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**ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
NITRIC ACID
(CAS Reg. No. 7697-37-2)**

**For
NAS/COT Subcommittee for AEGLs**

December 2008

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 to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) 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/m³]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory 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/m³) 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/m³) 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 levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory 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.

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SUMMARY

Nitric acid is a highly corrosive, strongly oxidizing acid. The course of toxicity following inhalation exposure to nitric acid is consistent between humans and animals. 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. After this time, a relapse may occur with death caused by bronchopneumonia and/or pulmonary fibrosis. For exposure to nonlethal concentrations, allergic or asthmatic individuals appear to be sensitive to acidic atmospheres (ACGIH 1991; NIOSH 1976a).

For derivation of the AEGL values, both human and animal data were utilized. For AEGL-1 a concentration of 0.53 ppm was adopted for all time points. The point of departure was based on the study of Sackner and Ford (1981) in which five healthy volunteers exposed to 1.6 ppm for 10 minutes showed no changes in pulmonary function. This is the highest NOAEL available in humans. An uncertainty factor of 3 was applied to account for sensitive populations because the mechanism of action of a direct acting irritant is not expected to differ greatly among individuals. Extrapolation to the 30-minute, 1-, 4-, and 8-hour time points was not performed because this was based on a no effect level and irritation is generally concentration dependent but not time dependent. The derived AEGL-1 value is above the odor threshold which provides a warning of exposure before an individual could experience notable discomfort.

AEGL-2 and -3 values were based on a lethality study in rats (Du Pont 1987). This was a well conducted study in which mortality ratios at each concentration were given. Groups of 5 Crl:CD[®]BR rats/sex were exposed nose-only for 1 hour to 260-3100 ppm of nitric acid aerosol followed by a 14-day observation period. Exposure of rats to 470 ppm for 1 hour, which resulted in transient body weight loss 1-2 days post-exposure, was used to derive AEGL-2 values. The point of departure is a NOAEL for AEGL-2 effects and would not be escape impairing; higher concentrations resulted in more severe clinical signs including partially closed eyes and lung noise. Extrapolations to the 10- and 30-minute, and 4-, and 8-hour time periods were done following the equation $C^n \times t = k$ (ten Berge et al., 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using $n = 3$ for extrapolating to the 10- and 30-minute time points and $n = 1$ for the 4- and 8-hour time points. A total uncertainty factor of 10 was used including a 3 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty factors was not considered to be necessary because the mechanism of action 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, a concentration-response could not be determined for nonlethal effects, and clear evidence of AEGL-2 effects did not occur in the study.

AEGL-3 was based on an estimated LC_{01} calculated by a log-probit analysis from the lethality study in rats (Du Pont 1987). The resulting LC_{01} of 919 ppm was used to derive AEGL-3 values. Values were 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 exponent, scaling was performed using $n = 3$ for extrapolating to the 10- and 30-minute time points and $n = 1$ for the 4- and 8-hour time points. A total uncertainty factor of 10 was used including a 3 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty factors was not considered to be necessary because the mechanism of action of a corrosive acid in the lung is not expected to differ greatly between species or among individuals.

The calculated values for the three AEGL classifications for the five time periods are listed in the table below. Note that if NO₂ is of concern the technical support document on AEGLs for NO₂ should be consulted.

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	0.53 [1.4]	0.53 [1.4]	0.53 [1.4]	0.53 [1.4]	0.53 [1.4]	NOAEL for changes in pulmonary function in humans (Sackner and Ford 1981)
AEGL-2	43 [111]	30 [77]	24 [62]	6.0 [15]	3.0 [8]	transient weight loss in rats 1-2 days after a 1-hour exposure to 470 ppm (Du Pont 1987)
AEGL-3	170 [439]	120 [310]	92 [237]	23 [59]	11 [28]	estimated LC ₀₁ from lethality data in rats (Du Pont 1987)

References

ACGIH. 1991. American Conference of Governmental Industrial Hygienists, Inc. Nitric Acid. In: Documentation of the Threshold Limit Values and Biological Exposure Indices, 6th ed., ACGIH, Cincinnati, OH, pp. 1088-1089.

Du Pont Co. 1987. One-hour inhalation median lethal concentration (LC₅₀) study with nitric acid. Haskell Laboratory Report No 451-87. Newark, Delaware. 26pp.

NIOSH. 1976a. National Institute for Occupational Safety and Health. NIOSH criteria for a recommended standard.... occupational exposure to nitric acid. U.S. Department of Health, Education, and Welfare, Washington, D.C., HEW publication No. (NIOSH) 76-141, 78pp.

ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mat. 13:301-309.

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.* 123:151.

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 (NO₂) which gives the liquid a yellow color. Concentrated nitric acid containing dissolved NO₂ is termed fuming nitric acid which evolves suffocating, poisonous fumes of nitrogen dioxide and nitrogen tetroxide (Budavari et al. 1996). White fuming nitric acid contains 0.5% dissolved NO₂ while red fuming nitric acid contains 14% dissolved NO₂ (ACGIH 1991).

Inhalation exposures to nitric acid involves exposure to nitric acid as well as nitrogen oxides such as nitrogen dioxide (NO₂) and nitric oxide (NO). Fuming nitric acid reacts with wood or metals and emits fumes of NO₂ which form equimolar amounts of nitrous and nitric acid when in contact with steam (Budavari et al. 1996; NIOSH 1976a). NO reacts quantitatively with oxygen in air to form NO₂ which then reacts with water to form nitric acid. Most reports of human occupational exposure are limited to measurements of nitrogen oxides (NIOSH 1976a). Note that if other oxides of nitrogen are of concern the technical support document on AEGLs for NO₂ should be consulted.

Production of nitric acid atmospheres for inhalation exposure experiments potentially results in a variety of physical states (i.e., gas, fume, vapor) depending on the production method used. For each study description in this technical support document, the physical state and atmosphere generation methods are given 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). The chemical contributes to acid deposition (or acid rain). Nitric acid is a large contributor to acid deposition in the western United States compared to the eastern states (NARSTO 2004). Selected physicochemical properties of nitric acid are listed in Table 1.

TABLE 1. PHYSICOCHEMICAL DATA FOR NITRIC ACID

Parameter	Value	Reference
Common name	nitric acid	
Synonyms	Aquafortis	Budavari et al., 1996
CAS registry no.	7697-37-2	
Chemical formula	HNO ₃	Budavari et al., 1996
Molecular weight	63.2	Budavari et al., 1996
Physical state	colorless liquid; fumes in moist air	Budavari et al., 1996
Vapor pressure	47.9 mm Hg at 20°C	ACGIH, 1991
Vapor density (air = 1)	2-3 (estimated)	HSDB, 1996
Specific gravity	1.50269	Budavari et al., 1996
Melting/boiling	-41.59°C/83°C	Budavari et al., 1996; HSDB, 1996
Solubility in water	freely soluble	U.S. EPA, 1993a
Conversion factors in air	1 mg/m ³ = 0.388 ppm 1 ppm = 2.58 mg/m ³	U.S. EPA, 1993a
Flammability	noncombustible	U.S. EPA, 1993a
pH (0.5% in saline)	1.6	Coalson and Collins, 1985

2. HUMAN TOXICITY DATA

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

2.1 Acute Lethality

Hall and Cooper (1905) described the 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. 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 persisting an average of 15.5 days. Four individuals died, two on the second day following exposure and two several weeks later from relapse. The two who died during relapse appeared to be recovering as well as the other survivors, however, both were exposed to cold air and almost immediately entered relapse. Autopsy revealed hemorrhagic edema and coagulation necrosis. Exposure concentrations were not measured but the authors 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 1736 L of 68% nitric acid. Escape from the building took 10-15 minutes. No respiratory problems were apparent upon medical examination immediately following exposure, however, increasing respiratory difficulties developed 4-6 hours later. On admission to the hospital, all were cyanotic with frothy fluid escaping from the nose and mouth. All died within 21 hours after the accident. Pathological evaluation of the lungs revealed degranulated and necrotic neutrophils within the alveolar capillaries. The 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. The first symptoms of respiratory distress occurred 30 minutes later; approximately 1 hour later he entered a hospital emergency room with dyspnea, expiratory stridor, peripheral cyanosis, and general paleness. Chest x-ray showed pulmonary edema. With intense treatment the patient stabilized for 3 days and lung function improved. However, on the fourth day the patient died from refractory respiratory failure and pulmonary edema was observed at autopsy (Bur et al. 1997).

Other lethal exposure scenarios have been summarized (ACGIH 1991; NIOSH 1976a). 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. After this time, a relapse may occur with death caused by bronchopneumonia and/or pulmonary fibrosis. Unfortunately exposure concentrations were not given in the primary reports.

2.2 Nonlethal Toxicity

Nitric acid is described as having a characteristic choking odor (Budavari et al. 1996). Low and high odor thresholds in air were listed as 0.29 and 0.97 ppm, respectively (U.S. EPA 1993a).

2.2.1 Case Reports

A 42-year old male with no history of respiratory disease was exposed for 3 hours 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 the 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 *per se* was not specifically associated with any respiratory symptom analyzed. The nitric acid concentrations ranged from 0.06 to 13.54 $\mu\text{g}/\text{m}^3$ (0.15 to 34.93 ppb) during the study period.

The health effects of exposure to acidic air pollution among children aged 8 to 12 years 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, the children were administered pulmonary function tests consisting of forced vital capacity (FVC) and forced expiratory volume (FEV) measurements. The concentration 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% 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 levels of both acid and NO_2 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.

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, the exposure concentrations were expressed as total nitric acid content and are listed here in ppm as reported by NIOSH (1976b). One of these researchers exposed himself to 62 ppm (160 mg/m^3) for 1 hour and reported irritation of the larynx, thirst, and an objectionable odor. He was then exposed to 74-101 ppm (190-260 mg/m^3) for 1 hour followed by 23-43 ppm (60-110 mg/m^3) for another hour and experienced immediate severe irritation with cough and an increase in pulse and respiratory rates after 40 minutes. He was able to tolerate exposure to 158 ppm (408 mg/m^3) but for only 10 minutes 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. Based on their results of human exposures and by comparing this to other work, the authors estimated that the concentration causing no significant adverse effects would be below 50 ppm (130 mg/m³).

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/m³) for 1 hour (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 minutes, all symptoms except nasal secretion abated somewhat and a slight frontal headache developed. Some of these symptoms persisted for about 1 hour postexposure. For a second experiment, the author could tolerate 85 ppm (219 mg/m³) for only 2-3 minutes. In these experiments, the exposure concentrations were produced by warming the acid and samples of the chamber air were measured for concentration by simple titration with the indicator Congo red. The 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 9 allergic adolescents ranging in age from 12-18 years old, was exposed to nitric acid gas and pulmonary function was assessed. All subjects had exercise-induced bronchospasm defined as a >15% drop in FEV₁ after 6 minutes of exercise at 85% maximum oxygen consumption. Five individuals also had allergic asthma. Individuals were exposed through a rubber mouthpiece with nose clips to 0.05 ppm (0.129 mg/m³) nitric acid for 40 minutes (30 minutes at rest plus 10 minutes of moderate exercise on a treadmill). Each individual served as his or her own control with post exposure pulmonary function values compared to baseline. After exposure to nitric acid, as compared to preexposure, FEV₁ 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 the subjects were exposed to air only, FEV₁ decreased by 2% and respiratory resistance increased by 7% (Koenig et al. 1989).

No changes in pulmonary function occurred in five healthy volunteers exposed at rest for 10 minutes to 1.6 ppm (4.13 mg/m³) nitric acid fumes (Sackner and Ford 1981). No changes in pulmonary function, lavage constituents, and bronchial biopsy specimens were found in 10 healthy, athletic subjects exposed to 0.194 ppm (0.5 mg/m³) nitric acid gas for 4 hours during moderate exercise (Aris et al. 1993).

2.3 Developmental/Reproductive Toxicity

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

in humans.

2.4 Genotoxicity

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

2.5 Carcinogenicity

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

2.6 Summary

The course of toxicity following inhalation exposure to nitric acid is consistent among the case reports. 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. After this time, a relapse may occur with death caused by bronchopneumonia and/or pulmonary fibrosis. For exposure to nonlethal concentrations, allergic or asthmatic individuals are the most sensitive population.

3. ANIMAL TOXICITY DATA

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

3.1 Acute Lethality

3.1.1 Cats

Lehmann and Hasegawa (1913) conducted a series of experiments using cats exposed to gases of nitric acid which were produced as described in section 2.2.3. In general, as concentration and/or duration of exposure increased, death resulted from severe pulmonary edema. For concentrations less than ~388 ppm (1000 mg/m³), examination of the data as concentration × time revealed that Ct products greater than ~900 ppm·hr resulted in death while a Ct up to 760 ppm·hr resulted in only a slight increase in respiration for several hours after exposure. Further, exposure to 287 ppm (740 mg/m³) for 1.83 hours (Ct = 526 ppm·hr) caused no effects whereas exposure to either 341 ppm (880 mg/m³) for 3.83 hours (Ct = 1309 ppm·hr) or 217 ppm (560 mg/m³) for 4.25 hours (Ct = 922 ppm·hr) resulted in death. In contrast for concentrations of 388 ppm (1000 mg/m³) or greater, severe clinical signs or death occurred at a Ct product as low as 277 ppm·hr. The 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 in that only one animal was used at each

concentration and time combination.

3.1.2 Rats

Groups of 5 Crl:CD[®]BR rats/sex were exposed nose-only for 1 hour to 260-3100 ppm of nitric acid aerosol followed by a 14-day observation period (Du Pont Co. 1987). The atmospheres were generated with a nebulizer and the airborne test material was dispersed with a baffle. Although an aerosol was generated the concentrations were reported in the study as ppm instead of mg/m³. Aerosol content was assumed to be 100% at the three highest concentrations and ranged from 15-73% in the five lower concentrations as measured on a gravimetric filter sample. Except for the 2500 and 2700 ppm concentrations, all exposures contained $\geq 70\%$ respirable particles with a mass median aerodynamic diameter (MMAD) of $\leq 4.0 \mu\text{m}$. The 2500 and 2700 ppm concentrations contained 59 and 61% respirable particles and had a MMAD 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 not clear why the concentrations were reported in ppm instead of mg/m³. 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 ≥ 1300 ppm, lung noise and gasping at ≥ 1600 ppm, and extended weight loss up to 12 days post-exposure at ≥ 1500 ppm for males and ≥ 1600 ppm for females. Mortality results are shown in Table 2. The 1-hour LC₅₀ for males and females combined was 2500 ppm. Although males died at lower concentrations than females, no apparent differences in clinical responses or LC₅₀ values were observed between males and females (Du Pont 1987).

TABLE 2. Lethality in rats exposed nose-only to nitric acid for 1 hour		
Concentration (ppm)	Mortality	
	Males	Females
260	0/5	0/5
470	0/5	0/5
1300	1/5	0/5
1500	1/5	0/5
1600	2/5	0/5
2500	2/5	1/5
2700	2/5	1/5
3100	5/5	5/5

Data from Du Pont Co. 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. Although graphs of the dose-response curves were presented in the paper, unfortunately, the authors did not include the actual data from which those curves were plotted. Exposure concentrations for RFNA and WFNA in this paper were measured and reported as NO₂. Thirty-minute LC₅₀ values for nitrogen dioxide and RFNA were reported as 174 ppm (449 mg/m³) and 138 ppm as NO₂ (356 mg/m³), respectively, while that for WFNA was 244 ppm as NO₂ (630 mg/m³). Deaths were due to pulmonary edema. The dose-response curves for nitrogen dioxide and RFNA for 30-minute exposures were statistically parallel indicating a possible similar mode of action for the two gases. But, at lower concentrations for 240 minutes the curves differed somewhat. With exposures to WFNA, the authors stated that deaths were not as “predictable” as with the other gases. The approximate LC₅₀ indicates that WFNA is much less toxic (i.e., higher LC₅₀) than either RFNA or nitrogen dioxide. Therefore, the authors concluded that the main toxic component of these oxides of nitrogen is nitrogen dioxide. However, NIOSH (1976a) calculated the LC₅₀s for RFNA and WFNA in terms of total concentration, based on molecular weights and the percentage of NO₂ in each, and determined them to be 310 ppm (800 mg/m³) and 334 ppm (862 mg/m³), respectively. This suggests 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/week, dogs were anesthetized and a catheter placed in the mainstem bronchus; 1% nitric acid was delivered as a coarse spray via a nebulizer with approximately 5 mL to the left lung and 8 mL to the right lung. For an additional 2 exposures/week, dogs were intubated and spontaneously breathed 1% nitric acid as a mist for 2 hours. This exposure regime was continued for 4 weeks and the animals killed either immediately or after a 5 month recovery period. Within one week after exposure began, treated animals developed intermittent cough and produced clear mucoid sputum. After four weeks of exposure, there was 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 postexposure with significant reductions in maximal expiratory flows. At necropsy immediately after cessation of treatment, the lungs from nitric acid exposed dogs were edematous with areas of focal hemorrhage. The lungs appeared normal after 5 months of recovery. Histologically, there was chronic airway inflammation, slight epithelial changes, slight peribronchiolar fibrosis, and an increase in smooth muscle that persisted to 5 months postexposure. The severity of the pathological 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 by instillation of 1% nitric acid into the airways. Two instillations of three 5-mL aliquots were given approximately 2 weeks apart and pulmonary function tests performed two weeks later. Nitric acid treated dogs had mild cough with slight hemoptysis immediately following each treatment; several pulmonary function tests indicated increased peripheral airway resistance; and, at necropsy, acute and chronic inflammation of the small airways were observed (Mink et al. 1984).

3.2.2 Rats

Rats were given a single dose of 0.15 mL of 1% nitric acid by intratracheal instillation. At 1 day after administration, focal lung damage 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 (approximately 10/concentration) were exposed nose-only to 0, 5.1, 7.0, 13, or 19 ppm for 6 hours/day on alternate days for a total of six exposures. The animals 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 0.5% nitric acid in 0.5 mL saline/100 g body weight (Coalson and Collins 1985). "Several" animals (exact number not given) died before day 3 posttreatment and showed severe hemorrhagic pulmonary edema. Airway changes in the remaining hamsters included acute bronchitis, acute bronchiolitis, obliterative bronchiolitis, bronchiolectasia, and bronchiectasis. These pathological changes were accompanied by decreased lung volumes, decreased internal surface areas, increased lung weights, and increased elastin content. The airway dilatation and morphometric and biochemical endpoints persisted through day 60 posttreatment (the last day examined).

In a similar experiment, hamsters were exposed via an intratracheal instillation of 0.5 mL of 0.1N nitric acid. Up to 17 weeks postexposure, histological 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

The 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 reacting with bronchospasm to 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 initially, following 20 breaths of 2.5% carbachol (to induce bronchoconstriction), and following 4 hours of exposure to 1.6 ppm (4.13 mg/m³) nitric acid vapor. Immediately after nitric acid exposure, the animals 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 the allergic sheep. Pulmonary flow resistance from carbachol challenge prior to and postexposure 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/Reproductive Toxicity

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

3.4 Genotoxicity

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

3.5 Carcinogenicity

No information was found regarding the carcinogenicity of nitric acid in animals. Lung damage in rats, induced by intratracheal instillation of 0.25 mL 1% nitric acid, 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 changes in the lung in animal models of obstructive lung disease (Peters and Hyatt 1986; Fujita et al. 1988; Coalson and Collins 1985). Experiments in sheep (Abraham et al. 1982) have emphasized the sensitivity of allergic individuals to acidic atmospheres.

4. SPECIAL CONSIDERATIONS

4.1 Metabolism and Disposition

No information was found regarding the pharmacokinetics of nitric acid. 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/absorbed nitric acid transport to the lower respiratory tract.

4.2 Mechanism of Toxicity

Nitric acid is a highly corrosive, strongly oxidizing acid (Budavari et al. 1996). Contact with the liquid causes burns on the skin and corneal opacity (NIOSH 1976a). A 4-hour occluded patch test induced skin corrosion in rabbits at 8%, but not 6% (Vernot et al. 1977). The respiratory irritation attributed to nitric acid exposure 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/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 as nitrogen dioxide (NO₂) and nitric oxide (NO). Fuming nitric acid reacts with wood or metals and emits fumes of NO₂ which form equimolar amounts of nitrous and nitric acid when in contact with steam (Budavari et al. 1996; NIOSH 1976a). In the presence of light, nitric acid undergoes an oxidation-reduction reaction to produce nitrogen dioxide, water, and oxygen. NO reacts quantitatively with oxygen in air to form NO₂ 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/m³), the toxic response was the same whether the gas mixture contained nitric acid alone or a mixture of nitrous and nitric acid.

As discussed in Section 3.1.2, Gray et al. (1954) compared the toxicities of NO₂, red fuming nitric acid (RFNA), and white fuming nitric acid (WFNA) in male rats. The dose-response curves for nitrogen dioxide and RFNA for 30-minute exposures were statistically parallel indicating a similar mode of action for the two gases. For both gases, deaths were due to pulmonary edema. The thirty-minute LC₅₀ values for nitrogen dioxide and RFNA were 174 ppm (449 mg/m³) and 138 ppm as NO₂ (356 mg/m³), respectively. With exposures to WFNA, the authors stated that deaths were not as "predictable" as with the other gases. The approximate LC₅₀ (244 ppm as NO₂ [630 mg/m³]) indicates that WFNA is less toxic than either RFNA or nitrogen dioxide. Therefore, the authors concluded that the main toxic component of these oxides of nitrogen is nitrogen dioxide and that RFNA is approximately 25% more toxic than NO₂ because of the contribution by the acid component. However, NIOSH (1976a) calculated the LC₅₀s for RFNA and WFNA in terms of total nitric acid concentration and determined them to be 310 ppm (800 mg/m³) and 334 ppm (862 mg/m³), respectively. The calculations were based on molecular weights and the percentage of NO₂ in RFNA and WFNA. Because these values are very similar, this suggests the possibility of a synergistic effect between nitric acid vapor and

nitrogen dioxide since RFNA has a higher nitrogen dioxide content by weight than WFNA.

The supposition that nitric acid and NO₂ interact to cause enhanced toxicity is also supported, in part, by the inhalation experiments of Goldstein et al. (1977) in Rhesus monkeys. Approximately 50-60% of the inhaled NO₂ was retained by the animals and distributed throughout the lungs. Radioactivity was retained in the lungs during the 21-minute post exposure period with extrapulmonary distribution (per cent not quantified) via the bloodstream. The authors speculate that the reaction of inhaled NO₂ 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 can not be considered without taking into account the effects of NO₂. However, nitric acid fumes will contain NO₂ upon contact with water so that reports of experimental or accidental exposures to nitric acid fumes will account for the toxicity contributed by NO₂. NIOSH (1976b) summarized the effects of NO₂ in humans as 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 NO₂ (Hine et al. 1970). This course of toxicity is identical to that described for nitric acid albeit the concentrations eliciting similar responses are very different for the two chemicals. For example, deaths of rats from a one hour exposure were first observed at 75 ppm NO₂ (Hine et al. 1970) and at 1300 ppm nitric acid (Du Pont Co. 1987). Also, based on the LC₅₀ values discussed for the rat, it would appear that NO₂ is more toxic than nitric acid. Therefore, it seems that data from inhalation studies with NO₂ might be an overly conservative approach used for establishing the AEGL levels for nitric acid. If NO₂ is of concern the technical support document on AEGLs for NO₂ should be consulted.

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. After this time, a relapse may occur with death caused by bronchopneumonia and/or pulmonary fibrosis (ACGIH 1991; NIOSH 1976a). Because the 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 emphasized the sensitivity of allergic individuals.

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 of that 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 were seen in an experimental study in which allergic adolescents were exposed specifically to nitric acid (Koenig et al. 1989).

Abraham et al. (1982) showed that airway hyperreactivity to carbachol occurred in allergic sheep following a 4-hour exposure to 1.6 ppm (4.13 mg/m³) nitric acid. Specific airway resistance prior to and postexposure 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. The most reliable study found (Du Pont 1987) used only one duration over a large range of concentrations. However, from these lethality data in the rat it appears that 100% mortality is reached abruptly indicating a steep concentration-response.

5. DATA ANALYSIS FOR 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, non-sensory 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

A no-observed adverse effect level (NOAEL) of 1.6 ppm (4.13 mg/m³) was reported for changes in pulmonary function in five healthy volunteers exposed to nitric acid vapor at rest for 10 minutes (Sackner and Ford 1981). This is the highest NOAEL available in humans. An experimental self-exposure to 62 ppm (160 mg/m³) for 1 hour 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 experimental studies were either at a lethal concentration or administered nitric

acid by intratracheal instillation which is not comparable to inhalation exposure.

5.3 Derivation of AEGL-1

The highest NOAEL in humans of 1.6 ppm (4.13 mg/m³) for 10 minutes was used to derive AEGL-1 values. An uncertainty factor of 3 was applied to account for sensitive populations because the mechanism of action of a direct acting irritant is not expected to differ greatly among individuals. Extrapolations were not performed because this was based on a no effect level and because irritation is generally concentration dependent but not time dependent. AEGL-1 values are presented in Table 3.

AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	0.53 [1.4]	0.53 [1.4]	0.53 [1.4]	0.53 [1.4]	0.53 [1.4]

6. DATA ANALYSIS FOR AEGL-2

AEGL-2 is the airborne concentration (expressed as ppm or mg/m³) 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.

6.1 Summary of Human Data Relevant to AEGL-2

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

6.2 Summary of Animal Data Relevant to AEGL-2

The most relevant animal data to AEGL-2 were those from Du Pont (1987). This was a well conducted study which controlled for potential nitrogen dioxide contamination. Groups of 5 Crl:CD[®]BR rats/sex were exposed nose-only for 1 hour to 260-3100 ppm of nitric acid aerosol 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 ≥1300 ppm, lung noise and gasping at ≥1600 ppm, and extended weight loss up to 12 days post-exposure at ≥1500 ppm for males and ≥1600 ppm for females.

No long-term effects of exposure to nitric acid were observed in rats following six exposures

on alternate days to up to 19 ppm for 6 hours/day (Ballou et al. 1978).

6.3 Derivation of AEGL-2

Exposure of rats to 470 ppm for 1 hour, which resulted in transient body weight loss 1-2 days post-exposure (Du Pont 1987), was used to derive AEGL-2 values. The point of departure is a NOAEL for AEGL-2 endpoints and would not be escape-impairing. The next higher experimental concentration used in the study resulted in partially closed eyes which could definitely impair escape. Extrapolations to the 10- and 30-minute, and 4-, and 8-hour time periods were done following the equation $C^n \times t = k$ (ten Berge et al., 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using $n = 3$ for extrapolating to the 10- and 30-minute time points and $n = 1$ for the 4- and 8-hour time points. A total uncertainty factor of 10 was used including a 3 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty factors was not considered to be necessary because the mechanism of action 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, a concentration-response could not be determined for nonlethal effects, and clear evidence of AEGL-2 effects did not occur in the study. The values for AEGL-2 are given in Table 4.

AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	43 [111]	30 [77]	24 [62]	6.0 [15]	3.0 [8]

7. DATA ANALYSIS FOR 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

Limited human data useful for derivation of AEGL-3 are available. Case reports of lethal exposures from accidents do not contain exposure concentration information. An experimental self-exposure was reported by Lehmann and Hasegawa (1913). One of these researchers exposed himself to 74-101 ppm (190-260 mg/m^3) for 1 hour followed by 23-43 ppm (60-110 mg/m^3) for another hour and experienced immediate severe irritation with cough and an increase in pulse and respiratory rates after 40 minutes. Because the severe symptoms were immediate, it could be assumed that the average concentration of 88 ppm during the first hour of exposure

would be close to intolerable but not lethal. He was able to tolerate exposure to 158 ppm (408 mg/m³) but for only 10 minutes 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.

7.2 Summary of Animal Data Relevant to AEGL-3

Animal data relevant to derivation of AEGL-3 are limited to the LC₅₀ study by Du Pont (1987). This was a well conducted study which controlled for potential nitrogen dioxide contamination. Groups of 5 Crl:CD®BR rats/sex were exposed nose-only for 1 hour to 260-3100 ppm of nitric acid aerosol 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 ≥1300 ppm, lung noise and gasping at ≥1600 ppm, and extended weight loss up to 12 days post-exposure at ≥1500 ppm for males and ≥1600 ppm for females. The 1-hour LC₅₀ for males and females combined was 2500 ppm.

7.3 Derivation of AEGL-3

A 1-hour LC₅₀ in rats was calculated by Du Pont (1987). This was a well conducted study in which mortality ratios at each concentration were given. From these data, an LC₀₁ was calculated by a log-probit analysis. The resulting LC₀₁ of 919 ppm was used to derive AEGL-3 values. Values were 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 exponent, scaling was performed using n = 3 for extrapolating to the 10- and 30-minute time points and n = 1 for the 4- and 8-hour time points. A total uncertainty factor of 10 was used including a 3 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty factors was not considered to be necessary because the mechanism of action of a corrosive acid in the lung is not expected to differ greatly between species or among individuals. The values for AEGL-3 are given in Table 5.

AEGL level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	170 [439]	120 [310]	92 [237]	23 [59]	11 [28]

8. SUMMARY OF AEGLS

8.1 AEGL Values and Toxicity Endpoints

The derived AEGL values for various levels of effects and durations of exposure are summarized in Table 6. AEGL-1 was based on a no effect level in humans. AEGL-2 was based

on a concentration which produced transient weight loss in rats. The basis for AEGL-3 was an estimated LC₀₁ from the reported 1-hour LC₅₀ in the rat. Note that if NO₂ is of concern the technical support document on AEGLs for NO₂ should be consulted.

AEGL Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	0.53 [1.4]	0.53 [1.4]	0.53 [1.4]	0.53 [1.4]	0.53 [1.4]
AEGL-2	43 [111]	30 [77]	24 [62]	6.0 [15]	3.0 [8]
AEGL-3	170 [439]	120 [310]	92 [237]	23 [59]	11 [28]

8.2 Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 7. Some of these standards and guidance levels have been developed on the basis of nitrogen dioxide or comparison to other acids in the workplace. An occupational TWA of 2 ppm and a STEL of 4 ppm have been adopted by several groups (ACGIH 2003, NIOSH 1996, OSHA 1999). ACGIH (2003) set the TWA as intermediate between that for hydrogen chloride and sulfuric acid and considers both the TWA and STEL as sufficiently low to prevent ocular and upper respiratory tract irritation. International standards are also 2 ppm for a workday and 2-5 ppm for short-term limits (German Research Association 2002, National MAC List 2000, Swedish National Board of Occupational Safety and Health 1996). The MAK value in Germany is based on the results of the study by Diem (1907). The immediate danger to life and health (IDLH) of 25 ppm (NIOSH, 1996) is based on acute toxicity data in humans (conversion of lethal oral dose to inhalation equivalent) and animals (secondary source).

ERPG levels were developed specifically for white fuming nitric acid (AIHA, 2001) and are based on toxicity data in animals with nitric acid or nitrogen dioxide and dose-response estimates in humans exposed to nitrogen dioxide.

TABLE 7. Extant Standards and Guidelines for Nitric Acid					
Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	0.53 ppm	0.53 ppm	0.53 ppm	0.53 ppm	0.53 ppm
AEGL-2	43 ppm	30 ppm	24 ppm	6.0 ppm	3.0 ppm
AEGL-3	170 ppm	120 ppm	92 ppm	23 ppm	11 ppm
ERPG-1 (AIHA) ^a			1 ppm		
ERPG-2 (AIHA)			6 ppm		
ERPG-3 (AIHA)			78 ppm		
PEL-TWA (OSHA) ^b					2 ppm
IDLH (NIOSH) ^c		25 ppm			
REL-TWA (NIOSH) ^d					2 ppm
REL-STEL (NIOSH) ^e	4 ppm				
TLV-TWA (ACGIH) ^f					2 ppm
TLV-STEL (ACGIH) ^g	4 ppm				
MAK (Germany) ^h					2 ppm
MAK Peak Limit (Germany) ⁱ	2 ppm				
MAC (The Netherlands) ^j					2 ppm
OEL-LLV (Sweden) ^k					2 ppm
OEL-STV (Sweden) ^l	5 ppm				

^a**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA 2002)**

The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour 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-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

^b**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average) (OSHA 1999)** is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no

more than 10 hours/day, 40 hours/week.

^c**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 1996) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

^d**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 2003) is defined analogous to the ACGIH-TLV-TWA.

^e**NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit)** (NIOSH 2003) is defined analogous to the ACGIH TLV-STEL.

^f**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2003) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

^g**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 2003) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

^h**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] 2002) is defined analogous to the ACGIH-TLV-TWA.

ⁱ**MAK Spitzenbegrenzung (Peak Limit [Category I, 1])** (German Research Association 2002) constitutes the maximum average concentration to which workers can be exposed for a period up to 15 minutes with no more than 4 exposure periods per work shift and a minimum of 1 hour between excursions.

^j**MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])** (National MAC List 2000) is defined analogous to the ACGIH-TLV-TWA.

^k**OEL-LLV (Occupational Exposure Limits - Level Limit Value)** (Swedish National Board of Occupational Safety and Health, 1996) is an occupational exposure limit value for exposure during one working day.

^l**OEL-STV (Occupational Exposure Limits - Short-term Value)** (Swedish National Board of Occupational Safety and Health, 1996) is a recommended value consistin of a time-weighted average for exposure during a reference period of 15 minutes.

8.3 Data Adequacy and Research Needs

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

9. REFERENCES

- Abraham, W.M., C.S. Kim, M.M. King, W. Oliver, and L. Yerger. 1982. Effects of nitric acid on carbachol reactivity of the airways in normal and allergic sheep. *Arch. Environ. Health* 37:36-40.
- ACGIH. 1991. American Conference of Governmental Industrial Hygienists, Inc. Nitric Acid. In: Documentation of the Threshold Limit Values and Biological Exposure Indices, 6th ed., ACGIH, Cincinnati, OH, pp. 1088-1089.
- ACGIH. 2003. American Conference of Governmental Industrial Hygienists, Inc. TLVs[®] and BEIs[®] Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices, ACGIH, Cincinnati, OH, p. 43.
- AIHA. 2001. Nitric Acid (WFNA). Emergency Response Planning Guidelines. Fairfax, VA: AIHA Press.
- AIHA. 2002. Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook. Fairfax, VA: AIHA Press. p. 25.
- Aris, R., D. Christian, I. Tager, L. Ngo, W.E. Finkbeiner, and J.R. Balmes. 1993. Effects of nitric acid gas alone or in combination with ozone on healthy volunteers. *Am. Rev. Respir. Dis.* 148:965-973.
- Ballou, J.E., R.A. Gies, G.E. Dagle, F.G. Burton, and O.R. Moss. 1978. Toxicology of inhaled acid aerosols. Pacific NW Lab Annual Report to DOE Assist. Secy. Environment. 1978-PNL-2500ac, pp. 6.1-6.2. (cited in AIHA 2001).
- Blenkinsopp, W.K. 1968. Relationship of injury to chemical carcinogenesis in the lungs of rats. *J. Nat. Cancer Inst.* 40:651-661.
- Budavari, S., M.J. O'Neil, A. Smith, P.E. Heckelman, and J.F. Kinneary. Eds. 1996. The Merck Index, 11th ed. Merck and Co., Inc., Rahway, NJ.
- Bur, A., A. Wagner, M. Röggl, A. Berzlanovic, H. Herkner, F. Sterz, A.N. Laggner. 1997. Fatal pulmonary edema after nitric acid inhalation. *Resuscitation* 35:33-36.
- Christensen, T.G., E.C. Lucey, R. Breuer, and G.L. Snider. 1988. Acid-induced secretory cell metaplasia in hamster bronchi. *Environ. Res.* 45:78-90.
- Chen, L.C. and R.B. Schlesinger. 1996. Considerations for the respiratory -tract dosimetry of inhaled nitric acid vapor. *Inhal. Toxicol.* 8:639-654.
- Coalson, J.J. and J.F. Collins. 1985. Nitric acid-induced injury in the hamster lung. *Br. J. Exp. Path.* 66:205-216.
- Demerec, M., G. Bertani, and J. Flint. 1951. A survey of chemicals for mutagenic action on *E. coli*. *The Am. Naturalist* 85:119-136.
- Diem, L. 1907. [Experimentelle Untersuchungen über die Einatmung von Salpetersäure-Dämpfen]. Thesis, D-8700, Würzburg. (translated from German).
- Dockery, D.W., J. Cunningham, A.I. Damokosh, L.M. Neas, J.D. Spengler, P. Koutrakis, J.H. Ware, M. Raizenne, and F.E. Speizer. 1996. Health effects of acid aerosols on North American children: Respiratory symptoms. *Environ. Health Persp.* 104:500-505.

- Du Pont Co. 1987. One-hour inhalation median lethal concentration (LC₅₀) study with nitric acid. Haskell Laboratory Report No 451-87. Newark, Delaware. 26pp.
- Fujita, M., M.A. Schroeder, and R.E. Hyatt. 1988. Canine model of chronic bronchial injury. Lung mechanics and pathologic changes. *Am. Rev. Respir. Dis.* 137:429-434.
- Gardiner, T.H. and L.S. Schanker. 1976. Effect of oxygen toxicity and nitric acid-induced lung damage on drug absorption from the rat lung. *Res. Commun. Chem. Pathol. Pharmacol.* 15:107-120.
- German Research Association (Deutsche Forschungsgemeinschaft). 2002. List of MAK and BAT Values, 2002. Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Report No. 38. Weinheim, Federal Republic of Germany: Wiley VCH.
- Goldstein, E., N.F. Peek, N.J. Parks, H.H. Hines, E.P. Steffey, and B. Tarkington. 1977. Fate and distribution of inhaled nitrogen dioxide in Rhesus monkeys. *Am. Rev. Resp. Dis.* 115:403-412.
- Gray, E.Le B., F.M. Patton, S.B. Goldberg, and E. Kaplan. 1954. Toxicity of the oxides of nitrogen. II. Acute inhalation toxicity of nitrogen dioxide, red fuming nitric acid, and white fuming nitric acid. *Arch. Ind. Hyg. Occup. Med.* 10:418-422.
- Hajela, R., D.T. Janigan, P.L. Landrigan, S.F. Boudreau, and S. Sebastian. 1990. Fatal pulmonary edema due to nitric acid fume inhalation in three pulp-mill workers. *Chest* 97:487-489.
- Hall, J.N. and C.E. Cooper. 1905. The effects of the inhalation of the fumes of nitric acid with report of cases. *JAMA* 45:396-399.
- Hine, C.H., F.H. Meyers, and R.W. Wright. 1970. Pulmonary changes in animals exposed to nitrogen dioxide, effects of acute exposures. *Toxicol. Appl. Pharmacol.* 16:201-213.
- HSDB. 1996. Hazardous Substances Data Bank. TOXNET Online Information Retrieval System, National Library of Medicine.
- Koenig, J.Q., D.S. Covert, and W.E. Pierson. 1989. Effects of inhalation of acidic compounds on pulmonary function in allergic adolescent subjects. *Environ. Health Persp.* 79:173-178.
- Lehmann, K.B. and Hasegawa. 1913. [Studies on the effects of technically and hygienically important gases and vapors on man (31) -- The nitrous gases -- Nitric oxide, nitrogen dioxide, nitrous acid, nitric acid.] *Arch. Hyg.* 77:323-368. (translated from German)
- Mink, S.N., J.J. Coalson, L. Whitley, H. Greville, and C. Jadue. 1984. Pulmonary function tests in the detection of small airway obstruction in a canine model of bronchiolitis obliterans. *Am. J. Respir. Dis.* 130:1125-1133.
- Myint, S.S. and S.K. Lee. 1983. Pulmonary effects of acute exposure to nitrous fumes--a case report. *Singapore Med. J.* 24:312-313.
- NARSTO. 2004. Particulate Matter Assessment for Policy Makers: A NARSTO Assessment. McMurry, M. Shepherd, and J. Vickery, eds. Cambridge, UK: Cambridge University Press.
- National MAC List. 2000. The Hague, SDU Uitgevers (under the auspices of the Ministry of Social Affairs and Employment) The Netherlands.

- NIOSH. 1976a. National Institute for Occupational Safety and Health. NIOSH criteria for a recommended standard.... occupational exposure to nitric acid. U.S. Department of Health, Education, and Welfare, Washington, D.C., HEW publication No. (NIOSH) 76-141, 78pp.
- NIOSH. 1976b. National Institute for Occupational Safety and Health. NIOSH criteria for a recommended standard.... occupational exposure to oxides of nitrogen (nitrogen dioxide and nitric oxide). U.S. Department of Health, Education, and Welfare, Washington, D.C., HEW publication No. (NIOSH) 76-149, 195pp.
- NIOSH. 1996. National Institute for Occupational Safety and Health. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHs). NIOSH, Cincinnati, OH. retrieved on-line 7/11/2003.
- NIOSH. 2003. National Institute for Occupational Safety and Health. NIOSH Pocket Guide to Chemical Hazards. NIOSH, Cincinnati, OH.
- OSHA. 1999. Occupational Safety and Health Administration. Table Z-1. Limits for Air Contaminants. 29 CFR (§1910.1000), p. 14.
- Ostro, B.D., M.J. Lipsett, M.B. Wiener, and J.C. Selner. 1991. Asthmatic responses to airborne acid aerosols. *Am. J. Public Health* 81:694-702.
- Peters, S.G. and R.E. Hyatt. 1986. A canine model of bronchial injury induced by nitric acid. Lung mechanics and morphological features. *Am. Rev. Respir. Dis.* 133:1049-1054.
- Peters, J.M., Avol, E., Navidi, W., London, S.J., Gauderman, W.J., Lurmann, F., Linn, W.S., Margolis, H., Rappaport, E., Gong, H., Jr., and Thomas, D.C. 1999a. A study of twelve southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. *Am. J. Resp. Crit. Care Med.* 159:760-767.
- Peters, J.M., Avol, E., Navidi, W., London, S.J., Gauderman, W.J., Lurmann, F., Linn, W.S., Margolis, H., Rappaport, E., Gong, H., Jr., and Thomas, D.C. 1999b. A study of twelve southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. *Am. J. Resp. Crit. Care Med.* 159:768-775.
- Raizenne, M., L.M. Neas, A.I. Damokosh, D.W. Dockery, J.D. Spengler, P. Koutrakis, J.H. Ware, and F.E. Speizer. 1996. Health effects of acid aerosols on North American children: Pulmonary function. *Environ. Health Persp.* 104:506-514.
- Sackner, M.A., S. Birch, A. Friden, and B. Marchette. 1981. Effects of breathing low levels of nitrogen dioxide for four hours on pulmonary function of asthmatic adults. *Am. Rev. Resp. Dis.* 123:151.
- 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.* 123:151.
- Stavert, D.M. and B.E. Lehnert. 1990. Nitric oxide and nitrogen dioxide as inducers of acute pulmonary injury when inhaled at relatively high concentrations for brief periods. *Inhal. Toxicol.* 2:53-67.
- Swedish National Board of Occupational Safety and Health. 1996. Occupational Exposure Limit Values, Adopted 28th August 1996. p. 56.

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ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. *J. Hazard. Mat.* 13:301-309.

U.S. EPA. 1993a. U.S. Environmental Protection Agency. Monograph for Nitric Acid CAS No. 7697-37-2. Office of Pollution Prevention and Toxics, U.S. EPA, Washington, D.C. 17pp.

U.S. EPA. 1993b. U.S. Environmental Protection Agency. Monograph for Nitric Oxide CAS No. 10102-43-9. Office of Pollution, Prevention and Toxics, U.S. EPA, Washington, D.C. 20pp.

Vernot, E.H., J.D. MacEwen, C.C. Haun, and E.R. Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. *Toxic. Appl. Pharmacol.* 42:417-423.

APPENDIX A: Derivation of AEGL Values

DERIVATION OF AEGL-1 VALUES

Key study: Sackner and Ford, 1981

Toxicity endpoint: No changes in pulmonary function were reported in five healthy volunteers exposed to 1.6 ppm (4.13 mg/m³) nitric acid vapor at rest for 10 minutes.

Time scaling: Not applied

Uncertainty factors: 3 for intraspecies variability

Modifying factors: None

Calculations: None; 0.53 ppm value applied across AEGL-1 exposure durations

DERIVATION OF AEGL-2 VALUES

Key study: Du Pont 1987

Toxicity endpoints: Exposure to 470 ppm for 1 hour resulted in transient body weight loss 1-2 days post-exposure.

Scaling: $C^n \times t = k$ (ten Berge et al., 1986)
 $n = 3$ for extrapolating to the 10- and 30-minute timepoints
 $n = 1$ for extrapolating to the 4- and 8-hour timepoints

Uncertainty factors: Total 10: 3 for interspecies variability and 3 for intraspecies variability

Modifying factor: 2 because clinical observations were not well described, a concentration-response could not be determined for nonlethal effects, and clear evidence of AEGL-2 effects did not occur in the study

Calculations: 10- and 30-min timepoints: $(C/\text{uncertainty and modifying factors})^3 \times t = k$
 $(470 \text{ ppm}/20)^3 \times 1 \text{ hr} = 12977.875 \text{ ppm}^3 \cdot \text{hr}$

4- and 8-hr timepoints: $(C/\text{uncertainty and modifying factors})^1 \times t = k$
 $(470 \text{ ppm}/20)^1 \times 1 \text{ hr} = 23.5 \text{ ppm} \cdot \text{hr}$

10-minute AEGL-2: $C = (12977.875 \text{ ppm} \cdot \text{hour}/0.167 \text{ hours})^{1/3}$
 $C = 43 \text{ ppm}$

30-minute AEGL-2: $C = (12977.875 \text{ ppm} \cdot \text{hour}/0.5 \text{ hour})^{1/3}$
 $C = 30 \text{ ppm}$

1-hour AEGL-2: $C = (470 \text{ ppm}/20) = 24 \text{ ppm}$

4-hour AEGL-2: $C = (23.5 \text{ ppm} \cdot \text{hour}/4 \text{ hours})^1$
 $C = 6.0 \text{ ppm}$

8-hour AEGL-2: $C = (23.5 \text{ ppm} \cdot \text{hour}/8 \text{ hours})^1$
 $C = 3.0 \text{ ppm}$

DERIVATION OF AEGL-3 LEVELS

Key study: Du Pont 1987

Toxicity endpoint: An LC₀₁ of 919 ppm was calculated by a log-probit analysis of mortality data in the rat.

Scaling: $C^n \times t = k$ (ten Berge et al., 1986)
 $n = 3$ for extrapolating to the 10- and 30-minute timepoints
 $n = 1$ for extrapolating to the 4- and 8-hour timepoints

Uncertainty factors: Total 10: 3 for interspecies variability and 3 for intraspecies variability

Modifying factor: None

Calculations: 10- and 30-min timepoints: $(C/\text{uncertainty factors})^3 \times t = k$
 $(919 \text{ ppm}/10)^3 \times 1 \text{ hr} = 776151.559 \text{ ppm}^3 \cdot \text{hr}$

4- and 8-hr timepoints: $(C/\text{uncertainty factors})^1 \times t = k$
 $(919 \text{ ppm}/10)^1 \times 1 \text{ hr} = 91.9 \text{ ppm} \cdot \text{hr}$

10-minute AEGL-3: $C = (776151.559 \text{ ppm} \cdot \text{hour}/0.167 \text{ hours})^{1/3}$
 $C = 170 \text{ ppm}$

30-minute AEGL-3: $C = (776151.559 \text{ ppm} \cdot \text{hour}/0.5 \text{ hour})^{1/3}$
 $C = 120 \text{ ppm}$

1-hour AEGL-3: $C = (919 \text{ ppm}/10) = 92 \text{ ppm}$

4-hour AEGL-3: $C = (91.9 \text{ ppm} \cdot \text{hour}/4 \text{ hours})^1$
 $C = 23 \text{ ppm}$

8-hour AEGL-3: $C = (91.9 \text{ ppm} \cdot \text{hour}/8 \text{ hours})^1$
 $C = 11 \text{ ppm}$

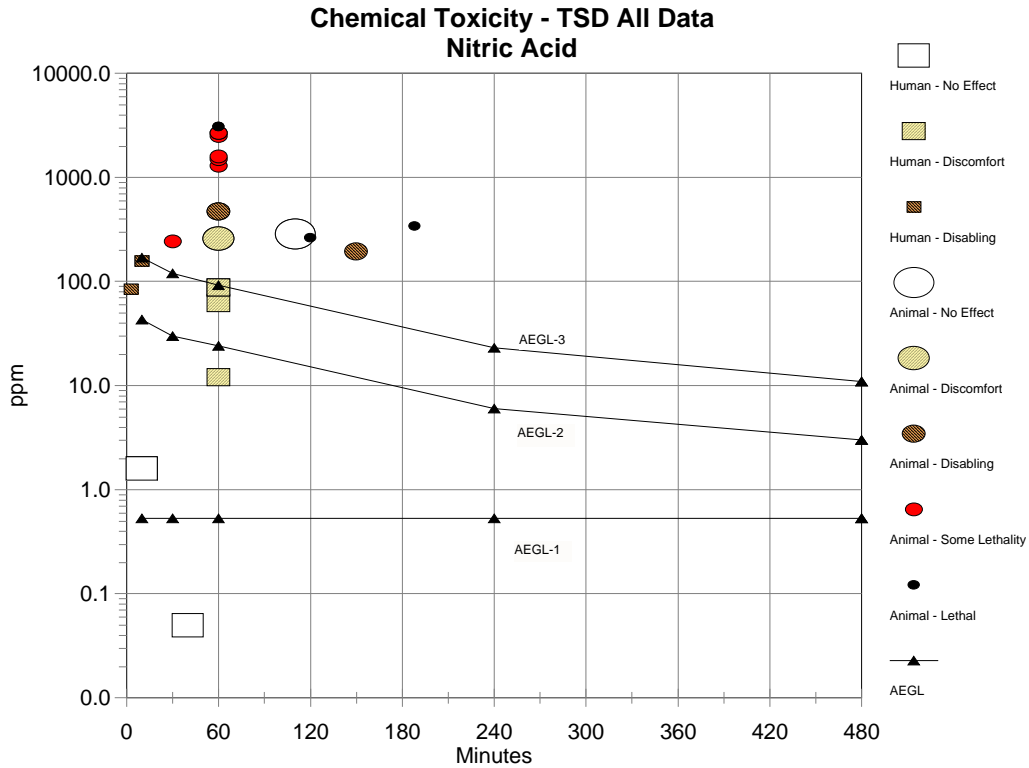
**APPENDIX B: Derivation Summary for AEGL Values
for Nitric Acid
(CAS No. 7697-37-2)**

AEGL-1 VALUES FOR NITRIC ACID				
10 minutes	30 minutes	1 hour	4 hours	8 hours
0.53 ppm	0.53 ppm	0.53 ppm	0.53 ppm	0.53 ppm
Reference: Sackner, M.A. and Ford, D. 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. 123:151.				
Test Species/Strain/Number: Human subjects, sex not given, healthy, 10				
Exposure Route/Concentrations/Durations: Inhalation: 1.6 ppm for 10 minutes				
Effects: no effects				
Endpoint/Concentration/Rationale: NOAEL for changes in pulmonary function (vital capacity, respiratory resistance, and FEV ₁); this is the highest NOAEL available in humans				
Uncertainty Factors/Rationale: Total uncertainty factor: 3 Interspecies: Not applicable; human data used Intraspecies: 3 - The mechanism of action, irritation, is not expected to differ greatly among individuals because nitric acid is a direct acting irritant.				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: Not applicable; human data used				
Time Scaling: Extrapolation to time points was not conducted.				
Data Quality and Support for the AEGL Values: Although no dose-response data was included in the study, the values are based on human data. The point of departure is the highest NOAEL available in humans.				

AEGL-2 VALUES FOR NITRIC ACID				
10 minutes	30 minutes	1 hour	4 hours	8 hours
43 ppm	30 ppm	24 ppm	6.0 ppm	3.0 ppm
Reference: Du Pont Co. 1987. One-hour inhalation median lethal concentration (LC ₅₀) study with nitric acid. Haskell Laboratory Report No 451-87. Newark, Delaware. 26pp.				
Test Species/Strain/Sex/Number: rat/Crl:CD®BR/males and females/5 per sex per concentration				
Exposure Route/Concentrations/Durations: inhalation/270-3100 ppm/1 hour				
Effects: 260 and 470 ppm: body weight loss for 1-2 days ≥ 1300 ppm: partially closed eyes ≥ 1600 ppm: lung noise and gasping ≥ 1500 ppm: extended weight loss up to 12 days post-exposure in males ≥ 1600 ppm: extended weight loss up to 12 days post-exposure in females 3100 ppm: 100% lethality				
Endpoint/Concentration/Rationale: 470 ppm for 1 hour; the point of departure is a NOAEL for AEGL-2 endpoints and would not be escape impairing.				
Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3 - The mechanism of toxicity, the direct reaction of nitric acid with biological tissue is not expected to vary between humans and animals. Intraspecies: 3 - The mechanism of action of a corrosive acid in the lung is not expected to differ greatly among individuals.				
Modifying Factor: 2 - Clinical observations were not well described, a concentration-response could not be determined for nonlethal effects, and clear evidence of AEGL-2 effects did not occur in the study				
Animal to Human Dosimetric Adjustment: not applicable				
Time Scaling: C ⁿ x t = k n = 3 for extrapolating to the 10- and 30-minute timepoints n = 1 for extrapolating to the 4- and 8-hour timepoints				
Comments: Nitrogen dioxide content monitored during exposures; none measured.				

AEGL-3 VALUES FOR NITRIC ACID				
10 minutes	30 minutes	1 hour	4 hours	8 hours
170 ppm	120 ppm	92 ppm	23 ppm	11 ppm
Reference: Du Pont Co. 1987. One-hour inhalation median lethal concentration (LC ₅₀) study with nitric acid. Haskell Laboratory Report No 451-87. Newark, Delaware. 26pp.				
Test Species/Strain/Sex/Number: rat/Crl:CD®BR/males and females/5 per sex per concentration				
Exposure Route/Concentrations/Durations: inhalation/270-3100 ppm/1 hour				
Effects: 260 and 470 ppm: body weight loss for 1-2 days; no death 1300 ppm: 1/10 died 1500 ppm: 1/10 died 1600 ppm: 2/10 died 2500 ppm: 3/10 died 2700 ppm: 3/10 died 3100 ppm: 100% lethality				
Endpoint/Concentration/Rationale: LC ₀₁ of 919 ppm estimated by log-probit analysis of mortality data				
Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3- The mechanism of toxicity, the direct reaction of nitric acid with biological tissue is not expected to vary between humans and animals. Intraspecies: 3 - The mechanism of action of a corrosive acid in the lung is not expected to differ greatly among individuals.				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: not applicable				
Time Scaling: C ⁿ x t = k n = 3 for extrapolating to the 10- and 30-minute timepoints n = 1 for extrapolating to the 4- and 8-hour timepoints				
Comments: Nitrogen dioxide content monitored during exposures; none measured.				

Appendix C: Time-scaling category plot for Nitric Acid



No effect = No effect or mild discomfort

Discomfort = Notable transient discomfort/irritation consistent with AEGL-1 level effects

Disabling = Irreversible/long lasting effects or an impaired ability to escape

Some lethality = Some, but not all, exposed animals died

Lethal = All exposed animals died