which

[1]See http://www.acgih.org for more information.

[2]EPA (U.S. Environmental Protection Agency). 2009. Glossary of IRIS Terms. Integrated Risk Information System, U.S. Environmental Protection Agency. [online]. Available: http://www.epa.gov/IRIS/help_gloss.htm [accessed May 5, 2009].

it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death."[3]

AEGL. *See* acute exposure guideline levels.

Aerosol. "A suspension of liquid or solid particles in a gas."[4]

Alveolar macrophage. "One of the rounded, granular, mononuclear phagocytes within the alveoli of the lungs that ingest inhaled particulate matter."[5]

ATSDR (Agency for Toxic Substances and Disease Registry). The ATSDR is an agency of the Department of Health and Human Services that was created by Congress under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA), commonly known as the Superfund Act. Its mission is to serve the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and disease related to toxic substances. ATSDR defines minimal risk levels (MRLs) for hazardous substances.[6]

CAMS. *See* central atmosphere monitoring system.

CEGL. *See* continuous exposure guidance level.

Ceiling concentration. A concentration that shall not be exceeded during any part of a working day.[7]

Central atmosphere monitoring system (CAMS). CAMS monitors the submarine atmosphere by using an infrared spectrometer to measure carbon monoxide and a fixed-collector mass spectrometer to measure oxygen, nitrogen, carbon dioxide, hydrogen, water vapor, and fluorocarbons 11, 12, and 114.[8]

Chronic exposure. A repeated exposure lasting more than approximately 10%

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[3]NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

[4]Hawley, G.G. 1981. The Condensed Chemical Dictionary, 10th Ed. New York: Van Nostrand Reinhold Company.

[5]Dorland, N. 1988. Dorland's Illustrated Medical Dictionary, 28th ed. Philadelphia, MD: W.B. Saunders Company.

[6]See http://www.atsdr.cdc.gov/ for more information.

[7]29 CFR 1910.1000(a)(1) [online]. Available: http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_id=9991&p_table=STANDARDS [accessed May 5, 2009].

[8]NRC (National Research Council). 1988. Submarine Air Quality. Washington, DC: National Academy Press.

of the lifespan in humans or approximately 90 days to 2 years in laboratory animals.[2]

Continuous exposure guidance level (CEGL). A CEGL is defined as a ceiling concentration designed to prevent any immediate or delayed adverse health effect or degradation in crew performance resulting from a continuous exposure lasting up to 90 days.[9]

EEGL. See emergency exposure guidance level.

Electrostatic precipitator. A system to clear particles and aerosols from air.[8]

Emergency exposure guidance level (EEGL). An EEGL is defined as a ceiling concentration that will not cause irreversible harm or prevent performance of essential tasks, such as closing a hatch or using a fire extinguisher, during a rare emergency situation usually lasting 1-24 hours.[9]

EPA (U.S. Environmental Protection Agency). "The mission of [EPA] is to protect human health and the environment." The agency is responsible for developing and enforcing pertinent environmental regulations, providing grants, studying environmental issues, sponsoring partnerships, and teaching the public about the environment.[10]

Forced expiratory volume at 1 second (FEV_1). FEV_1 is a standard test of lung function. It is the "volume of air that can be forcibly exhaled during the first second of expiration following a maximal inspiration."[2]

Forced vital capacity (FVC). FVC is a standard test of lung function. It is "the maximal volume of air that can be exhaled as forcibly and rapidly as possible after a maximal inspiration."[2]

Fumes. "The particulate, smoke-like emanation from the surface of heated metals. Also, the vapor evolved from concentrated acids (sulfuric, nitric); from evaporating solvents; or as a result of combustion or other decomposition reactions (exhaust fume)."[4]

FVC. *See* forced vital capacity.

Gas. One of the three states of matter, "characterized by very low density and

[9]NRC (National Research Council). 1986. Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-Term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance Level (CEGL) Documents. Washington, DC: National Academy Press.

[10]See http://www.epa.gov/ for more information.

viscosity (relative to liquids and solids); comparatively great expansion and contraction with changes in pressure and temperature; ability to diffuse readily into other gases; and ability to occupy with almost complete uniformity the whole of any container."[4]

IARC (International Agency for Research on Cancer). IARC is an agency of the World Health Organization. IARC's carcinogenicity classifications are as follows:[11]

> Group 1. "The agent is carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in humans."
> Group 2A. "The agent is probably carcinogenic to humans. This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals."
> Group 2B. "The agent is possibly carcinogenic to humans. This category is used for agents for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals."
> Group 3. "The agent is not classifiable as to its carcinogenicity in humans. This category is used most commonly for agents for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals."
> Group 4. "The agent is probably not carcinogenic to humans. This category is used for agents for which there is evidence suggesting lack of carcinogenicity in humans and in experimental animals"

Irritant. A toxicant that exerts deleterious effects by causing inflammation of tissues on contact. Irritants can act on the respiratory system and cause pulmonary edema at high concentrations. At low concentrations, most effects are reversible with cessation of exposure.[12]

Irreversible harm. Permanent damage or injury to health. Emergency exposure guidance levels (EEGLs) are designed to avoid or prevent irreversible harm.[9]

LC_{01}. Statistical determination of the lethal concentration for 1% of the sample population.[12]

LC_{50}. Statistical determination of the lethal concentration for 50% of the sample population.[12]

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[11]IARC (International Agency for Research on Cancer). 2006. Preamble to the IARC Monographs on the Evaluation of Carcinogenic Risk to Humans [online]. Available: http://monographs.iarc.fr/ENG/Preamble/index.php [accessed July 8, 2009].

[12]Hodgson, E., R.B. Mailman, and J.E. Chambers, eds. 1988. Dictionary of Toxicology. New York: Van Nostrand Reinhold Company.

LOAEL. *See* lowest observed-adverse-effect level.

Lowest observed-adverse-effect level (LOAEL). A LOAEL is the "lowest exposure level at which there are [statistically or] biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group."[2]

Minimal risk level (MRL). ATSDR's "estimate of daily human exposure to a hazardous substance at or below which that substance is unlikely to pose a measurable risk of harmful (adverse), noncancerous effects. MRLs are calculated for a route of exposure (inhalation or oral) over a specified time period (acute, intermediate, or chronic)."[13]

MRL. *See* minimal risk level.

NIOSH (National Institute for Occupational Safety and Health). The Occupational Safety and Health Act of 1970 created NIOSH and the Occupational Safety and Health Administration (OSHA). NIOSH is the "federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness." It is part of the Centers for Disease Control and Prevention and the Department of Health and Human Services.[14]

NOAEL. *See* no-observed-adverse-effect level.

NOEL. *See* no-observed-effect level.

No-observed-adverse-effect level (NOAEL). A NOAEL is "the highest exposure level at which there are no [statistically or] biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered as adverse or precursors of adverse effects."[2]

No-observed-effect level (NOEL). "An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control."[2]

OSHA (Occupational Safety and Health Administration). OSHA is an agency of the U.S. Department of Labor. It is authorized to set workplace health and safety standards for a wide variety of physical and chemical hazards and occupational situations. OSHA establishes permissible exposure limits (PELs)

[13]ATSDR (Agency for Toxic Substances and Disease Registry). 2003. ATSDR Glossary of Terms [online]. Available: http://www.atsdr.cdc.gov/glossary.html [accessed May 5, 2009].

[14]See http://www.cdc.gov/niosh/about.html for more information.

for a typical 8-hour workday within a 40-hour workweek and short-term exposure limits (STELs) applicable to a 15-min period within a workday.[15]

PEL. *See* permissible exposure limit.

PEL-TWA. *See* permissible exposure limit.

Permissible exposure limit (PEL). A PEL is a regulatory limit on the amount or concentration of a substance to which a worker may be exposed.[16] The permissible exposure limit–time-weighted average (PEL-TWA) "must not be exceeded during any 8-hour workshift of a 40-hour workweek."[17]

RD_{50}. A statistically estimated concentration resulting in 50% reduction in respiratory rate.[18]

Recommended exposure limit (REL). For NIOSH, a REL is "a time-weighted average concentration [TWA] for up to a 10-hour workday during a 40-hour workweek… ceiling REL should not be exceeded at anytime."[17]

Reference concentration (RfC). "An estimate…of a continuous inhalation exposure to the human population…that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or a benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's non-cancer health assessments."[2]

REL. *See* recommended exposure limit.

Relative risk. The "ratio of the risk of a disease or death among the exposed to that among the unexposed" or the "ratio of the cumulative incidence rate in the exposed to the cumulative incidence rate in the unexposed."[19]

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[15]See http://www.osha.gov/ for more information.

[16]OSHA (Occupational Safety and Health Administration). 2006. Permissible Exposure Limits (PELs) [online]. Available: http://www.osha.gov/SLTC/pel/ [accessed May 5, 2009].

[17]NIOSH (National Institute for Occupational Safety and Health). 2005. NIOSH Pocket Guide to Chemical Hazards. [online]. Available: http://www.cdc.gov/niosh/npg/pgintrod.html [accessed May 5, 2009].

[18]Kuwabara, Y., G. Alexeeff, R. Broadwin, and A. Salmon. 2007. Evaluation and application of the RD_{50} for determining acceptable exposure levels of airborne sensory irritants for the general public. Environ. Health Perspect. 115(11):1609-1616.

[19]IUPAC (International Union of Pure and Applied Chemistry). 1993. Glossary for Chemists of Terms Used in Toxicology. [online]. Available: http://www.sis.nlm.nih.gov/enviro/glossarymain.html [accessed May 5, 2009].

Reversible effect. An injury from which a target tissue or organ can recover or regenerate.[20]

RfC. *See* reference concentration.

SEAL. *See* submarine escape action levels.

Sensory Irritation. Stimulation of trigeminal nerves causing sensations of tickling, itching, or pain in the nose of humans and changes in specific breathing patterns in rodents that consist of a pause at the onset of each expiration.[21]

Short-term exposure limit (STEL). "A 15-minute TWA exposure that should not be exceeded at any time during a workday."[17]

Short-term public emergency guidance levels (SPEGLs). "A suitable concentration for unpredicted, single, short-term, emergency exposures, of the general public."[9]

SMAC. *See* spacecraft maximum allowable concentrations.

Spacecraft maximum allowable concentrations (SMACs). "Short-term SMACs refer to concentrations of airborne substances (such as gas, vapor, or aerosol) that will not compromise the performance of specific tasks during emergency conditions lasting up to 24 hr. Exposure to 1- or 24-hr SMACs will not cause serious or permanent effects but may cause reversible effects that do not impair judgment or interfere with proper responses to emergencies such as fires or accidental releases. Long-term SMACs are intended to avoid adverse health effects (either immediate or delayed) and to avoid degradation in crew performance with continuous exposure in a closed space-station environment for as long as 180 days." SMACs were developed for astronauts (healthy individuals)[22]

SMR. *See* standardized mortality ratio.

SPEGL. *See* short-term public emergency guidance levels.

Standardized mortality ratio (SMR). SMR is a measure of population health.

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[20]Stedman, L.S. 1982. Stedman's Medical Dictionary, 24th Ed. Baltimore, MD: Williams and Wilkins.

[21]Alarie, Y. 1973. Sensory irritation of the upper airways by airborne chemicals. Toxicol. Appl. Pharmacol. 24(2): 279-297.

[22]NRC (National Research Council). 1994. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol.1. Washington, DC: National Academy Press.

It is "the relative measure of the difference in risk between the exposed and unexposed populations in a cohort study. . .This measure is usually standardized to control for any differences in age, sex, and/or race between the exposed and reference populations."[2]

STEL. *See* short-term exposure limit.

Subchronic exposure. Repeated exposures over an intermediate period of time (about 1 to 3 months).[12]

Submarine escape action levels (SEALs). "SEAL 1 is defined as the maximum concentration of a gas in a disabled submarine below which healthy submariners can be exposed for up to 10 days without experiencing reversible health effects. SEAL 2 is defined as the maximum concentration of a gas in a disabled submarine below which healthy submariners can be exposed for up to 24 hours without experiencing irreversible heath effects."[23]

Threshold Limit Value (TLV). A TLV is the "recommended guidelines for occupational exposure to airborne contaminants published by the American Conference of Governmental Industrial Hygienists (ACGIH). TLVs represent the average concentration in mg/m^3 for an 8-hour work day and a 40-hour work week to which nearly all workers may be repeatedly exposed, day after day, without adverse reaction."[2]

Time-weighted average (TWA). A TWA is the average concentration of a regulated chemical to which a worker may be repeatedly exposed during a conventional 8-hour workday and a 40-hour workweek without adverse effect.[17]

TLV. *See* Threshold Limit Value.

TWA. *See* time-weighted average.

UF. *See* uncertainty factor.

Uncertainty factor (UF). A UF (for example, 1, 2, 3, or 10) can be used when deriving human health risk reference values from experimental data to account for inter- or intraspecies differences, database gaps, extrapolations from high to low dose, or other adjustments required. Multiple UFs can be used in a calculation. A UF of 10 is considered to be a health-protective default value to be employed when little is known about a particular source of variability or uncertainty, such as intraspecies differences or lack of information on a relevant

[23]NRC (National Research Council). 2002. Review of Submarine Escape Action Levels for Selected Chemicals. Washington, DC: National Academy Press.

health effect. As additional research becomes available, UFs change as indicated by the new information.[2]

Vent fog precipitator. A system used in the submarine engine room to clear the air of oil mists.[8]

Volatile organic compounds. Volatile organic compounds are "organic compounds that evaporate readily into the air. [They] include substances such as benzene, toluene, methylene chloride, and methyl chloroform."[13]