Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 14

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases or intentional releases by terrorists. 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. Subsequently, *Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for more than 270 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 (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the fourteenth volume in that series. AEGL documents for BZ (2-quinuclidinyl benzilate), ethyl

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

phosphorodichloridate, hexane, methanesulfonyl chloride, nitric acid, propargyl alcohol, and vinyl acetate monomer are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes 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.

The committee's review of the AEGL documents involved both oral and written presentations to the committee by the authors of the documents. The committee examined the draft documents and provided comments and recommendations for how they could be improved in a series of interim reports. The authors revised the draft AEGL documents based on the advice in the interim reports and presented them for reexamination by the committee as many times as necessary until the committee was satisfied that the AEGLs were scientifically justified and consistent with the 1993 and 2001 NRC guideline reports. After these determinations have been made for an AEGL document, it is published as an appendix in a volume such as this one.

The interim reports of the committee that led to this report were reviewed in draft form 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 the committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for BZ (interim reports 19a, 20a, and 21a), ethyl phosphorodichloridate (interim reports 20a and 21a), hexane (interim reports 17 and 21a), methanesulfonyl chloride (interim reports 20a and 21a), nitric acid (interim reports 15, 18, and 21a), propargyl alcohol (interim reports 16 and 19a), and vinyl acetate monomer (interim reports 18 and 21a): Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), James McDougal (Wright State University [retired], Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Kenneth Still, Occupational Toxicology Associates, Joyce Tsuji (Exponent, Inc.), and Judith Zelikoff (New York University).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of interim reports 15-21 was overseen by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, he was responsible for making certain that an independent examination of the interim reports was

carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by Ernest Falke and Iris A. Camacho from EPA. The committee also acknowledges Susan Martel, the project director for her work this project. Other staff members who contributed to this effort are James J. Reisa (director of the Board on Environmental Studies and Toxicology), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), and Tamara Dawson (program associate). Finally, I would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Donald E. Gardner, *Chair*
Committee on Acute Exposure
Guideline Levels

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 14

National Research Council Committee Review of Acute Exposure Guideline Levels of Selected Airborne Chemicals

This report is the fourteenth 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, or what steps to take in an 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 U.S. 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.

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 values, developed by the National Institute for Occupational Safety and Health. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists, 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 hour (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 U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a, 1987, 1988, 1994, 1996a,b, 2000a, 2002a, 2007a, 2008a). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992, 2000b). 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 November 1995, the National Advisory Committee (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances 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 replaced by the term 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 minutes (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:

[1]NAC completed its chemical reviews in October 2011. The committee was composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. From 1996 to 2011, the NAC discussed over 300 chemicals and developed AEGLs values for at least 272 of the 329 chemicals on the AEGLs priority chemicals lists. Although the work of the NAC has ended, the NAC-reviewed technical support documents are being submitted to the NRC for independent review and finalization.

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 idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. Various types of evidence are assessed in establishing AEGL values for a chemical. These 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 extrap-

olation 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 for 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, data from the most sensitive animal species are used. 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, 2001a). The NRC assigned this project to the COT Committee on Acute Exposure Guideline Levels. The committee has expertise in toxicology, epidemiology, occupational health, pharmacology, medicine, pharmacokinetics, industrial hygiene, and risk assessment.

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

The NRC committee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the committee by the authors of the reports. The NRC committee provides advice and recommenda-

tions for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001a). The revised reports are presented at subsequent meetings until the committee is satisfied with the reviews.

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared thirteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c). This report is the fourteenth volume in that series. AEGL documents for BZ (2-quinuclidinyl benzilate), ethyl phosphorodichloridate, hexane, methanesulfonyl chloride, nitric acid, propargyl alcohol, and vinyl acetate monomer are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes 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

5

Nitric Acid[1]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P.L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review, and interpret relevant toxicologic and other scientific data and develop AEGLs for high-priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, 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 parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Carol Wood (Oak Ridge National Laboratory), Gary Diamond (SRC, Inc.), Chemical Managers Loren Koller and George Woodall (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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 health effects or death.

Airborne concentrations below the AEGL-1 represent exposure concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory 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 concentrations 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 idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Nitric acid is a highly corrosive, strongly oxidizing acid. Nitric acid may exist in the air as a gas, vapor, mist, fume, or aerosol. Nitric acid mist will probably be scrubbed in the mouth or nasal passages, gas and vapor in the upper respiratory tract, and fume and aerosol in the alveolar region of the lungs. Toxicity after inhalation exposure to nitric acid is similar in humans and animals. Nitric acid fumes may cause immediate irritation of the respiratory tract, pain, and dyspnea, followed by a period of recovery that may last several weeks. A relapse may occur resulting in death caused by bronchopneumonia and pulmonary fibrosis. At nonlethal concentrations, allergic or asthmatic individuals appear to be sensitive to acidic atmospheres (NIOSH 1976a; ACGIH 1991).

Both human and animal data were used to derive AEGL values. The point of departure for AEGL-1 values was selected on the basis of a study in which five healthy volunteers were exposed to nitric acid at 1.6 ppm for 10 min and had no changes in pulmonary function (vital capacity, respiratory resistance, and forced expiratory volume [FEV_1]) (Sackner and Ford 1981). That was the highest no-effect level available in humans. An uncertainty factor of 10 was applied to account for variability in the general population and possibly greater sensitivity of asthmatics to effects of a direct-acting irritant on pulmonary function. The 10-min AEGL value of 0.16 ppm was adopted for all the other AEGL durations, because the point of departure was a no-effect level for pulmonary irritation and

such irritation is generally concentration dependent but not time dependent. AEGL-1 values are higher than the odor threshold for nitric acid, which provides a warning about exposure before an individual could experience notable discomfort.

AEGL-2 and AEGL-3 values were based on a well-conducted, lethality study in rats (DuPont 1987). Groups of five male and five female Crl:CD®BR rats were exposed nose-only to nitric acid aerosol at 260-3,100 ppm for 1 h, and were observed for 14 days. Rats exposed at 470 ppm exhibited transient body weight loss 1-2 days post-exposure. At the next higher concentration, partially closed eyes (a possible sign of severe ocular irritation), which could definitely impair escape, and lung noise were reported. Thus, 470 ppm was used as the point of departure for deriving AEGL-2 values, because it is a no-effect level for impaired ability to escape. Time scaling to the 10- and 30-min and 4- and 8-h AEGL durations was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Because an empirical value for n could not be derived from the data, scaling was performed using default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolation to longer durations. A total uncertainty factor of 10 was applied: a factor of 3 to account for interspecies differences and another factor of 3 for intraspecies variability. Larger uncertainty factors were considered unnecessary because the mechanism of action for a direct ocular irritant and for a corrosive acid in the lung is not expected to differ greatly between species or among individuals. In addition, a modifying factor of 2 was applied because clinical observations were not well described, and AEGL-2 and AEGL-3 values overlap, suggesting a very steep concentration-response relationship.

AEGL-3 values were based on an LC_{01} (lethal concentration, 50% lethality) of 919 ppm, calculated by log-probit analysis of lethality data in rats (DuPont 1987). Time scaling was performed as was done for the AEGL-2 values, and the same uncertainty factors were applied.

AEGL values for nitric acid are presented in Table 5-1. If nitrogen dioxide is of concern, AEGL values for that chemical are available (see NRC 2012).

1. INTRODUCTION

Nitric acid is a corrosive, inorganic acid. Commercial formulations of the compound contain approximately 56-68% nitric acid. Exposure to light causes the formation of nitrogen dioxide, which gives the liquid a yellow color. Concentrated nitric acid containing dissolved nitrogen dioxide is termed fuming nitric acid, which evolves suffocating, poisonous fumes of nitrogen dioxide and nitrogen tetroxide (O'Neil et al. 2006). White fuming nitric acid contains 0.5% dissolved nitrogen dixoide while red fuming nitric acid contains 14% dissolved nitrogen dioxide (ACGIH 1991).

Inhalation of nitric acid involves exposure to nitric acid as well as nitrogen oxides, such a nitrogen dioxide and nitric oxide. Fuming nitric acid reacts with wood or metals and emits fumes of nitrogen dioxide, which form equimolar amounts of nitrous and nitric acid when in contact with steam (NIOSH 1976a;

O'Neil et al. 2006). Nitrogen oxide reacts quantitatively with oxygen in air to form nitrogen dioxide, which then reacts with water to form nitric acid. Most reports of human occupational exposure are limited to measurements of nitrogen oxides (NIOSH 1976a). If other oxides of nitrogen are of concern, NRC (2012) should be consulted for relevant AEGL values for nitrogen dioxide, nitric oxide, and nitrogen tetroxide.

Production of nitric acid atmospheres for inhalation exposure experiments potentially results in a variety of physical states (gas, fume, and vapor) depending on the production method used. For each study described in this chapter, the physical state and atmosphere-generation methods are presented as described by the study authors.

Nitric acid is used to dissolve noble metals, for etching and cleaning metals, to make nitrates and nitro compounds found in explosives, and, primarily, to make ammonium nitrate fertilizer (ACGIH 1991). Nitric acid contributes to acid deposition (or acid rain). It is a large contributor to acid deposition in the western United States compared with the eastern states (NARSTO 2004). Selected chemical and physical properties of nitric acid are presented in Table 5-2.

TABLE 5-1 AEGL Values for Nitric Acid

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	No-effect level for notable discomfort in humans (changes in pulmonary function: vital capacity, respiratory resistance, and FEV_1) (Sackner and Ford 1981).
AEGL-2 (disabling)	43 ppm (110 mg/m^3)	30 ppm (77 mg/m^3)	24 ppm (62 mg/m^3)	6.0 ppm (15 mg/m^3)	3.0 ppm (7.7 mg/m^3)	No-effect level for inability to escape; eye closure in rats exposed at 470 ppm for 1 h (DuPont 1987).
AEGL-3 (lethal)	170 ppm (440 mg/m^3)	120 ppm (310 mg/m^3)	92 ppm (240 mg/m^3)	23 ppm (59 mg/m^3)	11 ppm (28 mg/m^3)	No-effect level for lethality (estimated LC_{01}, 919 ppm) in rats (DuPont 1987).

Abbreviations: FEV_1, forced expiratory volume; LC_{01}, lethal concentration, 50% lethality).

TABLE 5-2 Chemical and Physical Data for Nitric Acid

Parameter	Value	Reference
Common name	Nitric acid	
Synonyms	Aqua fortis, azotic acid	O'Neil et al. 2006
CAS registry no.	7697-37-2	
Chemical formula	HNO_3	O'Neil et al. 2006
Molecular weight	63.01	O'Neil et al. 2006
Physical state	Colorless liquid; fumes in moist air	O'Neil et al. 2006
Melting point	-41.59°C	O'Neil et al. 2006
Boiling point	83°C	HSDB 2012
Density/specific gravity	1.51269	O'Neil et al. 2006
Vapor density (air = 1)	2-3 (estimated)	HSDB 2012
Solubility in water	Freely soluble	EPA 1993
Vapor pressure	47.9 mm Hg at 20°C	ACGIH 1991
Flammability	Noncombustible	HSDB 2012
pH (0.5% in saline)	1.6	Coalson and Collins 1985
Conversion factors in air	1 mg/m^3 = 0.388 ppm 1 ppm = 2.58 mg/m^3	EPA 1993

2. HUMAN TOXICITY DATA

Nitric acid may exist in the following airborne forms: gas, vapor, mist, fume, and aerosol. Nitric acid mist will probably be scrubbed in the mouth or nasal passages, gas and vapor in the upper respiratory tract, and fume and aerosol in the alveolar region of the lungs. For each study description below, the physical state and atmosphere-generation methods are presented as described by the study authors.

2.1. Acute Lethality

Hall and Cooper (1905) described case reports of firemen exposed to nitric acid fumes. Approximately 10 gallons of a 38% nitric acid solution were spilled and came in contact with zinc. Sawdust used to absorb the spill rapidly oxidized and burst into flame. Therefore, firemen were exposed to a mixture of nitric acid fumes and reaction products (e.g., nitrogen monoxide), which may have contributed to clinical outcomes observed. Of the 20 individuals exposed to the fumes, dyspnea was present in 100%, cough in 93%, pain in the sides, stomach, lungs,

throat, loins, and head was present in 87%, dizziness and nausea in 73%, and vomiting in 53%. Relapse of these symptoms occurred in 33% of the cases generally 3 weeks after exposure and persisted an average of 15.5 days. Four individuals died, two on the second day after exposure and two several weeks later after relapse. The two who died after relapse appeared to be recovering as well as the other survivors, however, both were exposed to cold air and almost immediately relapsed. Autopsy revealed hemorrhagic edema and coagulation necrosis. Exposure concentrations were not measured but the investigators concluded that the severity of the initial exposure was the most important factor in determining recovery or death (Hall and Cooper 1905).

Three men died of rapidly progressive pulmonary edema after inhalation of fumes from an explosion of nitric acid (Hajela et al. 1990). The men entered the area with the heaviest concentration of fumes and dust following an explosion of a tank containing approximately 1,736 L of 68% nitric acid. Escape from the building took 10-15 min. No respiratory problems were apparent during medical examination immediately after exposure; however, increasing respiratory difficulties developed 4-6 h later. On admission to the hospital, all subjects were cyanotic and had frothy fluid escaping from the nose and mouth. All died within 21 h after the accident. Pathologic evaluation of the lungs revealed degranulated and necrotic neutrophils within the alveolar capillaries. Concentrations of nitric acid or its oxides were not determined at the site of the accident.

A man cleaned a copper chandelier with a 60% nitric acid solution by placing the chemical and chandelier in a bowl. Exposure was very likely to nitrogen monoxide (a reaction product of nitric acid with silver and other metals) or a mixture of the monoxide and nitric acid. The first symptoms of respiratory distress occurred 30 min later; approximately 1 h later he entered a hospital emergency room with dyspnea, expiratory stridor, peripheral cyanosis, and general paleness. Chest X-ray showed pulmonary edema. The patient stabilized for 3 days after intense treatment and lung function improved. However, the patient died from refractory respiratory failure on the fourth day, and pulmonary edema was observed at autopsy (Bur et al. 1997).

Other lethal exposure scenarios have been summarized by others (see NIOSH 1976a; ACGIH 1991). Nitric acid fumes may cause immediate irritation of the respiratory tract, pain, and dyspnea, which are followed by a period of recovery that may last several weeks. Relapse may occur, with death caused by bronchopneumonia or pulmonary fibrosis. Nitric acid concentrations were not provided in the primary reports.

2.2. Nonlethal Toxicity

Nitric acid is described as having a characteristic choking odor (O'Neil et al. 2006). Low and high odor thresholds were reported as 0.29 and 0.97 ppm, respectively (EPA 1993).

2.2.1. Case Reports

A 42-year old man with no history of respiratory disease was exposed for 3 h to fumes from a leaking nitric acid drum (air concentrations not measured). Twelve hours post-exposure he presented with dry cough and acute dyspnea and was admitted to a hospital. Chest X-rays showed opacities compatible with pulmonary edema; he was treated with oxygen and high doses of corticosteroids. After 3 months his chest X-ray was clear and lung function tests were normal (Myint and Lee 1983).

2.2.2. Epidemiologic Studies

Ostro et al. (1991) correlated acidic aerosols and other air pollutants with respiratory symptoms in asthmatics in Denver, Colorado. Daily concentrations of several pollutants, including nitric acid were measured while a panel of asthmatics recorded respiratory symptoms, frequency of medication use, and related information. Airborne acidity, as measured by H^+, significantly correlated with such symptoms as cough and shortness of breath; however, nitric acid itself was not specifically associated with any respiratory symptom analyzed. Nitric acid concentrations ranged from 0.06 to 13.54 $\mu g/m^3$ (0.15 to 34.93 ppb) during the study period.

Health effects from exposure to acidic air pollution in children (8-12 years old) were monitored in 24 communities in the United States and Canada (Dockery et al. 1996; Raizenne et al. 1996). Air quality and meteorology were measured for 1 year in each community and parents completed a respiratory health questionnaire. At the end of the 1-year monitoring period, children were administered pulmonary function tests consisting of forced vital capacity (FVC) and forced expiratory volume (FEV) measurements. Cconcentrations of nitric acid ranged from 0.3 to 2.1 ppb, and nitrous acid ranged from 0.1 to 1.4 ppb; these were combined as gaseous acids. Gaseous acids were associated with a significantly higher risk of asthma (odds ratio = 2.00; 95% confidence interval[CI], 1.14-3.53) and showed a positive correlation with higher reporting of attacks of wheezing, persistent wheeze, and any asthmatic symptoms (Dockery et al. 1996). However, no changes in FVC or FEV were associated with gaseous acid concentrations in the communities (Raizenne et al. 1996).

In a more recent study, children from 12 communities in California were assessed for respiratory disease prevalence and pulmonary function (Peters et al. 1999a,b). Wheeze prevalence was positively correlated with concentrations of both acid and nitrogen dioxide in boys, whereas regression analysis showed that acid vapor was significantly associated with lower FVC, FEV_1, peak expiratory flow rate, and maximal midexpiratory flow in girls. When the data were further analyzed by month (Millstein et al. 2004), wheezing during the spring and summer months was not associated with either nitric acid or nitrogen dioxide. However, in asthmatics, the monthly prevalence of asthma medication use was asso-

ciated with monthly concentrations of ozone, nitric acid, and acetic acid (Millstein et al. 2004).

2.2.3. Experimental Studies

An experimental self-exposure was reported by Lehmann and Hasegawa (1913). Nitrogen oxide gas was produced by reaction of copper with nitric acid; the gas produced was collected over water and mixed with fresh air. Concentrations of total oxidation products, expressed as nitrous acid concentration, were determined analytically by either oxidation of hydrogen peroxide or by reduction using potassium iodide. Although the generated atmospheres were likely a mixture of nitrogen oxides, exposure concentrations were expressed as total nitric acid content and are reported in ppm as was done by NIOSH (1976b). One researcher exposed himself to nitric acid at 62 ppm (160 mg/m^3) for 1 h and reported irritation of the larynx, thirst, and an objectionable odor. He was then exposed at 74-101 ppm (190-260 mg/m^3) for 1 h and then at 23-43 ppm (60-110 mg/m^3) for another hour. Immediate severe irritation with cough and an increase in pulse and respiratory rates were reported after 40 min. He was able to tolerate exposure at 158 ppm (408 mg/m^3) but for only 10 min, due to coughing, severe burning in the nose and throat, lacrimation and heavy mucous secretion from the nose, a feeling of suffocation, headache, dizziness, and vomiting. On the basis of their results and comparing them with other work, the investigators estimated that the concentration causing no significant adverse effects would be below 50 ppm (130 mg/m^3).

In contrast to the above report, another researcher exposed himself and another individual to nitric acid fumes at a concentration of 11.6-12.4 ppm (30-32 mg/m^3) for 1 h (Diem 1907). Symptoms included irritation of the nasal mucosa, pressure in the chest, slight stabbing pains in the trachea and larynx, coughing, marked secretion from the nose and salivary glands, burning of the eyes and lacrimation, and burning and itching of facial skin. After 20 min, all symptoms except nasal secretion abated somewhat and a slight frontal headache developed. Some of these symptoms persisted for about 1 h post-exposure. In a second experiment, the researcher could tolerate 85 ppm (219 mg/m^3) for only 2-3 min. In these experiments, concentrations of nitric acid were produced by warming the acid and samples of the chamber air were measured by simple titration with the indicator Congo red. Differences in the methods used by Lehmann and Hasegawa (1913) and Diem (1907) for the production of nitric acid fumes as well as the detection methods probably account for the differences in effect levels.

A group of nine allergic adolescents (12-18 years old) was exposed to nitric acid gas and their pulmonary function was assessed. All subjects had exercise-induced bronchospasm defined as a greater than 15% drop in FEV_1 after 6 min of exercise at 85% maximum oxygen consumption. Five individuals also had allergic asthma. Individuals were exposed to nitric acid at 0.05 ppm (0.129

mg/m^3) through a rubber mouthpiece with nose clips for 40 min (30 min at rest, 10 min of moderate exercise on a treadmill). Each individual served as his or her own control with post-exposure pulmonary function values compared with baseline. After exposure to nitric acid, FEV_1 decreased by 4% and respiratory resistance increased by 23%. A post-exposure survey taken later that day or the following day did not indicate any correlation between exposure and symptoms of respiratory distress such as cough, pain or burning of the chest, fatigue, shortness of breath, or wheezing. On a separate testing day when subjects were exposed to only air, FEV_1 decreased by 2% and respiratory resistance increased by 7% (Koenig et al. 1989).

No changes in pulmonary function (vital capacity, respiratory resistance, and FEV_1) occurred in five healthy volunteers exposed at rest to nitric acid fumes at 1.6 ppm (4.13 mg/m^3) for 10 min (Sackner and Ford 1981). No changes in pulmonary function, lavage constituents, or bronchial biopsy specimens were found in 10 healthy, athletic subjects exposed to nitric acid gas at 0.194 ppm (0.5 mg/m^3) for 4 h during moderate exercise (Aris et al. 1993).

2.3. Developmental and Reproductive Toxicity

No information regarding the developmental or reproductive toxicity of nitric acid in humans was found.

2.4. Genotoxicity

No information regarding the genotoxicity of nitric acid in humans was found.

2.5. Carcinogenicity

No information regarding the carcinogenicity of nitric acid in humans was found.

2.6. Summary

Studies and case reports of exposure to nitric acid fumes and reaction products (e.g., nitrogen monoxide) are not directly relevant to nitric acid mists and vapor. However, the course of toxicity following inhalation exposures to atmospheres resulting from spills of nitric acid is consistent among the case reports. Nitric acid fumes may cause immediate irritation of the respiratory tract, pain, and dyspnea, followed by a period of recovery that may last several weeks. Relapse may occur, with death caused by bronchopneumonia or pulmonary fibrosis. Allergic or asthmatic individuals are the most sensitive populations when considering nonlethal concentrations of nitric acid.

3. ANIMAL TOXICITY DATA

Production of nitric acid atmospheres for inhalation exposure experiments potentially results in a variety of physical states (gas, fume, and vapor) depending on the production method used. For each study description below, the physical state and atmosphere generation methods are presented as described by the investigators.

3.1. Acute Lethality

3.1.1. Cats

Lehmann and Hasegawa (1913) conducted a series of experiments using cats exposed to nitric acid gases produced as described in Section 2.2.3. In general, as concentration or duration of exposure to nitric acid increased, death resulted from severe pulmonary edema. At concentrations less than about 388 ppm (1,000 mg/m^3), examination of the concentration and time relationship indicated that Ct products greater than about 900 ppm-h resulted in death whereas Ct products up to 760 ppm-h resulted in only a slight increase in respiration for several hours after exposure. Further, exposure at 287 ppm (740 mg/m^3) for 1.83 h (Ct = 526 ppm-h) caused no effects, whereas exposure at either 341 ppm (880 mg/m^3) for 3.83 h (Ct = 1,309 ppm-h) or 217 ppm (560 mg/m^3) for 4.25 h (Ct = 922 ppm-h) resulted in death. In contrast, at concentrations of 388 ppm (1,000 mg/m^3) or greater, severe clinical signs or death occurred at a Ct product as low as 277 ppm-h. Response probably depended on whether either the concentration of the acid or the duration of exposure was great enough to induce corrosive effects leading to edema. The data are limited because only one animal was tested at each concentration and time combination.

3.1.2. Rats

Groups of five male and five female Crl:CD®BR rats were exposed nose-only for to nitric acid aerosol at 260-3,100 ppm for 1 h, followed by a 14-day observation period (DuPont 1987). Atmospheres were generated with a nebulizer and airborne test material was dispersed with a baffle. Although an aerosol was generated, concentrations were reported in the study as ppm instead of mg/m^3. Aerosol content was assumed to be 100% at the three highest concentrations and ranged from 15-73% at the five lower concentrations as measured on a gravimetric filter sample. Except for the 2,500 and 2,700 ppm concentrations, all exposures contained 70% or more respirable particles, with a mass median aerodynamic diameter (MMAD) of 4.0 μm or less. The 2,500- and 2,700-ppm concentrations contained 59 and 61% respirable particles and had mass median aerodynamic diameters of 6.5 and 6.6 μm, respectively. Despite generation of the small particle size resulting in a high percentage of respirable particles, it is un-

clear why the concentrations were reported in ppm rather than mg/m^3. Nitrogen dioxide was not detected in the exposure atmospheres.

Clinical signs included clear nasal discharge at "some" concentrations, body weight loss for 1-2 days at 260 and 470 ppm, partially closed eyes at 1,300 ppm or higher, lung noise and gasping at 1,600 ppm or higher, and extended weight loss up to 12 days post-exposure at 1,500 ppm or higher for males and 1,600 ppm or higher for females. Mortality results are presented in Table 5-3. The 1-h LC_{50} for males and females combined was 2,500 ppm. Although males died at lower concentrations than females, no apparent differences in clinical responses or LC_{50} values were observed between males and females (DuPont 1987).

Gray et al. (1954) compared the toxicities of nitrogen dioxide, red fuming nitric acid (RFNA) (containing 8-17% nitrogen dioxide), and white fuming nitric acid (WFNA) (containing 0.1-0.4% nitrogen dioxide) by inhalation in rats. Outcomes related to exposure to RFNA and nitrogen dioxide are reported here to provide a complete description of the study; however, the chemicals are not directly relevant to nitric acid fumes. Although graphs of the dose-response curves were presented in the paper, the authors did not include the data from which those curves were plotted. Exposure concentrations for RFNA and WFNA were measured and reported as nitrogen dioxide. Thirty-minute LC_{50} values were reported to be 174 ppm (449 mg/m^3) for nitrogen dioxide, 138 ppm (356 mg/m^3) for RFNA as nitrogen dioxide, and 244 ppm (630 mg/m^3) for WFNA as nitrogen dioxide. Deaths were from pulmonary edema. The dose-response curves for nitrogen dioxide and RFNA for 30-min exposures were parallel statistically, indicating a possible similar mode of action for the two gases. But the curves were somewhat different at lower concentrations for an exposure duration of 240 min. For WFNA, the investigators reported that deaths were not as "predictable" as with the other gases. The approximate LC_{50} indicates that WFNA is much less toxic (has a higher LC_{50}) than either RFNA or nitrogen dioxide. Therefore, the investigators concluded that the main toxic component of these oxides of nitrogen is nitrogen dioxide. However, NIOSH (1976a) calculated LC_{50}s for RFNA and WFNA of 310 ppm (800 mg/m^3) and 334 ppm (862 mg/m^3), respectively, on the basis of total nitric acid concentration. The calculations were based on molecular weights and the percentage of nitrogen dioxide in RFNA and WFNA. These estimates suggest the possibility that both nitric acid vapor and nitrogen dioxide contribute to the toxicity.

3.2. Nonlethal Toxicity

3.2.1. Dogs

Mongrel dogs were used as a model of bronchial injury induced by nitric acid (Peters and Hyatt 1986; Fujita et al. 1988). One day per week, dogs were anesthetized and a catheter placed in the mainstem bronchus; nitric acid at 1% was delivered as a course spray via a nebulizer with approximately 5 mL to the

left lung and 8 mL to the right lung. For an additional two exposures per week, dogs were intubated and spontaneously breathed nitric acid mist at 1% for 2 h. This exposure regime was continued for 4 weeks and the dogs were killed either immediately or after a 5-month recovery period. Dogs developed intermittent cough and produced clear mucoid sputum within one week after treatment began. After 4 weeks, animals exhibited a decrease in total lung capacity and vital capacity with evidence of obstruction, as measured by a decrease in forced expiratory volume and expiratory flow. Increased flow resistance was observed after 14 days and continued to increase throughout the exposure period. Airway obstruction persisted for 5 months post-exposure with significant reductions in maximal expiratory flows. Necropy performed on dogs killed immediately after exposure revealed edematous lungs with areas of focal hemorrhage. Lungs appeared normal in dogs after 5 months of recovery. Histologically, chronic airway inflammation, slight epithelial changes, slight peribronchiolar fibrosis, and an increase in smooth muscle that persisted for 5 months post-exposure were found. Severity of the pathologic lesions directly correlated with decreases in pulmonary function (Peters and Hyatt 1986; Fujita et al. 1988). However, it is not possible to determine from this protocol which method of exposure was the most damaging to the airways.

Bronchiolitis obliterans was produced in dogs after instillation of nitric acid at 1% into the airways. Two instillations of three 5-mL aliquots were given approximately 2 weeks apart and pulmonary function tests performed 2 weeks later. Treated dogs had mild cough with slight hemoptysis immediately after each treatment. Several pulmonary function tests indicated increased peripheral airway resistance, and acute and chronic inflammation of the small airways were observed at necropsy (Mink et al. 1984).

TABLE 5-3 Mortality in Rats Exposed Nose-Only to Nitric Acid for 1 Hour

	Mortality	
Concentration (ppm)	Males	Females
260	0/5	0/5
470	0/5	0/5
1,300	1/5	0/5
1,500	1/5	0/5
1,600	2/5	0/5
2,500	2/5	1/5
2,700	2/5	1/5
3,100	5/5	5/5

Source: DuPont 1987.

3.2.2. Rats

Rats were treated once with 0.15 mL of nitric acid at 1% by intratracheal instillation. Focal lung damage found 1 day after administration consisted of bronchiolar inflammation with inflammatory cell infiltration. Absorption rates from the lung were significantly ($p \leq 0.05$) increased for both lipid-soluble and lipid-insoluble drugs (Gardiner and Schanker 1976).

To study the long-term effects of exposure to nitric acid, rats (about 10 per group) were exposed nose-only to nitric acid at 0, 5.1, 7.0, 13, or 19 ppm for 6 h/day on alternate days for a total of six exposures. Rats were then held for 22 months. Mortality was not affected in any group and no adverse effects were noted (Ballou et al. 1978).

3.2.3. Hamsters

Lung injury was induced in Syrian golden hamsters by a single tracheal instillation of nitric acid at 0.5% (0.5 mL saline/100 g body weight) (Coalson and Collins 1985). Several animals (number not specified) died before day 3 post-treatment and had severe hemorrhagic pulmonary edema. Airway changes in the remaining hamsters included acute bronchitis, acute bronchiolitis, obliterative bronchiolitis, bronchiolectasia, and bronchiectasis. These pathologic changes were accompanied by decreased lung volumes, decreased internal surface areas, increased lung weights, and increased elastin content. Airway dilatation and morphometric and biochemical changes persisted through day 60 post-treatment (the last day animals were examined).

In a similar experiment, hamsters were exposed via intratracheal instillation to 0.5 mL of nitric acid at 0.1 N. Up to 17 weeks post-exposure, histologic lesions in the lung included secretory cell metaplasia, interstitial fibrosis, bronchiolectasis, and diffuse extension of hyperplastic bronchiolar epithelium into adjacent alveoli (Christensen et al. 1988).

3.2.4. Sheep

Effects of nitric acid vapor on carbachol reactivity in normal and allergic sheep were investigated (Abraham et al. 1982). Allergic sheep are those with a history of developing bronchospasm after inhalation challenge with *Ascaris suum* antigen; the induced airway response is similar to that which occurs in humans with allergic airway disease. Measurements of lung resistance were taken before exposure, after 20 breaths of carbachol at 2.5% (to induce bronchoconstriction), and after exposure to nitric acid vapor at 1.6 ppm (4.13 mg/m^3) for 4 h. Immediately after treatment with nitric acid, sheep were given a second bronchial challenge with aerosolized carbachol. Nitric acid exposure alone did not

result in bronchoconstriction in either normal or allergic sheep, as measured by specific lung resistance. However, airway hyperreactivity to carbachol after nitric acid exposure occurred in allergic sheep. Pulmonary flow resistance from carbachol challenge before and after exposure to nitric acid increased by 68 and 78%, respectively, in normal sheep and 82 and 120% ($p \leq 0.05$), respectively, in allergic sheep (Abraham et al. 1982).

3.3. Developmental and Reproductive Toxicity

No information regarding the developmental or reproductive toxicity of nitric acid in animals was found.

3.4. Genotoxicity

Nitric acid at up to 0.008% was negative in mutagenicity tests with *Escherichia coli* (Demerec et al. 1951).

3.5. Carcinogenicity

No information regarding the carcinogenicity of nitric acid in animals was found. Lung damage in rats, induced by intratracheal instillation of 0.25 mL of nitric acid at 1%, did not enhance the rate of lung cancer caused by 3-methylcholanthrene (Blenkinsopp 1968).

3.6. Summary

Because of the corrosive nature of nitric acid, the chemical has been used to produce pulmonary changes in animal models of obstructive lung disease (Coalson and Collins 1985; Peters and Hyatt 1986; Fujita et al. 1988). Experiments with sheep (Abraham et al. 1982) have demonstrated the sensitivity of allergic individuals to acidic atmospheres.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information regarding the pharmacokinetics of nitric acid was found. Because of its high water solubility and reactivity, nitric acid would be expected to undergo significant removal in the upper respiratory tract. However, in a model system, Chen and Schlesinger (1996) showed that particulates can act as vectors for adsorbed or absorbed nitric-acid transport to the lower respiratory tract.

4.2. Mechanism of Toxicity

Nitric acid is a highly corrosive, strongly oxidizing acid (O'Neil et al. 2006). Contact with the liquid causes burns on the skin and corneal opacity (NIOSH 1976a). A 4-h occluded patch test induced skin corrosion in rabbits with nitric acid at 8%, but not 6% (Vernot et al. 1977). Respiratory irritation attributed to nitric acid is almost certainly due to the corrosive properties of the chemical. Because of its high water solubility and reactivity, nitric acid would be expected to undergo significant removal in the upper respiratory tract. However, some experiments indicate that bronchial responsiveness can be altered. In a model system, Chen and Schlesinger (1996) showed that particulates can act as vectors for adsorbed or absorbed nitric-acid transport to the lower respiratory tract. Reaction with endogenous ammonia and water may also produce particulates which can act as vectors.

4.3. Structure-Activity Relationships

Inhalation exposures to nitric acid fumes involve exposure to nitric acid as well as nitrogen oxides such a nitrogen dioxide (NO_2) and nitric oxide (NO). Fuming nitric acid reacts with wood or metals and emits fumes of nitrogen dioxide, which form equimolar amounts of nitrous and nitric acid when in contact with steam (NIOSH 1976a; O'Neil et al. 2006). In the presence of light, nitric acid undergoes an oxidation-reduction reaction to produce nitrogen dioxide, water, and oxygen. Nitric oxide reacts quantitatively with oxygen in air to form nitrogen dioxide which then reacts with water to form nitric acid. Most reports of human occupational exposure are limited to measurements of nitrogen oxides (NIOSH 1976a). In animal experiments, Lehmann and Hasagawa (1913) showed that up to a concentration of about 272 ppm (700 mg/m^3), toxic response was the same whether the gas contained nitric acid alone or was a mixture of nitrous and nitric acid.

As discussed in Section 3.1.2, Gray et al. (1954) compared the toxicities of nitrogen dioxide, RFNA, and WFNA in male rats. The dose-response curves for nitrogen dioxide and RFNA for 30-min exposures were parallel statistically, indicating a similar mode of action for the two gases. For both gases, deaths were from pulmonary edema. The 30-min LC_{50} value was 174 ppm (449 mg/m^3) for nitrogen dioxide and 138 ppm as nitrogen dioxide (356 mg/m^3) for RFNA. With exposures to WFNA, the authors stated that deaths were not as "predictable as with the other gases". The approximate LC_{50} for WFNA (244 ppm as nitrogen dioxide [630 mg/m^3]) indicates it is less toxic than either RFNA or nitrogen dioxide. Therefore, the investigators concluded that the main toxic component of these oxides of nitrogen is nitrogen dioxide, and that RFNA is approximately 25% more toxic than nitrogen dioxide because of the contribution by the acid component. However, NIOSH (1976a) calculated LC_{50}s for RFNA and WFNA of 310 ppm (800 mg/m^3) and 334 ppm (862 mg/m^3), respectively,

on the basis of total nitric acid concentration. The calculations were based on molecular weights and the percentage of nitrogen dioxide in RFNA and WFNA. Because the values are very similar, it suggests the possibility of a synergistic effect between nitric acid vapor and nitrogen dioxide, because RFNA has a higher nitrogen dioxide content by weight than WFNA.

The supposition that nitric acid and nitrogen dioxide interact to cause enhanced toxicity is also supported, in part, by the inhalation toxicokinetics experiments of Goldstein et al. (1977) in Rhesus monkeys. Approximately 50-60% of inhaled nitrogen dioxide was retained by monkeys and distributed throughout the lungs. Radioactivity was retained in the lungs during a 21-min post-exposure period with extrapulmonary distribution (percent not quantified) via the bloodstream. The investigators speculate that the reaction of inhaled nitrogen dioxide with water vapor in the lungs and with liquid water in the mucous results in the formation of nitric acid and accounts for the long retention time in the lung.

It is apparent from the above discussion that the toxic action of nitric acid cannot be considered without taking into account the effects of nitrogen dioxide. However, nitric acid fumes will contain nitrogen dioxide upon contact with water, such that reports of experimental or accidental exposures to nitric acid fumes will account for the toxicity contributed by nitrogen dioxide. NIOSH (1976b) described the effects of nitrogen dioxide in humans as involving initial irritation with mild dyspnea during exposure followed by delayed onset of pulmonary edema after several hours of apparent recovery. A similar toxic response, including interstitial fibrosis, has been shown in five species of animals following acute inhalation exposure to nitrogen dioxide (Hine et al. 1970). This course of toxicity is identical to that described for nitric acid, but the concentrations eliciting responses are very different for the two chemicals. For example, 75 ppm is the concentration at which deaths were first observed in rats exposed to nitrogen dioxide for 1 h (Hine et al. 1970) whereas 1,300 ppm was the concentration for nitric acid (DuPont 1987). Also, on the basis of the LC_{50} values for the rat, nitrogen dioxide appears to be more toxic than nitric acid. Therefore, using data from inhalation studies of nitrogen dioxide might be an overly conservative approach for establishing AEGL values for nitric acid. If nitrogen dioxide is of concern, AEGL values for that chemical have been established (see NRC 2012).

4.4. Other Relevant Information

4.4.1. Species Variability

There are no apparent species differences in the toxic response to acute inhalation exposure to nitric acid. Nitric acid fumes may cause immediate irritation of the respiratory tract, pain, and dyspnea, which are followed by a period of recovery that may last several weeks. Relapse may occur, with death from bronchopneumonia or pulmonary fibrosis (NIOSH 1976a; ACGIH 1991). Toxic response is similar between humans and animals. Dogs (Peters and Hyatt 1986; Fujita et al. 1988) and hamsters (Coalson and Collins 1985) have been used as

models of obstructive airway disease, and experiments in sheep (Abraham et al. 1982) have demonstrated the sensitivity of allergic individuals to nitric acid.

4.4.2. Susceptible Populations

Epidemiologic studies indicate that asthmatics may be more sensitive to acidic atmospheres (Ostro et al. 1991; Dockery et al. 1996). Data from one of these studies indicates that children with a history of allergy or asthma may be a sensitive subpopulation. In 24 communities in the United States and Canada, the concentration of nitric acid ranged from 0.3 to 2.1 ppb and that of nitrous acid ranged from 0.1 to 1.4 ppb; these were combined as gaseous acids. Among children aged 8-12 years, these gaseous acids (but not nitric acid alone) were associated with a significantly higher risk of asthma (odds ratio = 2.00; 95% CI: 1.14-3.53) and showed a positive correlation with higher reporting of attacks of wheezing, persistent wheeze, and any asthmatic symptoms (Dockery et al. 1996). However, no effects in an experimental study in which allergic adolescents were exposed to nitric acid were reported (Koenig et al. 1989).

Abraham et al. (1982) showed that airway hyperreactivity to carbachol occurred in allergic sheep following a 4-h exposure to nitric acid at 1.6 ppm (4.13 mg/m^3). Specific airway resistance before and after exposure to nitric acid increased by 68 and 78%, respectively, in normal sheep and 82 and 120% ($p \leq 0.05$), respectively, in allergic sheep. These data confirm that allergic individuals are potentially a sensitive subpopulation.

4.4.3. Concentration-Exposure Duration Relationship

Little data were available to analyze the concentration-exposure duration relationship for nitric acid. The most reliable study (DuPont 1987) used a single duration over a large range of concentrations. However, lethality data in the rat indicates that 100% mortality is reached abruptly, indicating a steep concentration-response.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

A no-effect level of 1.6 ppm (4.13 mg/m^3) was reported for changes in pulmonary function (vital capacity, respiratory resistance, and FEV_1) in five healthy volunteers exposed at rest to nitric acid vapor for 10 min (Sackner and Ford 1981). That concentration is the highest no-observed-adverse-effect level available in humans. An experimental self-exposure to nitric acid at 62 ppm (160 mg/m^3) for 1 h resulted in irritation of the larynx, thirst, and an objectionable odor (Lehmann and Hasegawa 1913).

5.2. Summary of Animal Data Relevant to AEGL-1

Most animal studies of nitric acid involved lethal concentrations or were performed using intratracheal instillation, a route not comparable to inhalation exposure.

5.3. Derivation of AEGL-1 Values

The highest no-effect level for AEGL-1 effects in humans of 1.6 ppm (4.13 mg/m^3) for 10 min was used to derive AEGL-1 values. An uncertainty factor of 10 was applied to account for variability in response in the general population and possibly greater sensitivity of asthmatics to a direct-acting irritant. Time scaling was not performed because a no-effect level for irritation was used as the point of departure and such irritation is generally concentration dependent but not time dependent, so the 10-min value was applied to all the other AEGL durations. AEGL-1 values for nitric acid are presented in Table 5-4.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Human data relevant to AEGL-2 values were not found. Experimental studies in which results consistent with AEGL-2 end points were described did not expose individuals to pure nitric acid, but generated an atmosphere containing a mixture of nitrogen oxides (Diem 1907; Lehmann and Hasegawa 1913).

6.2. Summary of Animal Data Relevant to AEGL-2

The most relevant animal data for deriving AEGL-2 values were those from a study by DuPont (1987). The study was well conducted and controlled for potential nitrogen dioxide contamination. Groups of five male and five female Crl:CD®BR rats were exposed nose-only to nitric acid aerosol at 260-3,100 ppm for 1 h, followed by a 14-day observation period. Clinical signs included clear nasal discharge at "some" concentrations, body weight loss for 1-2 days at 260 and 470 ppm, partially closed eyes at concentrations of 1,300 ppm and higher, lung noise and gasping at 1,600 ppm and higher, and extended weight loss for up to 12 days post-exposure at 1,500 ppm and greater for males and 1,600 ppm and greater for females.

TABLE 5-4 AEGL-1 Values for Nitric Acid

10 min	30 min	1 h	4 h	8 h
0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)

No long-term effects from exposure to nitric acid were observed in rats exposed at up to 19 ppm for 6 h on alternate days for a total of six exposures (Ballou et al. 1978).

6.3. Derivation of AEGL-2 Values

A study of rats exposed to nitric acid at 470 ppm for 1 h (DuPont 1987) was used to derive AEGL-2 values. The point of departure is a no-effect level for impaired ability to escape. Effects observed at 470 ppm were transient body weight loss 1-2 days post-exposure. At the next higher concentration, rats exhibited partially closed eyes (a possible sign of severe ocular irritation), which could definitely impair escape, and lung noise. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific value for n, scaling was performed using the default values of n = 3 for extrapolating to the shorter durations (10 and 30 min) and n = 1 for extrapolating to the longer durations (4 and 8 h). A total uncertainty factor of 10 was used: a factor of 3 for interspecies differences and 3 for intraspecies variability. Larger uncertainty factors were considered unnecessary because the mechanism of action of a direct ocular irritant and of a corrosive acid in the lung is not expected to differ greatly between species or among individuals. In addition, a modifying factor of 2 was applied because clinical observations were not well described, and the AEGL-2 values overlap AEGL-3 values, suggesting a very steep concentration-response relationship. AEGL-2 values for nitric acid are presented in Table 5-5.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Limited human data useful for deriving AEGL-3 values are available. Case reports of lethal exposures from accidents do not contain information on exposure concentrations. An experimental self-exposure was reported by Lehmann and Hasegawa (1913). One of the researchers exposed himself to nitric acid at 74-101 ppm (190-260 mg/m^3) for 1 h and then at 23-43 ppm (60-110 mg/m^3) for another hour. He experienced immediate severe irritation with cough and an increase in pulse and respiratory rates after 40 min. Because severe symptoms were immediate, the average concentration of 88 ppm during the first hour of exposure was assumed to be close to intolerable but not lethal. The subject was able to tolerate exposure to nitric acid at 158 ppm (408 mg/m^3), but for only 10 min due to coughing, severe burning in the nose and throat, lacrimation, heavy mucous secretion from the nose, a feeling of suffocation, headache, dizziness, and vomiting.

TABLE 5-5 AEGL-2 Values for Nitric Acid

10 min	30 min	1 h	4 h	8 h
43 ppm (110 mg/m^3)	30 ppm (77 mg/m^3)	24 ppm (62 mg/m^3)	6.0 ppm (15 mg/m^3)	3.0 ppm (7.7 mg/m^3)

7.2. Summary of Animal Data Relevant to AEGL-3

Animal data relevant to derivation of AEGL-3 values are limited to the LC_{50} study by DuPont (1987). This well-conducted study controlled for potential nitrogen dioxide contamination. Groups of five male and five female Crl:CD®BR rats were exposed nose-only to nitric acid aerosol at 260-3,100 ppm for 1 h, followed by a 14-day observation period. Clinical signs included clear nasal discharge at some concentrations, body weight loss for 1-2 days at 260 and 470 ppm, partially closed eyes at 1,300 ppm and higher, lung noise and gasping at 1,600 ppm and higher, and extended weight loss for up to 12 days post-exposure at 1,500 ppm and higher for males and 1,600 ppm and higher for females. The 1-h LC_{50} for males and females combined was 2,500 ppm. Deaths occurred at concentrations of 1,300 ppm and higher (see Table 5-3).

7.3. Derivation of AEGL-3 Values

A 1-h LC_{50} in rats was calculated by DuPont (1987). In this study, mortality ratios at each concentration were determined. On the basis of these data, an LC_{01} of 919 ppm was calculated by log-probit analysis. Values were time scaled using the equation $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific value for n, time scaling was performed using default values of n = 3 for extrapolating to shorter durations (10 and 30 min) and n = 1 for longer durations (4 and 8 h). A total uncertainty factor of 10 was used: a factor of 3 for interspecies differences and 3 for intraspecies variability. Use of larger uncertainty factors was considered unnecessary because the mechanism of action of a corrosive acid in the lung is not expected to differ greatly between species or among individuals. AEGL-3 values for nitric acid are presented in Table 5-6.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

AEGL values for nitric acid are presented in Table 5-7. AEGL-1 values were based on a no-effect level in humans. AEGL-2 values were based on a concentration which produced transient weight loss in rats, and AEGL-3 values on an estimated 1-h LC_{01} in rats. If nitrogen dioxide is of concern, AEGL values for that chemical are available (see NRC 2012).

8.2. Comparison with Other Standards and Guidelines

Standards and guidelines for workplace and community exposures to nitric acid are presented in Table 5-8. Some of the standards and guidelines have been developed on the basis of nitrogen dioxide or comparisons with other acids in the workplace. An occupational time weighted average (TWA) concentration of 2 ppm and a short term exposure limit (STEL) of 4 ppm have been adopted by several organizations (ACGIH 2003; OSHA [29 CFR 1910.1000 (2006)]; NIOSH 2011). ACGIH (2003) set the TWA as an intermediate value between that for hydrogen chloride and sulfuric acid and considers both the TWA and STEL to be sufficiently low to prevent ocular and upper respiratory tract irritation. International standards for nitric acid are also 2 ppm for a workday and 2-5 ppm for short-term limits (DFG 2002; Swedish Work Environment Authority 2005). The German MAK value is based on the results of a study by Diem (1907). The immediately dangerous to life or health (IDLH) value of 25 ppm (NIOSH 1994) is based on acute toxicity data in humans (conversion of lethal oral dose to an equivalent inhalation concentration) and animals (secondary source).

Emergency response planning guideline (ERPG) levels were developed for WFNA (AIHA 2001), and are based on toxicity data in animals exposed to nitric acid or nitrogen dioxide and dose-response estimates in humans exposed to nitrogen dioxide.

8.3. Data Adequacy and Research Needs

Limited inhalation data were available for determining AEGL values. Only one well-conducted study in rats was available. Most animal data administered nitric acid by intratracheal instillation, a route that does not necessarily mimic inhalation exposures. Data from human case reports lacked exposure concentrations and durations.

TABLE 5-6 AEGL-3 Values for Nitric Acid

10 min	30 min	1 h	4 h	8 h
170 ppm (440 mg/m^3)	120 ppm (310 mg/m^3)	92 ppm (240 mg/m^3)	23 ppm (59 mg/m^3)	11 ppm (28 mg/m^3)

TABLE 5-7 AEGL Values for Nitric Acid

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabliing)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)
AEGL-2 (disabling)	43 ppm (110 mg/m^3)	30 ppm (77 mg/m^3)	24 ppm (62 mg/m^3)	6.0 ppm (15 mg/m^3)	3.0 ppm (7.7 mg/m^3)
AEGL-3 (lethal)	170 ppm (440 mg/m^3)	120 ppm (310 mg/m^3)	92 ppm (240 mg/m^3)	23 ppm (59 mg/m^3)	11 ppm (28 mg/m^3)

TABLE 5-8 Standards and Guidelines for Nitric Acid

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)
AEGL-2	43 ppm (110 mg/m^3)	30 ppm (77 mg/m^3)	24 ppm (62 mg/m^3)	6.0 ppm (15 mg/m^3)	3.0 ppm (7.7 mg/m^3)
AEGL-3	170 ppm (440 mg/m^3)	120 ppm (310 mg/m^3)	92 ppm (240 mg/m^3)	23 ppm (59 mg/m^3)	11 ppm (28 mg/m^3)
ERPG-1 (AIHA)[a]			1 ppm		
ERPG-2 (AIHA)			6 ppm		
ERPG-3 (AIHA)			78 ppm		
IDLH (NIOSH)[b]		25 ppm			
TLV-TWA (ACGIH)[c]					2 ppm
REL-TWA (NIOSH)[d]					2 ppm
PEL-TWA (OSHA)[e]					2ppm
TLV-STEL (ACGIH)[f]	4ppm				
REL-STEL (NIOSH)[g]	4 ppm				
MAK (Germany)[h]					2 ppm
MAK Peak Limit (Germany)[i]	2 ppm				
OELV-LLV (Sweden)[j]					2ppm
OELV-STV (Sweden)[j]	5ppm				

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2011).
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 or developing health effect more severe than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
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.
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.

[b]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.
[c]TLV-TWA (threshold limit value - time weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2003) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.
[d]REL-TWA (recommended exposure limit - time weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-TWA.
[e]PEL-TWA (permissible exposure limit - time weighted average, Occupational Safety and Health Administration) ((29 CFR 1910.1000 [2006]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.
[f]TLV-STEL (threshold limit value – short-term exposure limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2003) is defined as a 15-min TWA exposure which should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.
[g]REL-STEL (recommended exposure limit – short-term exposure limit) (NIOSH 2011) is defined analogous to the ACGIH TLV-STEL.
[h]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 2002) is defined analogous to the ACGIH TLV-TWA.
[i]MAK spitzenbegrenzung (peak limit [Category I, 1], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 2002) constitutes the maximum average concentration to which workers can be exposed for a period up to 15 min with no more than four exposure periods per work shift and a minimum of 1 h between excursions.
[j]OEL-LLV (occupational exposure limit – level-limit value). OEL-STV (occupational exposure limit – short-term value) (Swedish Work Environment Authority 2005) is the maximum acceptable average concentration (time-weighted average) of an air contaminant in respiratory air. An occupational exposure limit value is either a level-limit value (1 working day) or a ceiling-limit value (15 min or some other reference time period), and a short-time value is a recommended value consisting of a time-weighted average for exposure during a reference period of 15 min.

9. REFERENCES

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APPENDIX A

DERIVATION OF AEGL VALUES FOR NITRIC ACID

Derivation of AEGL-1 Values

Key study:	Sackner, M.A., and D. Ford. 1981. Effects of breathing nitrate aerosols in high concentrations for 10 minutes on pulmonary function of normal and asthmatic adults, and preliminary results in normals exposed to nitric acid fumes. Am. Rev. Resp. Dis. 123(4Pt 2):151.
Toxicity end point:	No changes in pulmonary function (vital capacity, respiratory resistance, and FEV_1) were reported in five healthy volunteers exposed to nitric acid vapor at 1.6 ppm (4.13 mg/m^3) for 10 min at rest.
Time scaling:	Values were set equal across all AEGL durations because the point of departure is a no-effect level for irritation.
Uncertainty factors:	10 for intraspecies variability; to account for variability in response in the general population and possible greater sensitivity of asthmatics to effects of a direct-acting irritant on pulmonary function.
Modifying factors:	None
Calculations:	
10-min AEGL-1:	1.6 ppm ÷ 10 = 0.16 ppm
30-min AEGL-1:	Set equal to 10-min AEGL value of 0.16 ppm
1-h AEGL-1:	Set equal to 10-min AEGL value of 0.16 ppm
4-h AEGL-1:	Set equal to 10-min AEGL value of 0.16 ppm
8-h AEGL-1:	Set equal to 10-min AEGL value of 0.16 ppm

Derivation of AEGL-2 Values

Key study:	DuPont. 1987. One-hour Inhalation Median Lethal Concentration (LC50) Study with Nitric Acid. Report No 451-87. Haskell Laboratory, DuPont, Newark, DE. 26 pp.
Toxicity end points:	Exposure to nitric acid at 470 ppm for 1 h resulted in transient body weight loss 1-2 days post-exposure and was a no-effect level for eye closure and impairment of escape.
Time scaling:	$C^n \times t = k$ (default of n = 3 for extrapolating to the 10- and 30-min durations; default of n = 1 for extrapolating to the 4- and 8-h durations $(470 \text{ ppm} \div 20)^3 \times 1 \text{ h} = 12{,}977.875 \text{ ppm-h}$ $(470 \text{ ppm} \div 20)^1 \times 1 \text{ h} = 23.5 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability Total uncertainty factor of 10
Modifying factor:	2, because clinical observations were not well described, and AEGL-2 and AEGL-3 values overlap suggesting a very steep concentration-response relationship.
Calculations:	
10-min AEGL-2:	$C = (12{,}977.875 \text{ ppm-h} \div 0.167 \text{ h})^{1/3}$ $C = 43 \text{ ppm}$
30-min AEGL-2:	$C = (12{,}977.875 \text{ ppm-h} \div 0.5 \text{ h})^{1/3}$ $C = 30 \text{ ppm}$
1-h AEGL-2:	$470 \text{ ppm} \div 20 = 24 \text{ ppm}$
4-h AEGL-2:	$C = (23.5 \text{ ppm-h} \div 4 \text{ h})^1$ $C = 6.0 \text{ ppm}$
8-h AEGL-2:	$C = (23.5 \text{ ppm-h} \div 8 \text{ h})^1$ $C = 3.0 \text{ ppm}$

Derivation of AEGL-3 Levels

Key study:	DuPont. 1987. One-hour Inhalation Median Lethal Concentration (LC50) Study with Nitric Acid. Report No 451-87. Haskell Laboratory, DuPont, Newark, DE. 26 pp.
Toxicity end point:	LC_{01} of 919 ppm was calculated by log-probit analysis of mortality data in rats.
Time scaling:	$C^n \times t = k$ (default of n = 3 for extrapolating to the 10- and 30-min durations; default of n = 1 for extrapolating to the 4- and 8-h durations $(919 \text{ ppm} \div 10)^3 \times 1 \text{ h} = 776{,}151.559 \text{ ppm-h}$ $(919 \text{ ppm} \div 10)^1 \times 1 \text{ h} = 91.9 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability Total uncertainty factor of 10
Modifying factor:	None
Calculations:	
10-min AEGL-3:	$C = (776{,}151.559 \text{ ppm-h} \div 0.167 \text{ h})^{1/3}$ C = 170 ppm
30-min AEGL-3:	$C = (776{,}151.559 \text{ ppm-h} \div 0.5 \text{ h})^{1/3}$ C = 120 ppm
1-h AEGL-3:	C = 919 ppm ÷ 10 = 92 ppm
4-h AEGL-3:	$C = (91.9 \text{ ppm-h} \div 4 \text{ h})^1$ C = 23 ppm
8-h AEGL-3:	$C = (91.9 \text{ ppm-h} \div 8 \text{ h})^1$ C = 11 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR NITRIC ACID

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)

Reference: Sackner, M.A., and D. Ford. 1981. Effects of breathing nitrate aerosols in high concentrations for 10 minutes on pulmonary function of normal and asthmatic adults, and preliminary results in normals exposed to nitric acid fumes. Am. Rev. Resp. Dis. 123(4Pt 2):151.

Test species/Strain/Number: Humans, sex not specified, 10

Exposure route/Concentrations/Durations: Inhalation, 1.6 ppm for 10 min

Effects: No effects

End point/Concentration/Rationale: No-effect level for changes in pulmonary function (vital capacity, respiratory resistance, and FEV_1); highest no-effect level available in humans.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Intraspecies: 10, to account for variability in response in the general population and possibly greater sensitivity of asthmatics to effects of a direct-acting irritant on pulmonary function.

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Not performed; values were set equal across all AEGL durations because the point of departure is a no-effect level for irritation.

Data adequacy: Although no dose-response data was included in the study, the values are based on human data. The point of departure is the highest no-observed-adverse-effect level in humans.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
43 ppm (110 mg/m^3)	30 ppm (77 mg/m^3)	24 ppm (62 mg/m^3)	6.0 ppm (15 mg/m^3)	3.0 ppm (7.7 mg/m^3)

Reference: DuPont. 1987. One-hour Inhalation Median Lethal Concentration (LC_{50}) Study with Nitric Acid. Report No 451-87. Haskell Laboratory, DuPont, Newark, DE. 26 pp.

(Continued)

AEGL-2 VALUES Continued

Test species/Strain/Sex/Number: Rat, Crl:CD®BR, 5 males and 5 females per group

Exposure route/Concentrations/Durations: Inhalation, 270-3,100 ppm for 1 h

Effects:

Concentration (ppm)	Effects
260 and 470	Body weight loss for 1-2 days
≥1,300	Partially closed eyes
≥1,600	Lung noise and gasping
≥1,500	Extended weight loss up to 12 days post-exposure in males
≥1,600	Extended weight loss up to 12 days post-exposure in females
3,100	100% lethality

End point/Concentration/Rationale: No-effect level for impaired ability to escape (eye closure) was 470 ppm for 1 h.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because the mechanism of toxicity (direct reaction of nitric acid with ocular or pulmonary tissue) is not expected to vary between humans and animals.
Intraspecies: 3, because the mechanism of action of a corrosive acid in the eye or lung is not expected to differ greatly among individuals.

Modifying factor: 2, because clinical observations were not well described, and AEGL-2 and AEGL-3 values overlap suggesting a very steep concentration-response relationship.

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$; n = 3 for extrapolating to the 10- and 30-min durations, and n = 1 for extrapolating to the 4- and 8-h duration

Comments: Nitrogen dioxide content monitored during exposures; none measured.

AEGL -3 VALUES

10 min	30 min	1 h	4 h	8 h
170 ppm (440 mg/m^3)	120 ppm (310 mg/m^3)	92 ppm (240 mg/m^3)	23 ppm (59 mg/m^3)	11 ppm (28 mg/m^3)

Reference: DuPont. 1987. One-hour Inhalation Median Lethal Concentration (LC_{50}) Study with Nitric Acid. Report No 451-87. Haskell Laboratory, DuPont, Newark, DE. 26 pp.

Test species/Strain/Sex/Number: Rat, Crl:CD®BR, 5 males and 5 females per group

Exposure rRoute/Concentrations/Durations: Inhalation, 270-3,100 ppm for 1 h

Effects:

Concentration (ppm)	Effects
260 and 470	Body weight loss for 1-2 days; no death
1,300	1/10 died
1,500	1/10 died
1,600	2/10 died
2,500	3/10 died
2,700	3/10 died
3,100	10/10 died

End point/Concentration/Rationale: LC_{01} of 919 ppm estimated by log-probit analysis of mortality data.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because the mechanism of toxicity (direct reaction of nitric acid with ocular or pulmonary tissue) is not expected to vary between humans and animals.
Intraspecies: 3, because the mechanism of action of a corrosive acid in the eye or lung is not expected to differ greatly among individuals.

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$; n = 3 for extrapolating to the 10- and 30-min durations, and n = 1 for extrapolating to the 4- and 8-h durations

Comments: Nitrogen dioxide content monitored during exposures; none measured.

APPENDIX C

CATEGORY PLOT FOR NITRIC ACID

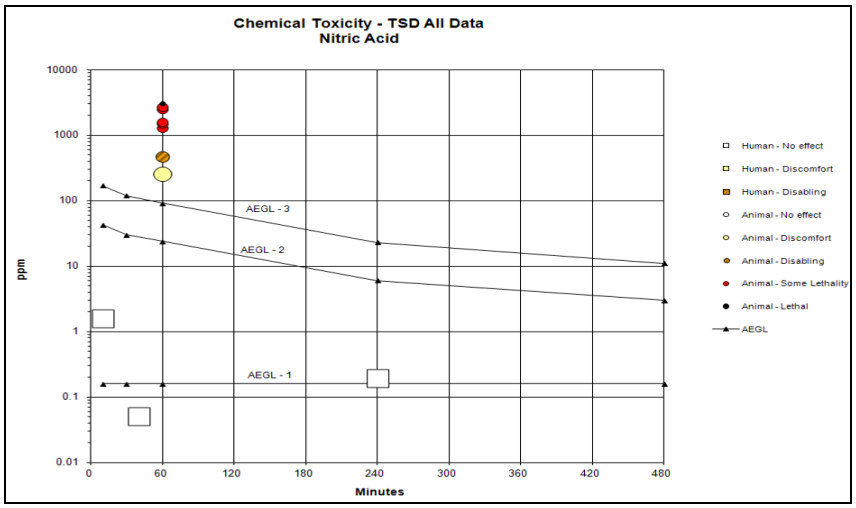

FIGURE C-1 Category plot of toxicity data and AEGL values for nitric acid.

TABLE C-1 Data Used in Category Plot for Nitric Acid

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
NAC/AEGL-1				0.16	10	AEGL	
NAC/AEGL-1				0.16	30	AEGL	
NAC/AEGL-1				0.16	60	AEGL	
NAC/AEGL-1				0.16	240	AEGL	
NAC/AEGL-1				0.16	480	AEGL	
NAC/AEGL-2				43	10	AEGL	
NAC/AEGL-2				30	30	AEGL	
NAC/AEGL-2				24	60	AEGL	
NAC/AEGL-2				6	240	AEGL	

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
NAC/AEGL-2				3	480	AEGL	
NAC/AEGL-3				170	10	AEGL	
NAC/AEGL-3				120	30	AEGL	
NAC/AEGL-3				92	60	AEGL	
NAC/AEGL-3				23	240	AEGL	
NAC/AEGL-3				11	480	AEGL	
Koenig et al. 1989	Human		1	0.05	40	0	
Sackner and Ford 1981	Human		1	1.6	10	0	
Aris et al. 1993	Human		1	0.194	240	0	
DuPont 1987	Rat	Both	1	260	60	1	Transient weight loss
	Rat	Both	1	470	60	2	Transient weight loss
	Rat	Both	1	1,300	60	SL	Mortality (1/10); partially closed eyes
	Rat	Both	1	1,500	60	SL	Mortality (1/10); weight loss
	Rat	Both	1	1,600	60	SL	Mortality (2/10); lung noise, gasping
	Rat	Both	1	2,500	60	SL	Mortality (3/10)
	Rat	Both	1	2,700	60	SL	Mortality (3/10)
	Rat	Both	1	3,100	60	3	Mortality (10/10)

For category: 0 = no effect, 1 = discomfort, 2 = disabling, 3 = lethal; SL = some lethality.

APPENDIX D

DERIVATION OF LC_{01} VALUE FOR NITRIC ACID

Filename: ten Berge Spreadsheet Data for Log Probit Model
Date: 01 March 2012 Time: 16:01:18

Sequence No.	Concentration (ppm)	Minutes	Exposed	Responded
1	260	60	10	0
2	470	60	10	0
3	1300	60	10	1
4	1500	60	10	1
5	1600	60	10	2
6	2500	60	10	3
7	2700	60	10	3
8	3100	60	10	10

Observations 1 through 8 considered!

Sequence No.	Concentration (ppm)	Minutes	Exposed	Responded
1	260	60	10	0
2	470	60	10	0
3	1300	60	10	1
4	1500	60	10	1
5	1600	60	10	2
6	2500	60	10	3
7	2700	60	10	3
8	3100	60	10	10

Used Probit Equation Y = B0 + B1*X1
X1 = ppm, ln-transformed

Chi-Square = 9.29
Degrees of freedom = 6
Probability Model = 1.58E-01

Ln(Likelihood) = -11.92

B 0 = -1.2890E+01 Student t = -2.7813
B 1 = 2.2809E+00 Student t = 3.7913

Variance B 0 0 = 2.1479E+01
Covariance B 0 1 = -2.7859E+00
Variance B 1 1 = 3.6193E-01

Estimation of ppm at response of 1%
Point estimate ppm = 9.192E+02 for response of 1%
Lower limit (95% CL) ppm = 3.509E+02 for response of 1%
Upper limit (95% CL) ppm = 1.273E+03 for response of 1%