Acute Exposure Guideline Levels for Selected Airborne Chemicals

Volume 4

Subcommittee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

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[1]This study was planned, overseen, and supported by the Board on Environmental Studies and Toxicology.

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Levels for Hazardous Chemicals (2001)
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Permissible Exposure Levels for Selected Military Fuel Vapors (1996)
Spacecraft Maximum Allowable Concentrations for Selected Airborne
Contaminants, Volume 1 (1994), Volume 2 (1996), Volume 3 (1996),
Volume 4 (2000)

Preface

Extremely hazardous substances (EHSs)[1] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. The people in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways potentially are at risk of being exposed to airborne EHSs during accidental releases. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993.

Using the 1993 NRC guidelines report, the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances —consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation, other federal and state governments, the chemical industry, academe, and other

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[1]As defined pursuant to the Superfund Amendments and Reauthorization Act of 1986.

organizations from the private sector—has developed acute exposure guideline levels (AEGLs) for approximately 80 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology the Subcommittee on Acute Exposure Guideline Levels, which prepared this report. This report is the fourth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the AEGLs for chlorine, hydrogen chloride, hydrogen fluoride, toluene 2,4- and 2,6-diisocyanate, and uranium hexafluoride for scientific accuracy, completeness, and consistency with the NRC guideline reports.

This report was reviewed in draft by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: David H. Moore of Battelle Memorial Institute; Sam Kacew of University of Ottawa; and Rakesh Dixit of Merck and Company, Inc.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Janice E. Chambers of Mississippi State University, appointed by the Division on Earth and Life Studies, who was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The subcommittee gratefully acknowledges the valuable assistance provided by the following people: Ernest Falke and Paul Tobin, EPA; George Rusch, Honeywell, Inc.; Sylvia Talmage, Cheryl Bast, and Carol Wood, Oak Ridge National Laboratory; and Aida Neel, senior project assistant for the Board on Environmental Studies and Toxicology. Kelly Clark edited the report. We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology, for his helpful comments. The subcommittee particularly acknowledges Kulbir Bakshi, project director for

the subcommittee, for bringing the report to completion. Finally, we would like to thank all members of the subcommittee for their expertise and dedicated effort throughout the development of this report.

Daniel Krewski, *Chair*
Subcommittee on Acute Exposure
Guideline Levels

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Committee on Toxicology

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

Volume 4

Introduction

This report is the fourth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals.*

In the Bhopal disaster of 1984, approximately 2,000 residents living near a chemical plant were killed and 20,000 more suffered irreversible damage to their eyes and lungs following accidental release of methyl isocyanate. The toll was particularly high because the community had little idea what chemicals were being used at the plant, how dangerous they might be, and what steps to take in case of emergency. This tragedy served to focus international attention on the need for governments to identify hazardous substances and to assist local communities in planning how to deal with emergency exposures.

In the United States, the Superfund Amendments and Reauthorization Act (SARA) of 1986 required that the U.S. Environmental Protection Agency (EPA) identify extremely hazardous substances (EHSs) and, in cooperation with the Federal Emergency Management Agency and the Department of Transportation, assist Local Emergency Planning Committees (LEPCs) by providing guidance for conducting health-hazard assessments for the development of emergency-response plans for sites where EHSs are produced, stored, transported, or used. SARA also required that the Agency for Toxic Substances and Disease Registry (ATSDR) determine whether chemical substances identified at hazardous waste sites or in the environment present a public-health concern.

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As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health (IDLH) values developed by the National Institute for Occupational Safety and Health (NIOSH) in experimental animals. Although several public and private groups, such as the Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH), have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels but of short duration, usually less than 1 h, and only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a,b, 1987, 1988, 1994, 1996a,b, 2000). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November1995, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC)[1] was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was re-

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[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academe, and other organizations. The roster of NAC is shown on page 8.

placed by "AEGLs" to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) 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. The three AEGLs are defined as follows:

> 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 it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death.

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON
GUIDELINES FOR DEVELOPING AEGLS

As described in the *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NAC guidelines report *Standing Operating Procedures on Acute Exposure Guideline Levels for Hazardous Substances*(NRC 2001), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information available on that chemical. Various types of evidence are assessed in establishing AEGL values for a chemical. They include information from (1) chemical-physical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when available in preference to data from animal studies and in vitro studies. Toxicity data from inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data from animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, the data from the most sensitive animal species are used to set AEGLs. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

For substances that affect several organ systems or have multiple effects, all end points, including reproductive (in both genders), developmental, neurotoxic, respiratory, and other organ-related effects, are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, excess carcinogenic risk is estimated, and the AEGLs corresponding to carcinogenic risks of 1 in 10,000 (1×10^{-4}), 1 in

100,000 (1×10^{-5}), and 1 in 1,000,000 (1×10^{-6}) exposed persons are estimated.

REVIEW OF AEGL REPORTS

As NAC began developing chemical-specific AEGL reports, EPA and DOD asked the NRC to review independently the NAC reports for their scientific validity, completeness, and consistency with the NRC guideline reports (NRC 1993, 2001). The NRC assigned this project to the COT Subcommittee on Acute Exposure Guideline Levels. The subcommittee has expertise in toxicology, epidemiology, pharmacology, medicine, industrial hygiene, biostatistics, risk assessment, and risk communication.

The AEGL draft reports are initially prepared by ad hoc AEGL Development Teams consisting of a chemical manager, two chemical reviewers, and a staff scientist of the NAC contractor—Oak Ridge National Laboratory. The draft documents are then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents are approved by NAC, they are published in the *Federal Register* for public comment. The reports are then revised by NAC in response to the public comments, elevated from "proposed" to "interim" status, and sent to the NRC Subcommittee on Acute Exposure Guideline Levels for final evaluation.

The NRC subcommittee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the subcommittee by the authors of the reports. The NRC subcommittee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001). The revised reports are presented at subsequent meetings until the subcommittee is satisfied with the reviews.

Because of the enormous amount of data presented in the AEGL reports, the NRC subcommittee cannot verify all the data used by NAC. The NRC subcommittee relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGLs reports.

This report is the fourth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. AEGL documents for chlorine, hydrogen chloride, hydrogen fluoride, toluene 2,4- and 2,6-diisocyanate, and uranium hexafluoride are published as an appendix to this report. The subcommittee concludes that the AEGLs developed in those documents are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

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Hydrogen Chloride[1]

Acute Exposure Guideline Levels

SUMMARY

Hydrogen chloride (HCl) is a colorless gas with a pungent, suffocating odor. It is used in the manufacture of organic and inorganic chemicals, oil-well acidizing, steel pickling, food processing, and minerals and metals processing. A large amount of HCl is released from solid rocket fuel exhaust. It is an upper respiratory irritant at relatively low concentrations and may cause damage to the lower respiratory tract at higher concentrations. HCl is very soluble in water, and the aqueous solution is highly corrosive.

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[1]This document was prepared by the AEGL Development Team comprising Cheryl Bast (Oak Ridge National Laboratory) and National Advisory Committee (NAC) for Acute Exposure Guideline Levels for Hazardous Substances member John Hinz (Chemical Manager). The NAC reviewed and revised the document and the AEGL values as deemed necessary. Both the document and the values were then reviewed by the National Research Council (NRC) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concluded that the AEGLs developed in this document are scientifically valid conclusions on the basis of the data reviewed by the NRC and are consistent wit the NRC guidelines reports (NRC 1993, 2001).

The lowest acute exposure guideline level (AEGL) values are based on a 45-minute (min) no-observed-adverse- effect level (NOAEL) of 1.8 parts per million (ppm) in exercising adult asthma patients (Stevens et al. 1992). No uncertainty factors (UFs) were applied for inter- or intraspecies variability because the study population consisted of sensitive humans. The same 1.8-ppm value was applied across the 10- and 30-min and 1-, 4-, and 8-hour (h) exposure times, because mild irritance generally does not vary greatly over time, and because it is not expected that prolonged exposure will result in an enhanced effect.

The AEGL-2 for the 30-min and 1- , 4- , and 8-h time points was based on severe nasal or pulmonary histopathology in rats exposed at 1,300 ppm for 30 min (Stavert et al. 1991). A modifying factor (MF) of 3 was applied to account for the relatively sparse database describing effects defined by AEGL 2. The AEGL-2 values were further adjusted by a total UF of 10—3 for intraspecies variability, supported by the steep concentration- response curve, which implies little individual variability; and 3 for interspecies variability. Using the default value of 10 for interspecies variability would bring the total adjustment to 100 (total UF × MF) instead of 30. That would generate AEGL-2 values that are not supported by the total data set, including data on exercising asthmatic subjects, an especially sensitive subpopulation, because exercise increases HCl uptake and exacerbates irritation; no effects were noted in exercising young adult asthmatic subjects exposed to HCl at 1.8 ppm for 45 min (Stevens et al. 1992). A total UF of 10, accompanied by the MF of 3, is most consistent with the total database (see Section 6.3 for detailed support of uncertainty factors). Thus, the total factor is 30. Time-scaling for the 1-h AEGL exposure period was accomplished using the $C^n \times t = k$ relationship (C = concentration, t = time, and k is a constant), where $n = 1$ based on regression analysis of combined rat and mouse LC_{50} data (concentrations lethal to 50% of subjects) (1 min to 100 min) as reported by ten Berge et al. (1986). The 4- and 8-h AEGL-2 values were derived by applying an MF of 2 to the 1-h AEGL-2 value, because time-scaling would yield a 4-h AEGL-2 of 5.4 ppm and an 8-h AEGL-2 of 2.7 ppm, close to the 1.8 ppm tolerated by exercising asthmatic subjects without adverse health effects. The 10-min AEGL 2 was derived by dividing the mouse RD_{50} (concentration expected to cause a 50% decrease in respiratory rate) of 309 ppm by a factor of 3 to obtain a concentration causing irritation (Barrow 1977). It has been determined that human response to sensory irritants can be predicted on the basis of the mouse RD_{50}. For example, Schaper (1993) has validated the correlation of $0.03 \times RD_{50} =$

TABLE 2-1 Summary of AEGLs Values for Hydrogen Chloride (ppm [mg/m^3])

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)	NOAEL in exercising asthmatic subjects (Stevens et al. 1992)
AEGL-2 (Disabling)	100 (156)	43 (65)	22 (33)	11 (17)	11 (17)	Mouse RD_{50} (Barrow et al. 1977); histopathology in rats (Stavert et al. 1991)
AEGL-3 (Lethal)	620 (937)	210 (313)	100 (155)	26 (39)	26 (39)	Estimated NOEL for death from 1-h rat LC_{50} (Wohlslagel et al. 1976; Vernot et al. 1977)

Abbreviations: LC_{50}, concentration lethal to 50% of subjects; mg/m^3, milligrams per cubic meter; NOAEL, no-observed-adverse-effect level; NOEL, no-observed-effect level; ppm, parts per million; RD_{50}, concentration expected to cause a 50% decrease in respiratory rate.

Threshold Limit Value (TLV) as a value that will prevent sensory irritation in humans. The multiplier 0.03 represents the half-way point between 0.1 and 0.01 on a logarithmic scale, and Alarie (1981) has shown that the RD_{50} multiplied by 0.1 corresponds to "some sensory irritation," while the RD_{50} value itself is considered "intolerable to humans." Thus, it is reasonable that one third of the RD_{50}, a value half-way between 0.1 and 1 on a logarithmic scale, may cause significant irritation to humans. Furthermore, one-third of the mouse RD_{50} for HCl corresponds to an approximate decrease in respiratory rate of 30%, and decreases in the range of 20-50% correspond to moderate irritation (ASTM 1991).

The AEGL-3 values were based on a 1-h rat LC_{50} study (Wohlslagel et al. 1976; Vernot et al. 1977). One-third of the 1-h LC_{50} of 3,124 ppm was

used to estimate a concentration causing no deaths. That estimate is inherently conservative (no deaths were observed in the same study at 1,813 ppm). A total UF of 10 will be applied—3 for intraspecies variation, because the steep concentration-response curve implies limited individual variability; and 3 to protect susceptible individuals. Using a full value of 10 for interspecies variability (total UF of 30) would yield AEGL-3 values that are inconsistent with the overall data set (see Section 7.3 for detailed support of UFs). Thus, the total UF is 10. The value was then time- scaled to the specified 10- and 30- min and 4-h AEGL exposure periods using the $C^n \times t = k$ relationship, where $n = 1$ based on regression analysis of combined rat and mouse LC_{50} data (1 min to 100 min) as reported by ten Berge et al. (1986). The 4-h AEGL-3 value was also adopted as the 8-h AEGL-3 value because of the added uncertainty of time scaling to 8-h using a value of n derived for exposure durations up to 100 min.

1. INTRODUCTION

HCl is a colorless gas with a pungent, suffocating odor. It is hygroscopic and produces whitish fumes in moist air. HCl is produced as a by-product of chemical syntheses of chlorinated compounds and is used in the manufacture of organic and inorganic chemicals, oil-well acidizing, steel pickling, food processing, and the processing of minerals and metals. A large amount of HCl is released from solid rocket fuel exhaust. It is very soluble in water, and the aqueous hydrochloric acid is quite corrosive (EPA 1994). The physicochemical data for hydrogen chloride are shown in Table 2-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

2.1.1. Case Reports

No data concerning human lethality from HCl exposure were located in the available literature.

TABLE 2-2 Physicochemical Data for Hydrogen Chloride

Parameter	Value	Reference
Synonyms	Muriatic acid, hydrochloric acid	AIHA 1989
Chemical formula	HCl	AIHA 1989
Molecular weight	36.47	AIHA 1989
CAS registry no.	7647-01-0	AIHA 1989
Physical state	Colorless, fuming gas	AIHA 1989
Relative density	1.268 at 25°C	AIHA 1989
Boiling/flash point	-85°C/nonflammable	AIHA 1989
Solubility in water	Very soluble (82.3 g/100 ml)	EPA 1994
Conversion factors in air	$1 \text{ mg/m}^3 = 0.67$ ppm 1 ppm = 1.49 mg/m^3	AIHA 1989

2.2. Nonlethal Toxicity

2.2.1. Experimental Studies

Five male and five female adult asthmatic subjects (age 18 to 25 years [y]) were exposed to filtered air or HCl at 0.8 ppm or 1.8 ppm for 45 min (Stevens et al. 1992). Exposure levels were verified by an online filtering system during exposures and analyzed by ion exchange chromatography. Actual mean exposure concentrations were 0, 0.8 ± 0.09, or 1.84 ± 0.21 ppm. The subjects were healthy, except for having asthma, and wore half-face masks to allow for nasal and oral breathing and to control exposure of the eyes. The 45-min exposure sessions consisted of 15 min of exercise (treadmill walking at 2 miles per hour at an elevation grade of 10%) followed by 15 min of rest followed by another 15 min of exercise. Exposures to the test atmospheres were separated by at least 1 week (wk). Subjects rated severity of symptoms before, during, and after exposure on a scale of 1 to 5 (5 being most severe). Symptoms rated included upper respiratory (sore throat and nasal discharge), lower respiratory (cough, chest pain or burning, dyspnea, wheezing), and other (fatigue, headache, dizziness, unusual taste or smell). Pulmonary function measurements were performed while subjects were seated in a pressure-compensated volume-displacement body plethysmograph. The following parameters were measured: total respiratory resistance, thoracic gas volume at functional residual capacity,

forced expiratory volume, forced vital capacity, and maximal flow at 50% and 75% of expired vital capacity. Nasal work of breathing and oral ammonia levels were also measured. No adverse treatment-related effects were observed. There were no treatment-related increases in severity of upper respiratory, lower respiratory, or other symptoms reported by participants. No significant differences were reported between test and control exposures with regard to any of the pulmonary function tests. No treatment-related changes were observed in nasal work of breathing data. Oral ammonia levels showed a significant increase after exposure to both concentrations of HCl but not after exposure to air; the study authors conclude that this finding is counterintuitive and offer no explanation for the observation.

2.2.2. Case Reports

Reactive airways dysfunction syndrome (RADS) is an asthma-like condition that develops after a single exposure to high levels of a chemical irritant. Symptoms occur within minutes to hours after the initial exposure and may persist as nonspecific bronchial hyper-responsiveness for months to years (Bernstein 1993). It was given the name RADS by Brooks et al. (1985) in a retrospective analysis of 10 previously healthy people who had developed persistent airway hyper-reactivity after a single, high-level exposure to a chemical irritant. The acronym then gained acceptance in the medical community (Nemery 1996), because a name had finally been given to a clinical entity that physicians had encountered. Little or no published evidence had been previously available to verify the claim that asthma symptoms could be a consequence of a single inhalation exposure. This syndrome has been described after exposure to HCl. Promisloff et al. (1990) reported RADS in three male police officers (36-45 y old) who responded to a roadside chemical spill. The subjects were exposed to unquantified amounts of sodium hydroxide, silicon tetrachloride, and HCl as a by-product of trichlorosilane hydrolysis; due to the mixture if irritants involved in the release, it is likely that all compounds contributed to the RADS observed after this accident. In another report, Boulet (1988) described the case of a 41-y-old male nonsmoker who had a 6-y history of mild asthma. After cleaning a pool for 1 h with a solution containing hydrochloric acid, he developed a rapidly progressive and severe bronchospasm that was eventually diagnosed as RADS. No exposure concentration was reported. Turlo and Broder (1989) describe a retrospective review of occupational asthma records. A 57-y-old male, with a smoking history of

12 pack-years, had symptoms consistent with RADS after occupational exposure to hydrochloric acid and phosgene. No exposure concentrations were reported.

Other data concerning acute inhalation exposure to HCl in humans are qualitative and dated, making accurate exposure assessment difficult. A summary of those data is presented in Table 2-3.

2.2.3. Epidemiologic Studies

Epidemiologic studies regarding human exposure to HCl were not available.

2.3. Developmental and Reproductive Toxicity

No human developmental or reproductive toxicity data concerning HCl were identified in the available literature.

2.4. Genetic Toxicology

No data concerning the genotoxicity of HCl in humans were identified in the available literature.

2.5. Carcinogenicity

Data concerning carcinogenicity from exposure to HCl are equivocal. A study of U.S. steel-pickling workers showed an excess risk for lung cancer in individuals exposed primarily to hydrochloric acid for at least 6 months (mo) (Beaumont et al. 1987, as cited in IARC 1992). However, no exposure concentrations were available and the subjects had also been exposed to mists of other acids. In a follow-up of the same cohort, Steenland et al. (1988) observed an excess incidence of laryngeal cancer. Again, the data are confounded by possible exposure to other acid gases, including sulfuric acid. In three case-control studies, no association was observed between occupational exposure to HCl and lung (Bond et al. 1986, as cited in IARC 1992), brain (Bond et al. 1983), or kidney (Bond et al. 1985) cancer. In another report, Bond et al. (1991) examined the records of 308 workers who

TABLE 2-3 Inhalation Exposure of Humans to Hydrogen Chloride

Approximate Concentration	Exposure Time	Effect	Reference
0.77 ppm; 1-5 ppm; 10 ppm	Unspecified	Geometric mean of odor thresholds; odor threshold; odor threshold	Amoore and Hautala 1983; Heyroth 1963; Leonard et al. 1969
0.8 ppm and 1.8 ppm	45 min	No effects in exercising asthmatic subjects	Stevens et al. 1992
≥5 ppm	Unspecified	Immediately irritating	Elkins 1959
>10 ppm	Occupational	Highly irritating, although workers develop some tolerance	Elkins 1959
10 ppm	Prolonged	Maximum tolerable	Henderson and Hagard 1943
10-50 ppm	A few hours	Maximum tolerable	Henderson and Hagard 1943
35 ppm	Short	Throat irritation	Henderson and Hagard 1943
50-100 ppm	1 h	Maximum tolerable	Henderson and Hagard 1943
1,000-2,000 ppm	Short	Dangerous	Henderson and Hagard 1943

died of lung, bronchus, or trachea cancer. The workers were divided into groups for exposure duration as follows: <1 y, 1-4.9 y, or >5 y. Exposure concentrations were 0, 0.25, 1.5, or 3.75 ppm. No association was found between HCl exposure and cancer incidence. In a Canadian population-based case-control study, an increased risk for oat cell carcinoma was suggested in workers exposed to hydrochloric acid; however, no excess risk was observed for all types of lung cancer combined or for other histological types of lung cancer individually (Siemiatycki 1991, as cited in IARC 1992).

2.6. Summary

No treatment-related effects were observed in exercising, young adult asthmatic subjects exposed to HCl at 0.8 ppm or 1.8 ppm for 45 min. Reac-

tive airway dysfunction syndrome (RADS) has been described in people exposed to undetermined concentrations of HCl. Data concerning carcinogenicity from exposure to HCl are equivocal and are confounded by occupational exposure to other chemicals. No data concerning genetic toxicology or developmental or reproductive toxicity in humans from HCl exposure were located in the available literature.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Guinea Pigs

Malek and Alarie (1989) observed 100% mortality in exercising guinea pigs exposed to HCl at 586 ppm for approximately 3 min, although no deaths were observed in guinea pigs exposed at 162 ppm for 30 min. Burleigh- Flayer et al. (1985) exposed guinea pigs to HCl at 320, 680, 1,040, or 1,380 ppm for 30 min. Mortality was as follows: 2/8 during exposure at 1,380 ppm; 1/8 following exposure at 1,380 ppm; and 2/8 following exposure at 1,040 ppm. These studies describe both lethal and nonlethal effects and are described in detail in Section 3.2.2.

No mortality was observed in guinea pigs (unspecified strain) exposed to HCl at 3,667 ppm for 5 min; however, at 4,333 ppm for 30 min or 667 ppm for 2 to 6 h, 100% mortality was observed (Machle et al. 1942).

3.1.2. Rats and Mice

Darmer et al. (1974) examined the acute toxicity of HCl vapor or aerosol in groups of 10 male Sprague-Dawley rats exposed to HCl at 410-30,000 ppm and groups of 10 male ICR mice exposed to HCl at 2,100-57,000 ppm for 5 or 30 min. HCl concentrations were monitored continuously during exposures, and chloride ion specific electrode analysis was utilized to determine actual concentrations. Particle size distribution was analyzed for aerosol generation. Animals were observed for 7 d post-exposure. Examination of animals dying during exposure revealed moderate to severe gross changes in the lungs and upper respiratory tract. Badly damaged nasal and tracheal epithelium, moderate to severe alveolar emphysema, atelectasis, and spotting of the lung were noted at necropsy. Survivors at the higher concentrations exhibited a clicking breathing noise, difficulty

TABLE 2-4 LC_{50} Values for Hydrogen Chloride Vapor and Aerosol in Rats and Mice (ppm)

Species	10-min LC_{50} Values		30-min LC_{50} Values	
	Vapor	Aerosol	Vapor	Aerosol
Rat	41,000	31,000	4,700	5,600
Mouse	13,700	11,200	2,600	2,100

Source: Darmer et al. 1974.

breathing, and bloody discharge from the nares. The authors conclude that there is no differential toxicity between the vapor and aerosol. Mice appear to be more sensitive than rats to the acute inhalation toxicity of HCl. LC_{50} values are presented in Table 2-4 (above).

Wohlslagel et al. (1976) also examined the acute toxicity of HCl in rats and mice (data are also reported in Vernot et al. 1977). Groups of 10 male CFE (Sprague-Dawley derived) rats and groups of 10 female CF-1 (ICR derived) mice were exposed to HCl vapor for 60 min. HCl concentrations were continuously monitored during exposures by specific ion analysis. Toxic signs observed during exposure included increased grooming and irritation of the eyes, mucous membranes, and exposed skin. By the end of the exposure period, rapid, shallow breathing and yellow-green fur discoloration were observed. Necropsy of animals that died during or after exposure revealed pulmonary congestion and intestinal hemorrhage in both species. Rats also showed thymic hemorrhages. Calculated LC_{50} values were 3,124 ppm for rats and 1,108 ppm for mice. As was also reported in the Darmer (1974) study, mice appear to be more sensitive than rats to the acute inhalation toxicity of HCl. Data are summarized in Table 2-5.

Higgins et al. (1972) also compared HCl toxicity in rats and mice. Groups of 10 Wistar rats and 15 ICR mice were exposed to various concentrations of HCl vapors for 5 min. HCl concentrations were monitored continuously during exposures via specific ion electrode analysis. Again, data suggest that mice are more sensitive to the lethal effects of HCl than are rats. Data are summarized in Table 2-6.

Buckley et al. (1984) exposed groups of 16-24 male Swiss-Webster mice (25-30 g) to HCl at 309 ppm (RD_{50}) 6 h/day (d) for 3 d. HCl concentrations were analyzed at least once per hour during exposures using infrared spectrometry. All mice were moribund or had died after the three exposures. Exfoliation, erosion, ulceration, and necrosis of the respiratory epithelium were observed.

TABLE 2-5 Mortality in Rats and Mice Exposed to Hydrogen Chloride for 60 Min

Rats		Mice	
Concentration (ppm)	Mortality	Concentration (ppm)	Mortality
1,813	0/10	557	2/10
2,585	2/10	985	3/10
3,274	6/10	1,387	6/10
3,941	8/10	1,902	8/10
4,455	10/10	2,476	10/10
LC_{50} (95% CI) = 3,124 ppm (2,829-3,450)		LC_{50} (95% CI) = 1,108 ppm (874-1,404)	

Abbreviation: CI, confidence interval.
Sources: Wohlslagel et al. 1976; Vernot et al. 1977.

In another study, Anderson and Alarie (1980) reported a 30-min LC_{50} value of 10,137 ppm for normal mice and a value of 1,095 ppm for trachea-cannulated mice.

3.1.3. Rabbits

No mortality was observed in rabbits (unspecified strain) exposed to HCl at 3,667 ppm for 5 min; however, at 4,333 ppm for 30 min or 667 ppm for 2 to 6 h, 100% mortality was observed (Machle et al. 1942).

3.2. Nonlethal Toxicity

3.2.1. Nonhuman Primates

Kaplan (1985) exposed juvenile male baboons (1 per concentration) to HCl at 190, 810, 2,780, 11,400, 16,570, or 17,290 ppm for 5 min. HCl exposure concentrations were continuously monitored using a "modified French standard test method." This method is based on continuous titration of the chloride ion with silver nitrate. The animals had been trained to perform an escape test. Escape was observed at 11,400 ppm and 17,290 ppm, and avoidance was observed at all other concentrations. The author

TABLE 2-6 Mortality in Rats and Mice Exposed to Hydrogen Chloride for 5 Min

Rats		Mice	
Concentration (ppm)	Mortality (%)	Concentration (ppm)	Mortality (%)
30,000	0	3,200	7
32,000	10	5,060	7
39,800	60	6,145	13
45,200	70	6,410	0
57,290	90	7,525	40
		8,065	13
		9,276	33
		13,655	40
		26,485	87
		30,000	87
LC_{50} (95% CI) = 40,989 ppm (34,803-48,272)		LC_{50} (95% CI) = 13,745 ppm (10,333-18,283)	

Abbreviation: CI, confidence interval.
Source: Higgins et al. 1972.

attributed these responses to irritation from the HCl exposure. No effects were noted at 190 ppm. Coughing and frothing at the mouth were observed in the animal exposed at 810 ppm, and shaking of the head, rubbing of the eyes, profuse salivation, and blinking were observed in animals exposed at higher concentrations. The baboons exposed to HCl at 16,570 ppm and 17,290 ppm died from bacterial infections several weeks after exposure. Necropsy indicated pneumonia, pulmonary edema, and tracheitis accompanied by epithelial erosion. In another study, Kaplan et al. (1988) exposed groups of three ketamine-anesthetized male baboons to HCl at target concentrations of 0, 500, 5,000, or 10,000 ppm for 15 min and observed for 3 mo. Exposures were accomplished in head boxes. HCl exposure concentrations were continuously monitored using a "modified French standard test method." Respiratory rates during exposure were increased approximately 30%, 50%, and 100% for the 500-, 5,000-, and 10,000-ppm groups, respectively. Arterial blood gas decreased 40% during the 15-min exposure at 5,000 ppm and 10,000 ppm, persisted for 10 min following exposure, and

returned to baseline values by 3 d post-exposure. The increased respiratory rates were attributed to a compensatory response to the decrease in arterial oxygen, which in turn was attributed to upper airway broncho-constriction. No difference in pulmonary function or CO_2 challenge response tests was observed 3 d or 3 mo post-exposure when compared with baseline values. In a follow-up report (Kaplan et al. 1993a), no exposure-related differences in pulmonary function or CO_2 challenge response tests were reported 6 or 12 mo post-exposure, with the exceptions of respiratory rate at 5,000 ppm and 10,000 ppm, tidal volume at 5,000 ppm, and minute volume at 5,000 ppm and 10,000 ppm. Histopathologic examination was performed 12 mo post-exposure on one control animal, three animals in the 5,000-ppm group, and three animals in the 10,000-ppm group. One high-concentration animal exhibited pulmonary hemorrhage, edema, fibrosis, and bronchiolitis in the median right lung lobe. In another animal in the 10,000-ppm group, zonal atelectasis and focal multiple hemorrhages were observed in the right lung lobe. Focal, patchy hemorrhages were also observed in the three animals in the 5,000- ppm group as well as in the control group.

3.2.2. Guinea Pigs

Outbred English short-haired male guinea pigs (2-4 per group, weight 325-400 g) were exposed to HCl at 0, 107, 140, 162, or 586 ppm while exercising on a wheel (Malek and Alarie1989). Actual HCl concentrations were determined by sampling from a port just above the head of the running animal. Impingers containing 0.1 N sodium hydroxide were utilized. Animals had been exercising on the wheel for 10 min prior to the start of HCl exposure. Animals were exposed for 30 min or until incapacitation occurred. The 107-ppm group showed signs of mild irritation, while the other groups exhibited coughing and gasping prior to incapacitation. Summary data are presented in Table 2-7.

These data are in apparent conflict with other guinea pig data. For example, no deaths were observed after exposure to HCl at 500 ppm for 15 min, and three of six guinea pigs died after exposure at 4,200 ppm for 15 min (Kaplan et al. 1993b).

In another study, Burleigh-Flayer et al. (1985) exposed groups of male English smooth-haired guinea pigs (4-8 per group, weight 330-450 g) to HCl at 320, 680, 1,040, or 1,380 ppm for 30 min. HCl concentrations were measured colorimetrically. Sensory irritation was defined as decreased respiratory rate and a prolonged expiratory phase, and respiratory irritation

TABLE 2-7 Summary Data for Guinea Pigs Exposed to Hydrogen
Chloride During Exercise

Concentration (ppm)	Number	% Incapacitated	Time to Incapacitation (min)	% Mortality
107 ± 26	3	0	NA	0
140 ± 5	3	100	16.5 ± 8.6	0
162 ± 0	2	100	1.3 ± 0.9	0
586 ± 51	4	100	0.65 ± 0.08	100[a]

[a]Time to death was 2.8 ± 0.8 min.
Abbreviation: NA, not applicable.
Source: Malek and Alarie 1989.

was defined as initial increased respiratory rate followed by a decrease due
to a pause following each expiration. Sensory irritation was observed al-
most immediately in animals exposed at 680, 1,040, and 1,380 ppm, and
appeared after 6 min of exposure in the 320-ppm group. Sensory irritation
was replaced by pulmonary irritation in a concentration-related manner as
sufficient HCl reached the deeper lung tissue. Time to onset of pulmonary
irritation was approximately 18, 12, 7, and 3.5 min for the 320-, 680-,
1,040-, and 1,380-ppm groups, respectively. Corneal opacity was observed
in one of four survivors from the 680-ppm group, five of five survivors
from the 1,380-ppm group, and four of six from the 1,040-ppm group; no
opacity was observed in the 320-ppm group. Histologic examination of the
lungs was performed only on animals exposed at 1,040 ppm. Alveolitis
accompanied by congestion and hemorrhage was observed 2 d post-expo-
sure, and inflammation, hyperplasia, and mild bronchitis were observed 15
d post-exposure.

   Kaplan et al. (1993b) exposed groups of six male English smooth-
haired guinea pigs to HCl at 0, 500, or 4,200 ppm (nominal concentration)
for 15 min. (Actual concentrations were 0, 520, or 3,940 ppm.) Exposure
at 500 or 4,200 ppm caused a 20% decrease in respiratory frequency accom-
panied by a compensatory 2-fold increase in transpulmonary pressure.
Exposure at 500 ppm had little effect on blood gases or arterial pH. Expo-
sure at 4,200 ppm also had little effect on blood gases; however, a decrease
in arterial pH was observed in exposed animals when compared with con-
trol animals. Necropsy performed 90 d post-exposure revealed lymphoid

hyperplasia of the nasal mucosa and lungs and hemorrhage of the lungs in both control animals and animals exposed at 500 ppm. Exposure at 4,200 ppm resulted in the deaths of three guinea pigs at 2 min, 2.5 min, and 27 d post-exposure, respectively. Necropsy of those decedents showed pulmonary congestion, severe congestion of the nasal turbinates, severe tracheitis, and desquamation of bronchiolar epithelia. In the three guinea pigs of the 4,200-ppm exposure group necropsied 90 d post-exposure, cloudy corneas, focal hemorrhage, focal pneumonia, esophageal hyperkeratosis, atelectasis, and pulmonary lymphoid hyperplasia were observed.

3.2.3. Rats

Groups of three adult male Sprague-Dawley rats were exposed head-only to HCl at 200, 295, 784, 1,006, or 1,538 ppm for 30 min (Hartzell et al. 1985). Concentration-related decreases in respiratory frequency ranging from 35% to 67% were observed starting at approximately 2 min into the exposure period. Concentration-related decreases in minute-volume ranging from 30% to 69% were also observed.

Groups of eight male Fischer-344 rats were exposed to filtered air or HCl at 1,300 ppm for 30 min (Stavert et al. 1991). HCl concentrations were determined a minimum of three times per exposure using ion-specific electrodes. Each treatment had a nose-breathing group and a mouth-breathing group. Animals were sacrificed 24 h post-exposure. Nose-breathing rats exposed to HCl (actual concentration 1,293 ± 36 ppm) exhibited severe, necrotizing rhinitis, turbinate necrosis, thrombosis of nasal submucosa vessels, and pseudomembrane formation in the anterior portion of the nasal cavity. No effects were observed in the lungs of nose-breathers. Nasal cavities of mouth-breathers exposed to HCl (actual concentration 1,295 ± 25 ppm) were essentially unaffected; however, severe, ulcerative tracheitis accompanied by necrosis and luminal ulceration was observed. Polymorphonuclear leukocytes were observed in the submucosa between tracheal rings, in connective tissue around the trachea, and in alveoli surrounding terminal bronchioles in the mouth-breathers.

Kaplan et al. (1993b) exposed groups of six female Sprague-Dawley rats to HCl at 0 or 4,200 ppm (nominal concentration) for 15 min. (Actual concentrations were 0 or 3,890 ppm.) Exposure at 3,890 ppm caused a 40% decrease in respiratory frequency accompanied by a compensatory 1.2-fold increase in arterial pressure. Exposure at 3,890 ppm also caused a decrease

in arterial pH, an increase in $PaCO_2$ values, and a transient decrease in PaO_2 values when compared with control animals. Necropsy performed 90 d post-exposure revealed microphthalmia in four rats and minimal focal atelectasis in one lobe of the lungs of two animals exposed at 3,890 ppm. Minimal focal atelectasis was also observed in two control animals.

3.2.4. Mice

Barrow et al. (1977) exposed groups of male Swiss-Webster mice (25-30 grams [g]) to HCl at concentrations ranging from 40 ppm to 943 ppm for 10 min. HCl concentrations were determined continuously using ion-specific electrodes. An RD_{50} of 309 ppm was defined.

In another study, Barrow et al. (1979) exposed groups of four male Swiss-Webster mice (25-30 g) to HCl at concentrations ranging from 20 ppm to 20,000 ppm for 10 min. Twenty-four hours after exposure, the mice were sacrificed by cervical dislocation. Precise individual group concentrations were not presented in the report. A decreased respiratory frequency, indicative of sensory irritation, was observed in animals exposed at >50 ppm. Deaths were observed in two of four mice exposed at 8,000 ppm and in four of four mice exposed at 19,300 ppm. Polymorphonuclear leukocyte infiltration of the conjunctiva was observed in animals exposed at 480 ppm, corneal necrosis was observed at 700 ppm, and ocular globe damage was observed at 3,000 ppm. Nasal epithelium ulceration was observed in the 120-ppm group, necrosis and damage to nasal bones in the 700-ppm group, and complete destruction of the nasal bones in the 7,000-ppm group.

Male Swiss-Webster mice were exposed to HCl at concentrations ranging from 17 ppm to 7,279 ppm for 10 min (Lucia et al. 1977). HCl concentrations were determined continuously using ion-specific electrodes. Animals were sacrificed 24 h post-exposure, and the upper respiratory tract was examined histologically. Small superficial ulcerations were observed in the respiratory epithelium at the junction with the squamous epithelium at 17 ppm. As HCl concentrations increased, the ulceration increased until it extended up the sides and into the nasal septum. The lower two-thirds of the upper respiratory tract was damaged at 723 ppm, and the entire mucosa was destroyed at 1,973 ppm. The squamous epithelium of the external nares was destroyed at 493 ppm, and the external support structures were destroyed at 1,088 ppm. Total destruction of mucosa and support structures as well as total destruction of the eyes was observed at 7,279 ppm.

Kaplan et al. (1993b) exposed groups of six male ICR mice to HCl at 0, 500, or 2,500 ppm (nominal concentration) for 15 min. (Actual concentrations were 0, 475, or 2,550 ppm.) Exposure to HCl at 475 ppm and 2,550 ppm caused 10% and 40% decreases in respiratory frequency, respectively, that were accompanied by compensatory increases in pressure. Four mice exposed at 475 ppm died within 90 d post-exposure, and all mice exposed at 2,550 ppm died by day 14 post-exposure. No histopathologic abnormalities were observed in controls or in mice exposed at 475 ppm. Moderate to severe lung congestion, necrosis of the tracheal mucosa, paranasal sinus exudate, and moderate lung edema were observed in animals exposed to HCl at 2,550 ppm. Results from this study are in apparent conflict with several other reported studies. For example, Darmer et al. (1974) reported a 5-min mouse LC_{50} of 13,700 ppm and a 30-min LC_{50} of 2,600 ppm, and Wholslagel et al. (1976) and Vernot et al. (1971) reported a 1-h LC_{50} of 1,108 ppm.

3.3. Developmental and Reproductive Toxicity

Female Wistar rats were exposed to HCl at 302 ppm for 1 h either 12 d prior to mating or on day 9 of gestation (Pavlova 1976). No information concerning test atmosphere concentration analysis was reported. One-third of the animals died, and dyspnea and cyanosis were observed. Congestion, edema, and hemorrhage were observed in the lungs of animals that died. Fetal mortality was higher (p < 0.05) in rats exposed during pregnancy and was possibly secondary to severe maternal effects. When female Wistar and mixed-strain rats were exposed to HCl at 302 ppm for 1 h prior to mating, 30% of the Wistar rats and 20% of the mixed-strain rats died from the exposure. In animals surviving 6 d, decreased blood oxygen saturation was observed as well as kidney, liver, and spleen damage. Treatment also altered the estrous cycle. In rats mated 12-16 d post-exposure and sacrificed on day 21 of gestation, increased fetal mortality, decreased fetal weight, and increased relative fetal lung weight were observed.

3.4. Genetic Toxicology

Genotoxicity results for HCl are equivocal. At a concentration of 25 μg/well, it was positive in a DNA repair assay in *E. Coli*, and it induced

chromosomal nondisjunction in *D. melanogaster* at 100 ppm for 24 h. However, negative results were obtained in a Syrian hamster embryo cell transformation assay and in an adenovirus SA7 assay (NTIS 2000).

3.5. Carcinogenicity

Rats exposed to HCl at 10 ppm for 6 h/d, 5 d/wk for life developed increased incidences of tracheal and laryngeal hyperplasia compared with controls; however, no increase in the incidence of cancerous lesions was observed over controls (Sellakumar et al. 1985). Male Sprague-Dawley rats exposed at 10.2 ppm for 6 h/d, 5 d/wk for 382 exposures over a 588-d period did not show an increased incidence of nasal tumors (Albert et al. 1982).

3.6. Summary

HCl is a sensory and respiratory irritant and causes changes in the upper respiratory tract at relatively low concentrations and short exposure times. As concentrations and exposure times increase, effects progress to the lower respiratory tract and may involve pulmonary edema and histopathologic changes. There appears to be no differential toxicity between HCl vapor and aerosol, and mice appear to be more sensitive than rats to the effects of HCl. Exposure at 190 ppm for 5 min was the no-effect level in baboons, while those exposed at 16,570 ppm and 17,290 ppm exhibited pulmonary edema, pneumonia, and died from bacterial infections weeks after exposure. Mild irritation was observed in guinea pigs exposed at 107 ppm for 30 min, and guinea pigs exposed at concentrations ranging from 140 ppm to 586 ppm exhibited gasping prior to incapacitation and/or death. Exercising guinea pigs exposed to HCl at 320-1,380 ppm for 30 min exhibited a continuum of effects from sensory irritation to pulmonary irritation to death. Nose-breathing rats exposed to HCl exhibited severe nasal pathology, and similarly exposed mouth-breathing rats showed tracheal pathology. Several studies in mice also confirm the progression of effects from sensory irritation to lower respiratory tract involvement.

Fetal mortality was higher in rats exposed to HCl during pregnancy and 12-16 d prior to mating than it was in unexposed rats; however, no validation of exposure concentrations was provided. No data concerning the genotoxicity of HCl were located. In two lifetime studies, there was no increase in the incidence of cancerous lesions in rats exposed to HCl.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Information concerning the metabolism and disposition of hydrogen chloride (HCl) is sparse. HCl is not metabolized; however, hydrogen and chloride ions adsorbed in the respiratory tract may be distributed throughout the body (NRC 2000).

4.2. Mechanism of Toxicity

HCl is a respiratory irritant and is corrosive. When inhaled, it solubilizes in mucous present in the nasal passages, and when the scrubbing mechanism of the upper respiratory tract is saturated, it may enter the lower respiratory tract (NRC 1991). At a molecular level, HCl dissociates in water to form hydronium and chloride ions. The hydronium ion is a proton donor. It could catalyze cleavage of organic molecules and be involved in hydroxylation of carbonyl groups and polymerization and depolymerization of organic molecules (EPA 1994).

4.3. Structure-Activity Relationships

Although the AEGL values for HCl are based on empirical toxicity data, it is important to consider the relative toxicities of HCl and other structurally similar chemicals. The compounds most closely related to HCl are other hydrogen halides, HF and HBr. It might be anticipated that relationships exist in this chemical class between structure and respective toxicities in animals and humans. However, because of differences in size and electron configuration in the various halogen atoms, substantial differences exist with respect to their chemical and physical properties, which in turn are responsible for their toxicologic properties. That is particularly true in the case of acutely toxic effects resulting from inhalation exposure.

For example, HCl has a considerably higher ionization constant than HF, and is therefore classified as a stronger acid than HF. Consequently, higher concentrations of proton-donor hydronium ions are generated from HCl in aqueous solutions under the same conditions. The protons readily react with cells and tissues, resulting in HCl's irritant and corrosive properties. On the other hand, the fluoride ion from dissociated HF is a strong nucleophile or Lewis base that is highly reactive with various organic and

inorganic electrophiles (biologically important substances), also resulting in irritation and tissue damage.

In addition to differences in chemical properties, difference in water solubility might be a significant factor in the acute inhalation toxicity of these substances. HF and HBr are characterized as infinitely and freely soluble in water, respectively, but the solubility of HCl, although still high, is lower (67 g/100 g of water at 30 C) (Budavari et al. 1989). Thus, it is likely that HF is more effectively scrubbed in the nasal cavity than HCl, resulting in less penetration to the lungs and less severe toxicity. The effectiveness of the scrubbing mechanism was demonstrated in a study that addressed the acute toxicities of HF, HCl, and HBr and the deposition (scrubbing) of those chemicals in the nasal passages. Stavert et al. (1991) exposed male Fischer-344 rats to each of the hydrogen halides at 1,300 ppm for 30 min and assessed damage to the respiratory tract 24 h after the exposure. The nasal cavity was divided into four regions and examined microscopically. For all three hydrogen halides, tissue injury was confined to the nasal cavity. Tissue injury in the nasal cavity was similar following exposures to HF and HCl and involved moderate to severe fibrinonecrotic rhinitis in nasal region 1 (most anterior region). For HF and HCl, the lesions extended into region 2, but regions 3 and 4 were essentially normal in appearance, as was the trachea. Nasal cavity lesions following exposure to HBr were limited to region 1 and were similar in extent to those produced by HF and HCl, showing that all three chemicals are well scrubbed. No lung or tracheal injury was evident for any of the chemicals, although accumulations of inflammatory cells and exudates in the trachea and lungs following exposure to HCl indicated that HCl may not be as well scrubbed in the nasal passages as HF and HBr. However, that possibility is modified by the authors' observation of lower minute-volumes in the HF- and HBr-exposed rats, so that greater amounts of HCl were inhaled. Morris and Smith (1982) also showed that at concentrations up to 226 ppm, >99.7% of inspired HF might be scrubbed in the upper respiratory tract of the rat.

In a series of experiments with HF and HCl that used guinea pigs and rabbits as the test species, Machle and coworkers (Machle and Kitzmiller 1935; Machle et al. 1934, 1942) concluded that the acute irritant effects of HF and HCl were similar, but the systemic effects of HF were more severe, presumably because chloride ion is a normal electrolyte in the body, and fluoride ion is not. However, the conclusions involving systemic effects followed repeated exposures.

Aside from lethality studies, no clear evidence is available to establish the relative toxicities of HCl and HF. At concentrations ranging from 100 ppm to 1,000 ppm for 30 min, Kusewitt et al. (1989) reported epithelial and

submucosal necrosis, accumulation of inflammatory cells and exudates, and extravasation of erythrocytes in the nasal region of rats exposed to HF, HCl, or HBr. The severity of injury increased with increasing concentration, and the relative toxicities of the hydrogen halides were reported as HF > HCl > HBr. However, in a later study by the same authors, Stavert et al. (1991) reported no difference in the toxicities to the nasal regions or the lung in nose-breathing or mouth-breathing rats exposed to HF, HCl, or HBr at 1,300 ppm for 30 min.

At the high concentrations necessary to cause lethality during exposure durations of 5 min to 1 h, HF is approximately twice (1.8-2.2 times) as toxic to the rat as HCl (Table 2-8). The relationship is similar for the mouse within this time period (2.2-3.2 times); however, for respiratory irritants such as HCl, the mouse "may not be a good model for extrapolation to humans," because "mice appear to be much more susceptible to the lethal effects of HCl than other rodents or baboons….To some extent, this increased susceptibility may be due to less effective scrubbing of HCl in the upper respiratory tract" (NRC 1991). Quantitative data for HBr were limited to one study, but that study also showed that HF was more toxic than either HCl or HBr.

On the basis of empirical lethality (LC_{50}) data in rats, rabbits, and guinea pigs, the exposure time-LC_{50} relationship for HCl using the equation $C^n \times t = k$ results in an n value of 1. That is comparable to an n value of

TABLE 2-8 Relative Toxicities of HF, HCl, and HBr indicated by LC_{50} Values (ppm)

Species	Exposure Duration	HF	HCl	HBr	Reference
Rat	5 min	18,200	41,000		Higgins et al. 1972
Mouse		6,247	13,750		
Rat	30 min	2,042	4,700		Rosenholtz et al. 1963 (HF);
Mouse			2,644		MacEwan and Vernot 1972 (HCl)
Rat	1 h	1,395	3,124		Wohlslagel et al. 1976
Mouse		342	1,108		
Rat	1 h	1,278	2,350	2,858	MacEwan and Vernot 1972
Mouse		501	1,322	814	

Abbreviations: HBr, hydrogen bromide; HCl, hydrogen chloride; HF, hydrogen fluoride; LC_{50}, lethal concentration in 50% of subjects.

2 empirically derived from rat and mouse lethality data for HF. Hence, although HF is more toxic than HCl at the higher concentrations and shorter exposure durations, the rate of decrease in the LC_{50} threshold is less (i.e., less slope in the curve derived from $C^n \times t = k$) for HF than for HCl. As a result, the LC_{50} values, and therefore the lethal toxicities of HCl and HF, are comparable at 4 h and 8 h. This shift in relative lethal toxicity across time also is reflected in the AEGL-3 values developed for HCl and HF.

Considering the greater water solubility of HF compared with HCl, it is possible that the more effective scrubbing of HF in the nasal passages is responsible for the apparent decrease in the relative toxicities of HF and HCl at lower concentrations associated with longer exposure durations. Conversely, the greater toxicity of HF at higher concentrations associated with the shorter exposure durations might be due to saturation of the scrubbing mechanism and higher concentrations in the lower respiratory system.

4.4. Other Relevant Information

4.4.1. Species Variability

Differences in responses to HCl exposure have been observed between primates and rodents. Rodents exhibit sensory and respiratory irritation upon exposure to high concentrations of HCl. Dose-related decreases in respiratory frequency, indicative of a protective mechanism, are observed in rodents, while baboons inhaling HCl at 500, 5,000, or 10,000 ppm exhibited concentration-dependent increases in respiratory frequency, indicative of a compensatory response to hypoxia and a possible increase in the total dose delivered to the lung (NRC 1991).

Kaplan (1988) found that five of six mice died when exposed to HCl at 2,550 ppm for 15 min; however, baboons survived exposure at 10,000 ppm for 15 min. The LC_{50} values reported by Darmer et al. (1974), Wohlslagel et al. (1976), and Higgins et al. (1972) indicate that mice are approximately 3 times more sensitive than rats to the effects of HCl. That increased susceptibility might be due to less effective scrubbing of HCl in the upper respiratory tract of mice compared with rats (NRC 1991). Guinea pigs also appear to be more sensitive than rats; however, various guinea pig studies have provided conflicting results (Kaplan et al. 1993b).

Because most rodents are obligatory nose-breathers, whereas humans may be mouth-breathers, especially during exercise, Stavert et al. (1991)

studied the effects of inhalation of HCl via the nose and mouth in rats. HCl was delivered directly to the trachea by cannulation; concentrations that produced effects confined to the nasal passages in nose-breathing rats resulted in serious lower respiratory tract effects and/or deaths in orally cannulated rats. These results indicate that the site of injury and resultant toxicologic effects differ with mouth- and nose-breathing, the former mode resulting in more severe responses under similar exposure situations. Thus, species that breathe through their mouth (humans) may be more sensitive to the effects of HCl than those that are obligate nasal breathers (rodents).

4.4.2. Unique Physicochemical Properties

HCl gas is hygroscopic and dissolves in water to produce hydrochloric acid. Concentrated hydrochloric acid is 37% HCl. When HCl gas absorbs moisture, it is highly reactive with metals and releases hydrogen gas (EPA 1994).

4.4.3. Concurrent Exposure Issues

Gases such as carbon monoxide, carbon dioxide, hydrogen cyanide, nitrogen dioxide, and nitrogen are often present with HCl during fires. The temperature, moisture content, and particular mix of gases can influence toxicity. For example, carbon monoxide has been shown to weaken the irritant effects of HCl (Sakurai 1989). However, Higgins et al. (1972) found no effect on mortality of rats and mice exposed to HCl alone or in combination with carbon monoxide.

Wohlslagel et al. (1976) examined the hazard of simultaneous acute inhalation exposure to HCl, HF, and alumina dust, which are components of solid rocket motor exhaust. Sixty-minute LC_{50} values were determined for both rats and mice. Exposures were to HCl alone, HF alone, and combination exposures to HCl and HF. Data suggested that in both species exposure to both gases simultaneously resulted in physiologically additive mortality incidences. No synergism, potentiation, or antagonism were observed. Gross and histopathologic examinations of rats and mice exposed to combinations of the corrosive gases showed no sites of damage additional to those observed in animals exposed to a single gas. The addition of alumina dust to atmospheres containing HCl and HF vapors did not increase or decrease mortality in either species.

HCl in smoke generated by flaming thermodegradation polyvinyl chloride (30-min LC_{50} of 2,141 ppm) was slightly more lethal to rats than HCl in smoke generated by nonflaming thermodegradation (30-min LC_{50} of 2,924 ppm), which was slightly more lethal than pure HCl (30-min LC_{50} of 3,817 ppm) (Hartzell et al. 1987).

4.4.4. Subchronic Exposure

Groups of 31 male and 21 female rats or 31 male and 21 female mice were exposed to HCl at 0, 10, 20, or 50 ppm for 6 h/d, 5 d/wk for 90 d (Toxigenics 1984). After the fourth exposure, 15 males and 10 females per group per species were sacrificed. Decreased body weight was observed in both genders of both species exposed at 50 ppm for 4 d. Hematology and urinalysis were unremarkable for those animals. Rats exhibited minimal to mild rhinitis after exposure to the three HCl concentrations for 4-90 d. The rhinitis was concentration- and duration-related and occurred in the anterior portion of the nasal cavity. After 90 d, mice in the 50-ppm group developed varying degrees of cheilitis with accumulations of hemosiderin-laden macrophages in the perioral tissues. In addition, at all three concentrations, mice developed signs of minor, reversible degeneration (eosinophilic globules) in the epithelial cells lining the nasal turbinates.

Machle et al. (1942) exposed three rabbits, three guinea pigs, and one monkey to HCl at 34 ppm for 6 h/d, 5 d/wk for 4 wk. No histopathologic effects were noted at necropsy. Clinical signs during or after exposure and other experimental details were not reported.

Mice exposed to HCl at 310 ppm for 6 h/d for 5 d exhibited necrosis, exfoliation, erosion, and ulceration of the nasal respiratory epithelium; however, no histopathologic effects were noted in the lung (Buckley et al. 1984).

5. RATIONALE AND PROPOSED AEGL-1

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m³]) 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.

5.1. Summary of Human Data Relevant to AEGL-1

Five male and five female exercising adult asthmatic subjects (ages 18-25 y) were exposed to filtered air or HCl at 0.8 ppm or 1.8 ppm for 45 min (Stevens et al. 1992). No treatment-related effects were observed.

5.2. Summary of Animal Data Relevant to AEGL-1

No animal data consistent with effects defined by AEGL-1 were available.

5.3. Derivation of AEGL-1

Because appropriate human data exist for exposure to HCl, they were used to identify AEGL-1 values. Exposure to HCl at 1.8 ppm for 45 min resulted in a no-observed-adverse-effect level (NOAEL) in 10 exercising young adult asthmatic subjects (Stevens et al. 1992). Because exercise will increase HCl uptake and exacerbate irritation, those asthmatic subjects are considered a sensitive subpopulation. Therefore, because the test subjects were a sensitive subpopulation and the end point was essentially a no-effect level, no uncertainty factory (UF) was applied to account for sensitive human subpopulations. Adequate human data were available, so no UF was applied for animal to human extrapolation. The no-effect level was held constant across the 10- and 30-min and 1-, 4-, and 8-h exposure time points. That approach was considered appropriate because mild irritant effects generally do not vary greatly over time, and the end point of a no-effect level in a sensitive population is inherently conservative. The values for AEGL-1 are given in Table 2-9. Figure 2-1 is a plot of the derived AEGLs and the human and animal data on HCl.

6. RATIONALE AND PROPOSED AEGL-2

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 serious, long lasting adverse health effects or an impaired ability to escape.
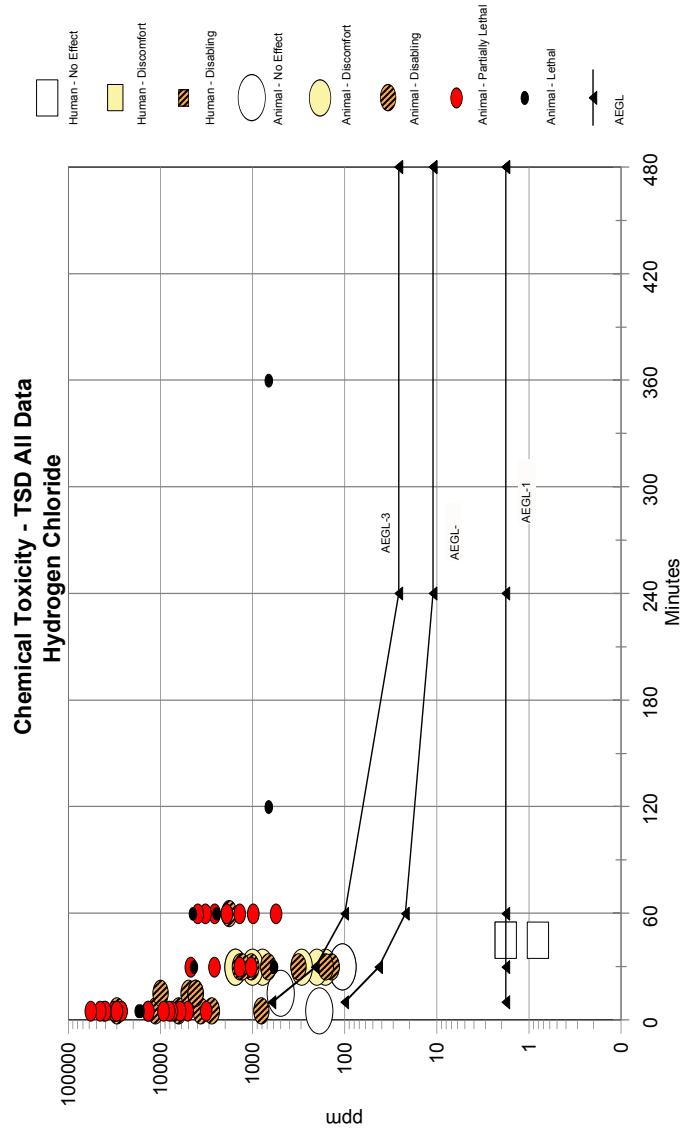
FIGURE 2-1 Toxicity data and AEGL values for hydrogen chloride. Toxicity data include both human and animal studies.

TABLE 2-9 AEGL-1 Values for Hydrogen Chloride (ppm [mg/m^3])

10 min	30 min	1 h	4 h	8 h
1.8 (2.7)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)

6.1. Summary of Human Data Relevant to AEGL-2

Human data consistent with effects defined by AEGL-2 from exposure to HCl are not appropriate for use in derivation because the descriptions of concentration, exposure time, and effects are subjective.

6.2. Summary of Animal Data Relevant to AEGL-2

Studies in baboons involving escape performance tests (Kaplan 1987) and pulmonary function (Kaplan et al. 1988, 1993a) resulted in effects consistent with those defined by AEGL-2. However, the baboon study descriptions suggest that individual baboons may have been used for more than one exposure. Responses of both guinea pigs (Malek and Alarie 1989; Burleigh-Flayer et al. 1985) and rats (Stavert et al. 1991) also are consistent with effects defined by AEGL-2. Other studies, although designed fairly well, produced effects more severe than that defined by AEGL-2 (Darmer et al. 1974; Buckley et al. 1984; Barrow et al. 1979; Hartzell et al. 1985).

6.3. Derivation of AEGL-2

The AEGL-2 for the 30-min and 1-, 4-, and 8-h time points was based on severe nasal or pulmonary histopathology in rats exposed to HCl at 1,300 ppm for 30 min (Stavert et al. 1991). A modifying factor (MF) of 3 was applied to account for the relatively sparse database describing effects defined by AEGL-2. The AEGL-2 values were further adjusted by a total UF of 10—3 for intraspecies variability, supported by the steep concentra-tion-response curve, which implies little individual variability; and 3 for interspecies variability. Using the default value of 10 for interspecies vari-ability would bring the total adjustment to 100 instead of 30. That would generate AEGL-2 values that are not supported by data on exercising asth-matic subjects, an especially sensitive subpopulation. Exercise increases HCl uptake and exacerbates irritation; no effects were noted in exercising

young adult asthmatic subjects exposed to HCl at 1.8 ppm for 45 min (Stevens et al. 1992). Using a total UF of 30 would yield 4- and 8-h values of 3.6 ppm (instead of 11 ppm). The prediction that humans would be disabled by exposure for 4 h or 8 h to 3.6 ppm cannot be supported when exercising asthmatic subjects exposed to one-half that concentration for 45 min exhibited no effects. The shorter time points would yield values 4 to 7 times the 1.8-ppm value; however, confidence in the time-scaling for HCl is good for times up to 100 min, because the value of n was derived from a regression analysis of rat and mouse mortality data with exposure durations ranging from 1 min to 100 min. The 30-min value of 43 ppm derived with a total UF of 10 is reasonable in light of the fact that baboons exposed at 500 ppm for 15 min experienced only a slightly increased respiratory rate. Therefore, a total UF of 10, accompanied by the MF of 3, is most consistent with the database. Thus, the total factor is 30. Time-scaling for the 1-h AEGL exposure period used the $C^n \times t = k$ relationship, where $n = 1$ based on regression analysis of combined rat and mouse LC_{50} data (1 min to 100 min) as reported by ten Berge et al. (1986). The 4- and 8-h AEGL-2 values were derived by applying an MF of 2 to the 1-h AEGL-2 value, because time-scaling would yield a 4-h AEGL-2 of 5.4 ppm and an 8-h AEGL-2 of 2.7 ppm, close to the 1.8 ppm tolerated by exercising asthmatic subjects without observed adverse health effects. Repeated-exposure rat data suggest that the 4- and 8-h values of 11 ppm are protective. Rats exposed to HCl at 10 ppm for 6 h/d, 5 d/wk for life exhibited only tracheal and laryngeal hyperplasia, and rats exposed to HCl at 50 ppm for 6 h/d, 5 d/wk for 90 d exhibited only mild rhinitis.

The 10-min AEGL-2 was derived by dividing the mouse RD_{50} of 309 ppm by a factor of 3 to obtain a concentration causing irritation (Barrow 1977). It has been determined that human response to sensory irritants can be predicted on the basis of the mouse RD_{50}. For example, Schaper (1993) has validated the correlation of $0.03 \times RD_{50} = TLV$ as a value that will prevent sensory irritation in humans. The 0.03 represents the half-way point between 0.1 and 0.01 on a logarithmic scale, and Alarie (1981) has shown that the RD_{50} multiplied by 0.1 corresponds to "some sensory irritation," whereas the RD_{50} value itself is considered "intolerable to humans." Thus, it is reasonable that one-third of the RD_{50}, a value half-way between 0.1 and 1 on a logarithmic scale, might cause significant irritation to humans. Furthermore, one-third of the mouse RD_{50} for HCl corresponds to an approximate decrease in respiratory rate of 30%, and decreases in the range of 20-50% correspond to moderate irritation (ASTM 1991). The values for AEGL-2 are given in Table 2-10.

TABLE 2-10 AEGL-2 Values for Hydrogen Chloride (ppm [mg/m^3])

10 min	30 min	1 h	4 h	8 h
100 (156)	43 (65)	22 (33)	11 (17)	11 (17)

The 10-min value is supported by the baboon studies, where no effects were noted in a baboon exposed at 190 ppm for 5 min (Kaplan 1987), and no exposure-related effects on tidal volume or PaO$_2$ were observed in anesthetized baboons exposed at 500 ppm for 15 min (Kaplan et al. 1988). Also, when the rat data of Stavert et al. (1991) are extrapolated back to 10 min, a value of 130 ppm is obtained, suggesting that the proposed 10-min value is protective.

7. RATIONALE AND PROPOSED AEGL-3

AEGL-3 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 life-threatening health effects or death.

7.1. Summary of Human Data Relevant to AEGL-3

No data concerning human lethality from HCl exposure were located in the available literature.

7.2. Summary of Animal Data Relevant to AEGL-3

Baboon exposure studies involving an escape performance test and pulmonary function tests resulted in effects consistent with those defined by AEGL-3 (Kaplan 1987; Kaplan et al. 1988). Other well-designed studies identified disabling effects and lethality in guinea pigs (Malek and Alarie 1989; Burleigh-Flayer et al. 1985), rats, and mice (Darmer et al. 1974; Wohlslagel et al. 1976; Vernot et al. 1977; Barrow et al. 1979; Buckley et al. 1984; Hartzell et al. 1985).

7.3. Derivation of AEGL-3

The AEGL-3 was based on a 1-h rat LC_{50} study (Wohlslagel et al. 1976; Vernot et al. 1977). One-third of the 1-h LC_{50} value of 3,124 ppm was used as an estimated concentration causing no deaths. That estimate is inherently conservative (no deaths observed in the same study at 1,813 ppm). A total UF of 10 will be applied—3 for intraspecies variation, because the steep concentration-response curve implies limited individual variability; and 3 to protect susceptible individuals. Using a full value of 10 for interspecies variability (total UF of 30) would yield AEGL-3 values that are inconsistent with the overall data set.

A number of factors argue for the use of a UF of 10 instead of 30: (1) the steep concentration-response curve for lethality observed in the Wohlslagel et al. (1976) study in which the estimated LC_0 (one-third of the LC_{50} of 3,124 ppm) is lower than the experimental LC_0 of 1,813 ppm. The LC_0 selection is conservative, and the steep concentration-response curve argues for little interindividual variability; (2) AEGL-3 values generated from a total UF of 30 would be close (within a factor of 2) to the AEGL-2 values generated from data on exercising asthmatic subjects; (3) Sellakumar et al. (1985) exposed rats to HCl at 10 ppm for 6 h/d, 5 d/wk for life and only observed increased trachael and laryngeal hyperplasia. The estimated 6-h AEGL-3 using an intraspecies UF of 3 is 17 ppm, close to the concentration inhaled in the lifetime study in which only mild effects were induced; and (4) rats exposed to HCl at 50 ppm for 6 h/d, 5 d/wk for 90 d (Toxigenics 1984) exhibited mild rhinitis. This level is already twice the AEGL-3 value, which is intended to protect against death.

Thus, the total UF was set at 10. It was then time-scaled to the specified 10- and 30-min and 4-h AEGL exposure periods using the $C^n \times t = k$ relationship, where $n = 1$ based on regression analysis of combined rat and mouse LC_{50} data (1 min to 100 min) as reported by ten Berge et al. (1986). The 4-h AEGL-3 also was adopted as the 8-h AEGL-3 because of the uncertainty of time-scaling to 8 h with an n value derived from exposure durations of up to 100 min. The values for AEGL-3 are given in Table 2-11.

The 5-min rat LC_0 of 30,000 ppm (Higgins et al. 1972) supports the 10-min AEGL-3 value. Extrapolating that value across time ($n = 1$) to 10 min and applying a UF of 10 yields a value of 1,500 ppm, suggesting that the proposed AEGL-3 value is protective. Also, if the 5-min rat LC_{50} of 41,000 ppm for HCl vapor (Darmer et al. 1974) is divided by 3 to estimate a no-effect level for death, extrapolated to 10 min, and a UF of 10 is applied, a supporting value of 683 ppm is obtained.

TABLE 2-11 AEGL-3 Values for Hydrogen Chloride (ppm [mg/m^3])

10 min	30 min	1 h	4 h	8 h
620 (937)	210 (313)	100 (155)	26 (39)	26 (39)

8. SUMMARY OF PROPOSED AEGLS

8.1. AEGL Values and Toxicity End Points

The derived AEGLs for various levels of effects and durations of exposure are summarized in Table 2-12. A NOAEL for sensory irritation in exercising asthmatic subjects was used for AEGL-1. Severe nasal and pulmonary effects in rats and a modification of the mouse RD_{50} were used for AEGL-2. An estimated no-effect level for death in rats was used for AEGL-3.

8.2. Other Exposure Criteria

Standards set by other organizations appear in Table 2-13.

8.3. Data Quality and Research Needs

Human data are limited to one study showing no significant effects in asthmatic subjects and to dated anecdotal information. Furthermore, the

TABLE 2-12 Summary of AEGL Values for Hydrogen Chloride (ppm [mg/m^3])

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)
AEGL-2 (Disabling)	100 (156)	43 (65)	22 (33)	11 (17)	11 (17)
AEGL-3 (Lethal)	620 (937)	210 (313)	100 (155)	26 (39)	26 (39)

TABLE 2-13 Extant Standards and Guidelines for Hydrogen Chloride (ppm)

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	1.8	1.8	1.8	1.8	1.8
AEGL-2	100	43	22	11	11
AEGL-3	620	210	100	26	26
ERPG-1[a]	3				
ERPG-2[a]	20				
ERPG-3[a]	150				
NIOSH IDLH[b]	50				
NIOSH REL[c]					5 (ceiling)
OSHA PEL-TWA[d]					5 (ceiling)
ACGIH TLV-STEL[e]	5				
NRC SPEGL[f]					1
NRC EEGL[g]			20		
NRC SMAC[h]	5				
German MAK[i]					5
Dutch MAC[j]					5

[a]ERPG (emergency response planning guidelines) of the American Industrial Hygiene Association (AIHA 2001). ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing symptoms other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for HCl is based on objectionable odor. The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action. The ERPG-2 for HCl is based on animal studies suggesting serious eye and respiratory irritation above 20 ppm and below 100 ppm. The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 for HCl is based on animal data suggesting that concentrations exceeding 150 ppm for 1 h may produce severe, possibly life-threatening health effects, such as pulmonary edema, in a heterogeneous population.

[b]IDLH (immediately dangerous to life and health standard of the National Institute of Occupational Safety and Health) (NIOSH 1994). The IDLH represents the maximum concentration from which one could escape within 30 min without any

escape-impairing symptoms or irreversible health effects. The IDLH for HCl is based on acute inhalation toxicity data in humans.

[c]NIOSH REL-STEL (recommended exposure limits-short-term exposure limit) (NIOSH 1997). The REL-STEL is defined analogous to the ACGIH TLV-TWA.

[d]OSHA PEL-TWA (permissible exposure limit-time-weighted average of the Occupational Safety and Health Administration) (OSHA 1997). The PEL-TWA is defined analogous to the ACGIH TLV-TWA but is for exposures of no more than 10 h/d, 40 h/wk.

[e]ACGIH TLV-STEL (Threshold Limit Value-short-term exposure limit of the American Conference of Governmental Industrial Hygienists) (ACGIH 2000). The TLV-STEL for HCl is based on corrosion and irritation.

[f]SPEGL (short-term public emergency guidance level) (NRC 1991).

[g]EEGL (emergency exposure guidance level) (NRC 1985). The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects, and long-term or chronic injury.

[h]SMAC (spacecraft maximum allowable concentration of NASA) (NRC 2000).

[i]MAK (Maximale Argeitsplatzkonzentration [Maximum Workplace Concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] 2000). The MAK is defined analogous to the ACGIH TLV-TWA.

[j]MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000). The MAC is defined analogous to the ACGIH TLV-TWA.

involvement of RADS in HCl toxicity is unclear. Many more data are available for animal exposures; however, many of those studies used compromised animals or very small experimental groups, resulting in limited data for many species but no in- depth database for a given species. Also, some studies involve very short exposures to high concentrations of HCl. Thus, confidence in the AEGL values is at best moderate.

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APPENDIX A

Time-Scaling Calculations for Hydrogen Chloride

Derivation of AEGL-1

Key study: Stevens et al. 1992

Toxicity
end point: No-observed-adverse-effect level in exercising
                    asthmatic subjects.

Time-scaling: $C^1 \times t = k$ (ten Berge 1986);
                    $(1.8 \text{ ppm})^1 \times 0.75 \text{ h} = 1.35 \text{ ppm·h}$

Uncertainty
factor: None

10- min, 30-min ,
1-h, 4-h, and
8-h AEGL-1:   1.8 ppm

Derivation of AEGL-2

10-min AEGL-2

Key study: Barrow et al. 1977

Toxicity
end point: Mouse RD_{50} of 309 ppm to obtain a concentration
                    causing irritation.

10-min AEGL-2:   309 ppm ÷ 3 = 100 ppm

30-min, 1-, 4-, and 8-h AEGL-2

Key Study: Stavert et al. 1991

Toxicity
end point: Severe nasal (nose-breathers) or pulmonary (mouth-breathers) effects in rats exposed at 1,300 ppm for 30 min.

Time-scaling: $C^1 \times t = k$ (ten Berge 1986);
$(1,300 \text{ ppm})^1 \times 0.5 \text{ h} = 650 \text{ ppm·h}$

Uncertainty
factors: 3 for intraspecies variability
3 for interspecies variability

Modifying
factor: 3 for sparse database

30-min AEGL-2: $C^1 \times 0.5 \text{ h} = 650 \text{ ppm·h}$
$C = 1,300 \text{ ppm}$
30 min AEGL-2 = 1,300 ppm ÷ 30 = 43 ppm

1-h AEGL-2: $C^1 \times 1 \text{ h} = 650 \text{ ppm·h}$
$C = 650 \text{ ppm}$
1-h AEGL-2 = 650 ppm ÷ 30 = 21.6 ppm

4-h AEGL-2: 1-h AEGL-2 ÷ 2 = 11 ppm

8-h AEGL-2: 1-h AEGL-2 ÷ 2 = 11 ppm

Derivation of AEGL-3

Key Study: Wholslagel et al. 1976; Vernot et al. 1977

Toxicity
end point: One-third of the rat 1-h LC_{50} as an estimate of a no-effect level for death (3,124 ppm ÷ 3 = 1,041 ppm)

Time-scaling: $C^1 \times t = k$ (ten Berge 1986)
$(1,041 \text{ ppm})^1 \times 1 \text{ h} = 1,041 \text{ ppm·h}$

Uncertainty
factors: 3 for intraspecies variability
                            3 for interspecies variability

10-min AEGL-3: $C^1 \times 0.167$ h = 1,041 ppm·h
                            C = 6,234 ppm
                            10-min AEGL-3 = 6,234 ppm ÷ 10 = 623.4 ppm

30-min AEGL-3: $C^1 \times 0.5$ h = 1,041 ppm·h
                            C = 2,082 ppm
                            30-min AEGL-3 = 2,082 ppm ÷ 10 = 208 ppm

1-h AEGL-3: $C^1 \times 1$ h = 1,041 ppm·h
                            C = 1,041 ppm
                            1-h AEGL-3 = 1,041 ppm ÷ 10 = 104.1 ppm

4-h AEGL-3: $C^1 \times 4$ h = 1,041 ppm·h
                            C = 260.25 ppm
                            4-h AEGL-3 = 260.25 ppm ÷ 10 = 26 ppm

8-h AEGL-3:   8-h AEGL-3 = 4-h AEGL-3 = 26 ppm

APPENDIX B

**ACUTE EXPOSURE GUIDELINE LEVELS
FOR HYDROGEN CHLORIDE (CAS Reg. No. 7647-01-0)**

DERIVATION SUMMARY

AEGL-1				
10 min	30 min	1 h	4 h	8 h
1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm

Key reference: Stevens, B. et al. 1992. Respiratory effects from the inhalation if hydrogen chloride in young adult asthmatics. JOM. 34: 923-929.
Test species/strain/number: human/adult asthmatic subjects/10
Exposure route/concentrations/durations: inhalation at 0, 0.8, or 1.8 ppm for 45 min while exercising (1.8 ppm was determinant for AEGL-1)
Effects: No treatment-related effects were observed in any of the individuals tested
End point/concentration/rationale: The highest concentration tested was a no-effect level for irritation in a sensitive human population (10 asthmatic individuals tested) and was selected as the basis for AEGL-1. Effects assessed included sore throat, nasal discharge, cough, chest pain or burning, dyspnea, wheezing, fatigue, headache, unusual taste or smell, total respiratory resistance, thoracic gas volume at functional residual capacity, forced expiratory volume, and forced vital capacity. All subjects continued the requisite exercise routine for the duration of the test period.

Uncertainty factors/rationale:
    Interspecies: 1, test subjects were human
    Intraspecies: 1, test subjects were sensitive population (exercising asthmatic subjects)

Modifying factor: Not applicable
Animal to human dosimetric adjustment: Insufficient data
Time-scaling: The AEGL-1 values for a sensory irritant were held constant across time because it is a threshold effect and prolonged exposure will not result in an enhanced effect. In fact one may become desensitized to the respiratory tract irritant over time. Also, this approach was considered valid since the end point (no treatment-related effects at the highest concentration tested in exercising asthmatics) is inherently conservative

AEGL-1 *Continued*
Data quality and research needs: The key study was well conducted in a sensitive human population and is based on no treatment-related effects. In addition, the direct-acting irritation response is not expected to vary greatly among individuals. Therefore, confidence in the AEGL values derived is high.

AEGL-2				
10 min	30 min	1 h	4 h	8 h
100 ppm	43 ppm	22 ppm	11 ppm	11 ppm

Key references:	Stavert et al. 1991. Relative acute toxicities of hydrogen chloride, hydrogen fluoride, and hydrogen bromide in nose- and pseudo-mouth-breathing rats. Fundam. Appl. Toxicol. 16: 636-655. (30-min, 1-, 4-, and 8-h) Barrow, C.S., Alarie, Y., Warrick, M., and Stock, M.F. 1977. Comparison of the sensory irritation response in mice to chlorine and hydrogen chloride. Arch. Environ. Health. 32:68-76. (10-min)

Test species/strain/number: F-344 rats, 8 males/concentration (30-min, 1-, 4-, and 8-h); Male Swiss Webster mice (10-min)

Exposure route/concentrations/durations: inhalation at 0 or 1,300 ppm for 30 min (1,300 ppm was determinant for 30-min, 1-, 4-, and 8-h AEGL-2)

Effects (30-min, 1-, 4-, and 8-h): 0 ppm, no effects; 1,300 ppm, severe necrotizing rhinitis, turbinate necrosis, thrombosis of nasal submucosa vessels in nose-breathers; 1,300 ppm, severe ulcerative tracheitis accompanied by necrosis and luminal ulceration in mouth-breathers (determinant for AEGL-2); RD_{50} = 309 ppm (determinant for 10-min AEGL-2)

End point/concentration/rationale:
1,300 ppm for 30 min, severe lung effects (ulcerative tracheitis accompanied by necrosis and luminal ulceration) or nasal effects (necrotizing rhinitis, turbinate necrosis, thrombosis of nasal submucosa vessels histopathology) in pseudo-mouth-breathing male F-344 rats (30-min, 1-, 4-, and 8-hr);
RD_{50} of 309 ppm ÷ 3 to estimate irritation (10-min)

Uncertainty Factors/Rationale (30-min, 1-, 4-, and 8-hr):
Total uncertainty factor: 10
    Intraspecies: 3, steep concentration-response curve implies limited individual variability
    Interspecies: 3, the use of an intraspecies uncertainty factor of 10 would bring the total uncertainty/modifying factor to 100 instead of 30. That would generate AEGL-2 values that are not supported by data on exercising asthmatic subjects, an especially sensitive subpopulation because exercise increases hydrogen chloride uptake and exacerbates irritation. No effects were noted in exercising young adult asthmatic subjects exposed to HCl at 1.8 ppm for 45 min (Stevens et al. 1992). Using a total UF of 30 would yield 4- and 8-h values of 3.6 ppm (instead of 11 ppm). It is not supportable to predict that humans would be disabled by exposure at 3.6 ppm for 4- or 8- h when exercising asthmatic subjects exposed to one-half that level for 45 min had no effects. The

AEGL-2 *Continued*
shorter time points would yield values 4-7 times above 1.8 ppm; however, the confidence in the time scaling for hydrogen chloride is good for times up to 100-min because the *n* value was derived from a regression analysis of rat and mouse mortality data with exposure durations ranging from 1 min to 100 minutes. The 30-min value of 43 ppm derived with the total UF of 10 is reasonable in light of the fact that baboons exposed to 500 ppm for 15 min experienced only a slightly increased respiratory rate
Modifying factor: 30-min, 1-, 4-, and 8-h: 3, based on sparse database for AEGL-2 effects and the fact that the effects observed at the concentration used as the basis for AEGL-2 were somewhat severe 10-min: the 10-min AEGL-2 was derived by dividing the mouse RD_{50} of 309 ppm by a factor of 3 to obtain a concentration causing irritation (Barrow et al. 1977). One-third of the mouse RD_{50} for hydrogen chloride corresponds to an approximate decrease in respiratory rate of 30%, and decreases in the range of 20-50% correspond to moderate irritation (ASTM 1991).
Animal to human dosimetric adjustment: Insufficient data
Time-scaling: $C^n \times t = k$ where $n = 1$, based on regression analysis of combined rat and mouse LC_{50} data (1 min to 100 min) reported by ten Berge et al. (1986). Data point used to derive AEGL-2 was 30 min. AEGL-2 values for 1-h exposure period was based on extrapolation from the 30-min value. The 4- and 8-h AEGL-2 values were derived by applying a modifying factor of 2 to the 1-h AEGL-2 value because time scaling would yield a 4-h AEGL-2 value of 5.4 ppm and an 8-h AEGL-2 of 2.7 ppm, close to the 1.8 ppm tolerated by exercising asthmatic subjects without adverse health effects.
Data quality and research needs: Confidence is moderate since the species used is more sensitive than primates to the effects of hydrogen chloride, the chemical is a direct-acting irritant, and a modifying factor was included to account for the relative severity of effects and sparse database.

AEGL-3				
10 min	30 min	1 h	4 h	8 h
620 ppm	210 ppm	100 ppm	26 ppm	26 ppm

Key references: Vernot, E.H., MacEwen, J.D., Haun, C.C., Kinkead, E.R. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42: 417-423. Wohlslagel, J., DiPasquale, L..C., Vernot, E.H. 1976. Toxicity of solid rocket motor exhaust: Effects of HCl, HF, and alumina on rodents. J. Combustion Toxicol. 3: 61-70.
Test species/strain/gender/number: Sprague-Dawley rats, 10 males/concentration
Exposure route/concentrations/durations: inhalation at 0, 1,813, 2,585, 3,274, 3,941, or 4,455 ppm for 1 h

Effects: *Concentration*   *Mortality*

Concentration	Mortality
0 ppm	0/10
1,813 ppm	0/10
2,585 ppm	2/10
3,274 ppm	6/10
3,941 ppm	8/10
4,455 ppm	10/10

LC_{50} reported as 3,124 ppm (determinant for AEGL-3)

End point/concentration/rationale: one-third of the 1-h LC_{50} (1,041 ppm) was the estimated concentration causing no deaths.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
    Intraspecies: 3, steep concentration-response curve implies limited individual variability
    Interspecies: 3, because (1) the steep concentration-response curve for lethality observed in the Wohlslagel et al. (1976) study in which 1,041 ppm (one-third of the LC_{50} of 3124 ppm) was lower than the LC_0 of 1,813 ppm. This is a conservative selection of the LC_0 and the steep concentration-response curve argues for little interindividual variability; (2) AEGL-3 values generated from a total uncertainty factor of 30 would be close to the AEGL-2 values (within a factor of 2) generated above which are reasonable when compared with data on exercising asthmatics; (3) Sellakumar et al. (1985) exposed rats to HCl at 10 ppm for 6 h/d, 5 d/wk for life and only observed increased trachael and laryngeal hyperplasia. The estimated 6-h AEGL-3 using an intraspecies uncertainty factor of 3 is 17 ppm, close to the level used in the lifetime

AEGL-3 *Continued*
study in which only mild effects were induced; (4) rats exposed at 50 ppm for 6 h/d, 5 d/wk for 90 d (Toxigenics 1984) exhibited mild rhinitis. This level is already 2 times that of the AEGL-3 value for death. Thus, the total uncertainty factor is 10.
Modifying factor: Not applicable
Animal to human dosimetric adjustment: Insufficient data
Time scaling: $C^n \times t = k$ where n = 1, based on regression analysis of rat and mouse mortality data (1 min to 100 min) reported by ten Berge et al. (1986). Reported 1-h data point was used to derive AEGL-3 values. AEGL-3 values for 10-min, 30-min, and 4-h were based on extrapolation from the 1-h value. The 4-h value was adopted as the 8-h value.
Data quality and research needs: Study is considered appropriate for AEGL-3 derivation because exposures are over a wide range of HCl concentrations and utilize a sufficient number of animals. Data were insufficient to derive a no-effect level for death. One-third of the LC_{50} has been utilized previously for chemicals with steep concentration-response curves. Also, in the key study, no deaths were observed in rats exposed at 1,813 ppm.