Interim: 09-2009

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

NITROGEN TRIFLUORIDE

(CAS Reg. No. 7783-54-2)

NF_3

INTERIM

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/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, 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/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 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

High purity nitrogen trifluoride (NF_3, CAS No. 7783-54-2) is a colorless gas with little odor. Traces of active fluorides give it a pungent, musty or moldy odor. Nitrogen trifluoride is rather inert chemically, but at elevated temperatures is a potent oxidizer. High purity NF_3 finds use in the manufacture of semiconductors, as an oxidizer of high energy fuels, for the preparation of tetrafluorohydrazine, as an etchant gas in the electronic industry, and as a fluorine source in high power chemical lasers.

The odor threshold is high. During a 2- to 3-minute exposure, one of five volunteers tentatively detected the odor at 500 ppm. No clinical studies were available for development of AEGL values. Lethality studies with the monkey, dog, rat, and mouse showed that these species were similarly sensitive to the lethal effects of NF_3. Inhaled NF_3 reacts with the hemoglobin (Hb) of the blood, forming methemoglobin (MetHb). One mole of NF_3 reacts with 3-4 moles of heme. Methemoglobin is unable to carry oxygen to the tissues, resulting in tissue anoxia. Methemoglobinemia is a reversible condition; MetHb is reduced to oxyhemoglobin by erythrocyte NADH-methemoglobin reductase. Studies with monkeys and dogs exposed to less than lethal concentrations of NF_3 addressed methemoglobinemia. Exposure of dogs to NF_3 also reduces hematology parameters including Hb, hematocrit, and erythrocyte count.

AEGL-1 values were based on an exposure of monkeys and dogs to 2000 ppm NF_3 for 60 minutes (120,000 ppm-minutes) (Vernot et al. 1973). This concentration-exposure duration resulted in 15% MetHb formation in dogs and 10% in monkeys. A MetHb concentration of ≤15% is without clinical signs or symptoms. The reduced erythrocyte count, Hb, and hematocrit of approximately 16%, seen only in dogs, were reversible. An interspecies uncertainty factor of 1 was applied because LC_{50} values measured under identical conditions were similar for all four species and because the dog was the most sensitive species for effects on hematology parameters. Furthermore, compared with rodents, the dog is more hematologically similar to humans regarding hematopoiesis and blood cell kinetics. An intraspecies uncertainty factor of 10 was applied because infants, lacking the NADH cofactor for methemoglobin reductase, are especially sensitive to MetHb-forming chemicals. Furthermore, some humans may be deficient in methemoglobin reductase or anemic as a result of abnormal Hb M or Hb H. The resulting 60-minute 200 ppm value was time-scaled using an n value of 1.0 from the dog lethality studies. The same endpoint of methemoglobinemia was the basis for time-scaling in the lethality studies with the dog.

A MetHb concentration of 40-45% is predicted to induce weakness, fatigue, dizziness, and lethargy in humans (Kiese 1974; Seger 1992). These symptoms are the threshold for an impaired ability to escape and meet the definition of an AEGL-2. Responses to MetHb forming chemicals are similar in dogs and humans. Data on an atmospheric concentration of NF_3 that would result in a MetHb concentration of approximately 43% in the dog were unavailable. The relationship between the atmospheric concentration of NF_3 and MetHb formation is linear. Therefore, a concentration of NF_3 of 43%, the midpoint between the 15% MetHb concentration that defines the AEGL-1 and the 70% predicted threshold for lethality as cited in several reviews (Kiese 1974; Seger 1992) and referenced in the key and supporting studies (Dost et al. 1970a; Vernot et al. 1973) was used as the endpoint for the AEGL-2. The AEGL-2 value for each

exposure duration was calculated as the midpoint concentration between each AEGL-1 and AEGL-3 value.

The AEGL-3 values were based on the threshold for lethality in the study of Vernot et al. (1973). The lethality data for the dog were used because, compared with rodents, the dog is more hematologically similar to humans regarding hematopoiesis and blood cell kinetics. The threshold for lethality at each AEGL-3 exposure duration was calculated using the probit-based, dose-response program of ten Berge (2006). The threshold for lethality was set at 1%. This value is similar to the benchmark dose BMC_{01}. The data indicated a time-scaling value of 1.0 ($C^{1.0} \times t = k$). An interspecies uncertainty factor of 1 was applied because mortality for four species differed by less than a factor of 2 and the dog is the more sensitive species for reductions in hematology parameters. An intraspecies uncertainty factor of 10 was applied because infants, lacking the NADH cofactor for methemoglobin reductase, are especially sensitive to MetHb-forming chemicals. Furthermore, humans who are anemic, deficient in methemoglobin reductase, or have abnormal Hbs are more sensitive to MetHb-generating chemicals.

The calculated values are listed in the table below.

S 1. Summary of AEGL Values for Nitrogen Trifluoride

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL–1 (Nondisabling)	1200 ppm (3500 mg/m^3)	400 ppm (1200 mg/m^3)	200 ppm (580 mg/m^3)	50 ppm (150 mg/m^3)	25 ppm (73 mg/m^3)	≤15% MetHb: 60-minute exposure of dogs and monkeys to 2000 ppm (Vernot et al. 1973)
AEGL–2 (Disabling)	3100 ppm (9000 mg/m^3)	1100 ppm (3200 mg/m^3)	530 ppm (1500 mg/m^3)	140 ppm (400 mg/m^3)	68 ppm (200 mg/m^3)	Estimated 43% MetHb: midpoint of AEGL-1 and AEGL-3, dog data (Vernot et al. 1973)
AEGL–3 (Lethal)	5000 ppm (15,000 mg/m^3)	1700 ppm (4900 mg/m^3)	860 ppm (2500 mg/m^3)	220 ppm (640 mg/m^3)	110 ppm (320 mg/m^3)	Regression analysis of dog lethality data of Vernot et al. (1973) calculated with the ten Berge program (2006)

1. INTRODUCTION

High purity nitrogen trifluoride (NF_3, CAS No. 7783-54-2) is a colorless gas with little odor. Traces of active fluorides give it a pungent, musty or moldy odor. Nitrogen trifluoride is rather inert chemically, but at elevated temperatures is a potent oxidizer. Solubility in and reaction with water is limited. It reacts explosively with reducing agents; thus, its use as a fluorinating agent for organic compounds is limited (ACGIH 2001; Henderson and Woytek 1994; O'Neil et al. 2001; AIHA 2005). The chemical and physical properties of NF_3 are listed in Table 1.

Nitrogen trifluoride is manufactured commercially by either of two processes: the electrolysis of molten ammonium acid fluoride or the direct fluorination of ammonia in the presence of molten ammonium fluoride. In the early 1990s, production in the United States was less than 100 tons/year (Henderson and Woytek 1994). World-wide production for 2002 was estimated at 5 million pounds (Air Products 2002). High purity NF_3 is used in the manufacture of semiconductors (to clean chemical vapor deposition chambers), as an oxidizer of high energy fuels, for the preparation of tetrafluorohydrazine, as an etchant gas in the electronic industry, and as a fluorine source in high power chemical lasers (Henderson and Woytek 1994; Air Products 2002). Nitrogen trifluoride is shipped as a gas under high pressure and is available in tube trailers and cylinders (Henderson and Woytek 1994).

TABLE 1. Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	Nitrogen fluoride; nitrogen trifluoride;perfluoroammonia; trifluoamine; trifluoroammonia	O'Neil et al. 2001; AIHA 2005
Chemical formula	NF_3	O'Neil et al. 2001
Molecular weight	71.00	O'Neil et al. 2001
CAS Reg. No.	7783-54-2	O'Neil et al. 2001
Physical state	Colorless gas	O'Neil et al. 2001
Solubility in water	Insoluble	O'Neil et al. 2001
Vapor pressure	>1 atm at 20ºC	ACGIH 2001
Vapor density (air =1)	2.4	AIHA 2005
Liquid density (water =1)	1.885 at −129ºC	O'Neil et al. 2001
Melting point	−208.5ºC	O'Neil et al. 2001
Boiling point	−129ºC	O'Neil et al. 2001
Flammability limits in air	Nonflammable but reacts explosively with reducing agents; strong oxidizer; decomposed by electric sparks	ACGIH 2001
Conversion factors	1 ppm = 2.90 mg/m^3 1 mg/m^3 = 0.34 ppm	Calculated

2. HUMAN TOXICITY DATA

Five volunteers were exposed to 100 or 500 ppm for 2-3 minutes to study odor detection (Torkelson et al. 1962). None of the volunteers detected any odor at 100 ppm, and one of five volunteers tentatively detected a faint odor at 500 ppm.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute toxicity studies were conducted with monkeys, dogs, rats, and mice. Where mortality data were sufficient for calculation of LC_{50} values, the values for the respective species are summarized in Tables 2, 3, 4, and 5. All LC_{50} values are summarized in Table 6.

3.1.1. Nonhuman Primates

Groups of 2-3 male and female Rhesus monkeys inhaled various concentrations of NF_3 for 15, 30, or 60 minutes (Vernot et al. 1973; see also MacEwen and Vernot 1969). Exposures took place in a modified Rochester chamber. Atmospheres were monitored with a gas chromatographic procedure. Surviving animals were observed for two weeks post-exposure. Clinical signs during exposure included eye irritation, tachypnea, gasping, cyanosis, and emesis. Tachypnea, gasping and cyanosis were attributed to tissue anoxia due to elevated concentrations of MetHb. Gross and histopathologic findings in animals that died revealed lung congestion, edema, and focal hemorrhage. Organs of the viscera were congested. These findings were consistent with anoxia and massive MetHb formation. The 15-, 30-, and 60-minute LC_{50} values were 24,000, 14,000, and 10,000 ppm, respectively (Table 2). Monkeys that died succumbed within one hour post-exposure.

TABLE 2. Mortality of Monkeys Exposed to NF3 for Various Exposure Durations

Exposure Duration	Mean Concentration in ppm (range)	Mortality	Approximate LC_{50} (ppm)[a]
15 min	21,250 (20,400-22,000) 23,490 (21,812-27,880) 25,026 (23,370-32,636) 27,150 (21,500-30,100)	0/3 1/2 1/2 3/3	24,000
30 min	13,038 (7790-18,040) 15,170 (14,432-15,580)	0/3 3/3	14,000
60 min	8519 (8446-8815) 9390 (7300-11,100) 9947 (9020-10,496) 11,273 (9922-11,808)	0/2 1/3 1/3 3/3	10,000

[a] Confidence limits could not be calculated due to the small number of animals.
Source: Vernot et al. 1973.

3.1.2. Dogs

Groups of 2-5 male and female beagle dogs inhaled various concentrations of NF_3 for 15, 30, or 60 minutes (Vernot et al. 1973). Exposures took place in a modified Rochester chamber. Atmospheres were monitored with a gas chromatographic procedure. Surviving animals were observed for two weeks post-exposure. Clinical signs during exposure included eye irritation, tachypnea, gasping, cyanosis, and emesis. Tachypnea, gasping and cyanosis were attributed to anoxia due to MetHb formation. Gross and histopathologic findings in animals that died revealed lung congestion, edema, and focal hemorrhage. Organs of the viscera were congested. These findings are consistent with tissue anoxia as a result of elevated circulating MetHb. The 15-, 30-, and 60-minute LC_{50} values were 38,000, 20,400, and 9600 ppm, respectively (Table 3). Dogs that died succumbed within one hour post-exposure. In a study that addressed recovery from NF_3-induced anemia, 14 of 18 dogs survived for 40 days following exposure to the 1-hour LC_{50} value of 9600 ppm for 60 minutes.

TABLE 3. Mortality of Dogs Exposed to NF3 for Various Exposure Durations			
Exposure Duration	**Mean Concentration in ppm (range)**	**Mortality**	**Approximate LC_{50} (ppm)[a]**
15 min	31,816 (22,468-45,100) 37,600 (35,900-39,200) 41,410 (23,780-53,546) 43,460 (37,228-50,184)	0/3 2/5 2/3 3/3	38,000
30 min	19,434 (14,760-21,484) 20,779 (16,810-23,158) 24,026 (21,484-25,092)	0/3 2/3 3/3	20,400
60 min	8550 (7790-8900) 9947 (9020-10,496) 11,450 (10,824-11-808)	0/2 2/3 2/2	9600
60 min	9600	4/18	—

[a] Confidence limits could not be calculated due to the small number of animals.
Source: Vernot et al. 1973.

3.1.3. Rats

In a preliminary study, Torkelson et al. (1962) allowed groups of 4-8 male rats (strain unspecified) to inhale NF_3 while they were placed in a 19-liter glass jar. The NF_3 (purity not specified) was metered into the chambers using a flow-through method; atmospheres were not measured. Surviving animals were observed for two weeks. Results presented graphically indicated that all rats survived exposure to 20,000 ppm for 0.2 hours, 10,000 ppm for 0.5 hours, 5000 ppm for 1 hour, 2500 ppm for 2 hours, and 1000 ppm for 7 hours. When exposure durations were extended, e.g., 20,000 ppm for 0.5 hours, or 10,000 ppm for one hour, mortality was increased to 100%. Deaths were ascribed to anoxia as a result of massive methemoglobinemia. Surviving animals recovered rapidly.

Dost et al. (1970a) exposed seven groups of 5 rats each (gender and strain unspecified) to 10,000 ppm NF_3 for periods of time ranging from 45-60 minutes (average time 63.5 minutes). Other groups of 10 rats inhaled 4000 ppm for 3 hours. Exposures took place in an 18x18x27-inch aluminum chamber. Atmospheres were analyzed with an infrared spectrophotometer. Whole-body exposure to 10,000 ppm resulted in mortality of 86% (30 of 35 rats) within a 5- to 15-minute post-exposure period. Methemoglobin levels at the time of death were equivalent to 60-70% of the available Hb. Rats in which 50% or more of circulating Hb was oxidized required about 2 hours to recover to 10% MetHb. The concentration of 4000 ppm was not lethal to any rats during a 3-hour exposure. All 10 rats died when the exposure duration was extended to 3.75 hours. Exposures below the lethal level caused no apparent distress other than accelerated respiration. At nearly lethal and lethal concentrations, severe respiratory distress was accompanied by MetHb reflected in the eye color and in the color of their mucus membranes and extremities. Rats that survived 1-2 minutes after cessation of exposure generally recovered.

Groups of 10 male Sprague-Dawley rats inhaled various concentrations of NF_3 for 15, 30, 60 or 120 minutes (Vernot et al. 1973). Whole-body exposures took place in a 30-liter bell-jar chamber. Atmospheres were monitored by gas chromatography. Surviving animals were observed for two weeks post-exposure. Clinical signs during exposure included eye irritation, tachypnea, gasping, and cyanosis, and the latter three signs were attributed to anoxia brought on

by elevated MetHb. Gross and histopathologic findings in animals that died revealed lung congestion, edema, and focal hemorrhage. Visceral organs were congested at necropsy. These findings are consistent with anoxia and massive MetHb formation. The 15-, 30-, and 60-minute LC_{50} values were 26,700, 11,700, and 6700 ppm, respectively (Table 4). During the 60-minute exposure, most deaths occurred within the first 10 minutes. There were no deaths after 24 hours. Nine of 10 rats died following exposure to 4500 ppm for 2 hours.

TABLE 4. Mortality of Rats Exposed to NF3 for Various Exposure Durations

Exposure Duration	Mean Concentration in ppm (range)	Mortality	Calculated LC_{50} (Confidence Limits)	Reference
12 min 30 min	20,000 20,000	0/4-8 100%	—	Torkelson et al. 1962
30 min 60 min	10,000 10,000	0/4-8 100%	—	Torkelson et al. 1962
60 min	5000	0/4-8	—	Torkelson et al. 1962
120 min	2500	0/4-8	—	Torkelson et al. 1962
7 h	1000	0/4-8	—	Torkelson et al. 1962
63.5 min	10,000	30/35	—	Dost et al. 1970a
180 min	4000	0/10	—	Dost et al. 1970a
225 min	4000	10/10	—	Dost et al. 1970a
15 min	19,316 (17,500-20,200) 21,430 (18,500-23,500) 25,200 (23,500-25,900) 28,257 (27,000-28,800) 28,930 (26,500-30,000) 30,714 (28,600-31,200)	0/10 0/10 3/10 7/10 8/10 10/10	26,700 (25,640-27,610)	Vernot et al. 1973
30 min	8204 (8036-8282) 10,250 (10.004-10,436) 11,257 (11,070-11,316) 12,281 (12,218-13,300) 13,226 (13,202-13,407)	0/10 3/10 1/10 7/10 9/10	11,700 (11,080-12,330	Vernot et al. 1973
60 min	4118 (4018-4428) 5117 (5002-5298) 6121 (5986-6232) 7190 (7134-7257) 8204 (8036-8282)	0/10 1/10 4/10 5/10 9/10	6700 (6130-7320)	Vernot et al. 1973
120 min	4500	9/10	—	Vernot et al. 1973

3.1.4. Mice

Groups of 10 male ICR mice inhaled various concentrations of NF_3 for 15, 30, 60 or 120 minutes (Vernot et al. 1973). Whole-body exposures took place in a 30-liter bell-jar chamber. Atmospheres were monitored with a gas chromatographic procedure. Surviving animals were observed for two weeks post-exposure. During exposure the animals displayed eye irritation, tachypnea, gasping, and cyanosis; the latter three signs were attributed to anoxia due to elevated circulating MetHb. Gross and histopathologic findings in animals that died revealed lung congestion, edema, focal hemorrhage, and visceral congestion. The findings were consistent with methemoglobinemia. The 15-, 30-, and 60-minute LC_{50} values were 19,300, 12,300, and 7500 ppm, respectively (Table 5). Half of the mice succumbed during exposure; all mice died

within 3 days. Mice dying after 1 day showed extensive pneumonia. Two of 10 mice died during or following exposure to 4500 ppm for 2 hours.

TABLE 5. Mortality of Mice Exposed to NF3 for Various Exposure Durations

Exposure Duration	Mean Concentration in ppm (range)	Mortality	Calculated LC_{50} (Confidence Limits)
15 min	17,515 (15,800-18,000) 20,130 (17,800-20,900) 22,030 (18,200-23,500) 23,570 (19,300-24,300)	3/10 6/10 7/10 9/10	19,300 (17,910-20,910)
30 min	8212 (8118-8323) 10,222 (9840-10,496) 10,906 (10,742-11,070) 11,234 (11,152-11,275) 12,327 (12,136-12,628) 16,293 (16,154-16,400)	0/10 1/10 1/10 5/10 6/10 9/10	12,300 (11,460-13,160)
60 min	4112 (3854-4264) 6469 (6297-6560) 7150 (6888-7544) 8200 (8150-8250) 12,218 (12,136-12,300)	0/10 3/10 4/10 6/10 10/10	7500 (7800-8280)
120 min	4500	2/10	—

Source: Vernot et al. 1973.

A comparison of LC_{50} values for four species is in Table 6.

TABLE 6. LC_{50} Values in Four Species of Animals (ppm)

Species	15 min	30 min	60 min
Monkey	24,000	14,000	10,000
Dog	38,000	20,400	9600
Rat	26,700	11,700	6700
Mouse	19,300	12,300	7500

Source: Vernot et al. 1973.

3.2. Acute Non-Lethal Toxicity

Groups of 6 monkeys, 6 dogs and an unspecified number of rats and mice were exposed to levels of NF_3 predicted to cause 15% conversion of Hb to MetHb (120,000 ppm-minutes) (Vernot et al. 1973). Gender and strain information for these animals are presented in the preceding section under lethality studies. These concentration-exposure durations were 7000 ppm for 15 minutes, 3500 ppm for 30 minutes, and 2000 ppm for 60 minutes (Table 7). Blood was sampled immediately post-exposure. No adverse signs were noted in any species during exposure, and no effects were seen on body weight gain during the 4-week post-exposure period. At necropsy, rat organ-to-body weight ratios were unaffected. Gross histopathologic examination revealed no differences from the unexposed controls.

Hematologic parameters were followed only in monkeys and dogs (Table 7). The 15% MetHb formation in monkeys and dogs was fairly well achieved: monkeys, 10.3-16.5% and dogs, 10.3-19.2% (Table 7). Hematologic parameters were unaffected in monkeys following NF_3

exposures. At 105,000-120,000 ppm-minutes, dogs developed average 16% reductions in hematocrit, Hb, and erythrocyte count, with the largest reductions seen at 7-14 days. The decrease in these parameters averaged 33% following the exposure to the LC_{50}. Blood samples also showed hemolysis; and the increased turbidity of the hemolyzed blood was due to the presence of Heinz bodies.

TABLE 7. Methemoglobin formation in monkeys and dogs

Time (minutes)	Concentration (ppm)	Mean methemoglobin (%)	
		Monkeys	Dogs
15	7000[a]	16.5±1.0 (n = 6)	19.2±1.6 (n = 6)
30	3500[a]	15.0±0.5 (n = 6)	10.3±1.0 (n = 6)
60	2000[a]	10.3±2.1 (n = 6)	15.2±1.8 (n = 6)
60	1075[b]	—	9.7 (n = 3)
60	510[c]	—	2.2 (n = 3)
60	290[d]	—	0.0 (n = 3)

[a] Dose of 105,000-120,000 ppm-minutes.
[b] Dose of 64,500 ppm-minutes.
[c] Dose of 31,000 ppm-minutes.
[d] Dose of 17,400 ppm-minutes
Source: Vernot et al. 1973.

Monkeys, dogs, rats, and mice were exposed to a 30,000 ppm-minute dose level (presumably target concentrations of 2000 ppm for 15 minutes, 1000 ppm for 30 minutes, or 500 ppm for 60 minutes). There were no body weight, organ weight, gross or microscopic changes in any species during a 28-day post-exposure period. In dogs, hematology values showed no decrease compared to controls during the post-exposure period. Methemoglobin data were provided only for dogs exposed to 510 ppm for 60 minutes, a 2.2% MetHb concentration (Table 7). The 60-minute exposure to 510 ppm was considered a NOAEL in dogs because the MetHb value of 2.2% was within the precision of the analytical technique.

3.3. Repeat-Exposure Studies

Groups of 5 male and 5 female Crl:CD(SD)BR rats were exposed whole body to 0, 22, 100, or 500 ppm NF_3 for 6 hours/day, 5 days/week, for 2 weeks (Bamberger 1998). Chamber atmospheres were monitored with gas chromatography. Rats were weighed throughout the exposure period, and clinical signs were evaluated during and after each exposure. After each exposure and prior to removal from the chamber, an alerting response to an auditory signal was checked. After the 10^{th} exposure, hematology, clinical chemistry, and urine analyses were performed. At sacrifice, organs were weighed and examined microscopically. Body weight was unaffected by treatment, and there were no treatment-related mortalities. No clinical signs and no failure to respond to an auditory stimulus were observed in any treatment group. Rats in the 500 ppm group had pallor during the 4^{th}, 5^{th}, 7^{th}, and 10^{th} exposures, and clinical pathology evaluations revealed hemolytic anemia in male and female rats in the 100 and 500 ppm groups. Circulating erythrocyte mass was marginally decreased in the 100 ppm male group and mildly to moderately decreased in females in the 100 ppm group and in males and females in the 500 ppm group. Mean erythrocyte counts were 89% and 60% of the concurrent control in males in the 100

and 500 ppm groups, respectively. Mean erythrocyte counts were 81% and 49% of the control group mean value in females in the 100 and 500 ppm groups, respectively. The 100 ppm concentration increased MetHb from 0.5% to 0.8% in male rats and from 0.4% to 0.6% in female rats (both statistically significant). Histopathological evaluation revealed increased erythropoiesis that was ascribed to a regenerative, hemolytic anemia. Changes in the liver, kidneys, spleen, and bone marrow all indicted a physiologic response to hemolytic anemia. The NOAEL and LOAEL values in the Bamberger (1998) study were 22 and 100 ppm, respectively.

TABLE 8. Summary of Repeat-Exposure Studies with Rats

Concentration (ppm)	Exposure Conditions	Effects	Reference
22	6 h/d, 5 d/wk, two wks	No-observed effects	Bamberger 1998
100		Hemolytic anemia; erythrocyte count, Hb, and hematocrit marginally (males) to moderately decreased (females)	
500		Hemolytic anemia; erythrocyte count, Hb, and hematocrit mildly to moderately decreased (both sexes)	
100	7 h/d, 5 d/wk, 19 wks	Hematology parameters unaffected; mild to moderate pathologic changes in liver and kidney	Torkelson et al. 1962

Twelve male and 12 female rats (strain unspecified) inhaled 100 ppm NF_3 7 hours/day, 5 days/week for 19 weeks (94 exposures) (Torkelson et al. 1962). Methemoglobin determinations were made initially and after 1, 2, 4, 8, and 66 exposures. Hematology parameters were unaffected, and there was no evidence of methemoglobinemia at any sampling time. There was no evidence of fluorosis in the teeth or bones. Mild to moderate changes consisted of cloudy swelling of the hepatocytes and interstitial and slight tubular nephritis in the kidney.

3.4. Neurotoxicity

No studies specifically addressed the neurotoxicity of NF_3. Rats exposed whole body to 0, 22, 100, or 500 ppm NF_3 for 6 hours/day, 5 days/week, for 2 weeks responded appropriately to an auditory stimulus following each exposure (Bamberger 1998).

3.5. Developmental/Reproductive Toxicity

Groups of eight time-mated female Crl:CD®(SD)IGS BR rats were exposed to NF_3 at 0, 5, 20, 50, or 100 ppm for six hours/day on days 6 through 20 of gestation ((Munley 2003). Atmospheres were generated by dilution of the metered gas in air, and the concentrations were measured with gas chromatography. Maternal body weight, food consumption, and clinical observations were recorded. On day 21 of gestation, the dams were sacrificed and examined grossly. Uterine contents were examined, and all fetuses were sexed, weighed, and examined for external alterations. There were no maternal deaths or abnormal gross changes; clinical observations were unremarkable. There were no differences between the control and treatment groups in the numbers of implantations, resorptions, litter size, sex ratio, or fetal body weight. There were no substance-related external malformations.

3.6. Genotoxicity

High purity NF_3 was tested for genotoxic potential in *in vitro* and *in vivo* assays (Winegar et al. 1996; Air Products 2002). Nitrogen trifluoride was non-mutagenic in *Salmonella typhimurium* strains TA1535, TA98, TA100, and TA102 and in *Escherichia coli* strain WP2 (uvra), both in the presence and absence of metabolic activation. Tested concentrations in air ranged up to 50,000 ppm. In a repeat assay, NF_3 elicited a weak mutagenic response. In the mouse lymphoma assay, dose levels of 1, 2, 4, 6, and 10% in an atmosphere of 5% carbon dioxide in air induced non-significant increases in mutant frequency with increasing concentration. At 92,600 ppm in air, no cytotoxicity was observed in mouse lymphoma L5178Y cells.

Nitrogen trifluoride was assayed for clastogenic activity in the bone marrow micronucleus assay with male and female Swiss-Webster mice. Concentrations in air were 0, 842, 1277, or 2474 ppm. Gavage with urethane served as a reference mutagen. Nitrogen trifluoride failed to statistically significantly increase the number of micronucleated polychromatic erythrocytes.

3.7. Subchronic and Chronic Toxicity/Carcinogenicity

In a 90-day study, groups of 15 male and 15 female Crl:CD(IGS)BR rats were exposed to NF_3 atmospheres of), 5, 20, 50, or 100 ppm for 6 hours/day, 5 days/week (O'Neill 2003). Chamber atmospheres were measured with gas chromatography. The study design followed U.S. EPA OPPTS 870.3465 guidelines for subchronic inhalation toxicity. Rats were observed daily for clinical signs and weighed weekly. Food consumption was monitored. Prior to sacrifice, blood was sampled for hematology and clinical chemistry determinations and urine was collected for urinalysis. At sacrifice, organs were weighed and major organs and tissues were examined microscopically. Five rats per group were allowed a one-month recovery period following which they were subjected to the same clinical chemistry and tissue analysis.

There were no deaths during the study, and there were no treatment-related clinical signs or effects on body weight or food consumption. At termination of exposure, red cell mass parameters (erythrocyte count, Hb, hematocrit) were mildly to moderately decreased in male and female rats exposed to 20 ppm and above. At day 94, red cell counts in the 5, 20, 50, and 100 ppm groups were 98%, 93%, 93%, and 85% of control (males) and 99%, 93% 82%, and 81% of control (females), respectively. These decrements were accompanied by increased erythropoiesis in bone marrow, spleen, and liver. Congestion was observed in the spleen and pigment deposition was found in the spleen, liver, and kidney. Spleen weight was increased. Fluoride was increased in urine, but not in plasma. Following the recovery period, erythropoiesis returned to normal, pigment deposition in the spleen, liver, and kidneys was reduced, and organ weight and gross and microscopic pathology were considered normal. The author concluded these changes were reversible physiological responses to hemolysis, i.e., the changes were reversible following a 4-week recovery period. At day 128, erythrocyte counts ranged from 105-110% of control in males and 105-109% of control in females. Based on the severity of the increased erythrocyte turnover, the study author considered 100 ppm the LOAEL for male rats and 50 ppm the LOAEL for female rats.

There were no chronic toxicity/carcinogenicity studies with NF_3.

3.8. Summary

Acute lethality studies have been conducted with monkeys, dogs, rats, and mice. The 15-, 30-, and 60-minute LC_{50} values for monkeys were 24,000, 14,000, and 10,000 ppm, respectively. The 15-, 30-, and 60-minute LC_{50} values for dogs were 38,000, 20,400, and 9600 ppm, respectively. The 15-, 30-, and 60-minute LC_{50} values for rats were 26,700, 11,700, and 6700 ppm, respectively. The 15-, 30-, and 60-minute LC_{50} values for mice were 19,300, 12,300, and 7500 ppm, respectively (Vernot et al. 1973). In an earlier study, no rats died when exposed to 20,000 ppm for 12 minutes, 10,000 ppm for 30 minutes, 5000 ppm for 1 hour, 2500 ppm for 2 hours, or 1000 ppm for 7 hours (Torkelson et al. 1962). Mortality was 100% when the exposure to 20,000 ppm was extended to 30 minutes and the exposure to 10,000 ppm was extended to 1 hour. An NF_3 concentration of 4000 ppm for 3 hours was non-lethal, but all rats died when the exposure was extended to 225 minutes (Dost et al. 1970a). In all studies, deaths occurred within a few minutes post-exposure and were attributed to tissue anoxia as a result of circulating MetHb.

Exposure to 120,000 ppm-minutes (7000 ppm for 15 minutes, 3500 ppm for 30 minutes, or 2000 ppm for 60 minutes) oxidized 15% of oxyHb to MetHb in monkeys and dogs (Vernot et al. 1973). There were no clinical signs of NF_3 intoxication. Hematology parameters were affected only in dogs, with an average 16% decrease in erythrocyte count, Hb and hematocrit. Following a 30,000 ppm-minute exposure, (presumably 2000 ppm for 15 minutes, 1000 ppm for 30 minutes, or 500 ppm for 60 minutes), hematology parameters were unaffected in dogs.

In a two-week, repeat exposure study, 22 ppm for 6 hours/day, 5 days/week, was a NOAEL for methemoglobinemia in rats as observed by changes in erythrocyte count, reduced Hb, and hematocrit (Bamberger 1998). A 100 ppm concentration increased MetHb from 0.5% to 0.8% in male rats and from 0.4% to 0.6% in female rats. Increased erythropoiesis indicated that the effect was reversible. In a 19-week study, exposure to 100 ppm NF_3 for 7 hours/day, 5 days/week, failed to change hematology parameters, but mild to moderate histologic changes were seen in the liver and kidneys (Torkelson et al. 1962).

In a 90-day study, rats were exposed to NF_3 atmospheres of 0, 5, 20, 50, or 100 ppm for 6 hours/day and 5 days/week (O'Neill 2003). Mild to moderate reductions in erythrocyte count, Hb, and hematocrit seen at the end of exposure resolved following a 4-week recovery period.

Nitrogen trifluoride concentrations of 5, 20, 50, or 100 ppm for six hours/day on days 6 through 20 of gestation were not developmentally toxic to the fetal rat (Munley 2003), and there is no evidence from standard short-term tests to suggest NF_3 presents a genotoxic or mutagenic hazard (Winegar et al. 1996; Air Products 2002).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Nitrogen trifluoride oxidizes erythrocyte (oxy)Hb to MetHb which is unable to bind oxygen. Methemoglobin is normally <1% of the total blood Hb. Methemoglobinemia is

diagnosed when the percent MetHb is greater than 1.5%. Methemoglobin is reduced the NADH-dependent cytochrome b_5 reductase (also called MetHb reductase or NADH-diaphorase) which is present in the erythrocyte (Bloom and Brandt 2008). This enzyme accounts for 60-95% of the MetHb reduction. Two other less important reducing systems are present. The combined MetHb reduction pathways can reduce the ferric (Fe^{+3}) iron of MetHb at a rate of approximately 15% per hour. Rats in which 50% or more of Hb was oxidized required about two hours to reduce the MetHb levels to less than 10% (Dost et al. 1970a). Methemoglobin levels remained elevated at 2-5% for several days.

Exposure of male Sprague-Dawley rats to 10,000 ppm NF_3 for 45 minutes converted 37% of the total Hb to MetHb when measured immediately after exposure (Coppoc and Leger 1970). At the same time, there was a 6-fold increase in blood lactate, but both parameters returned to normal two hours later. Serum isocitric dehydrogenase did not change measurably. Serum glutamic oxalacetic transaminase was unchanged at 1 hour, but was increased 2- to 3-fold by 6 hours post-exposure.

Acute inhalation of NF_3 by rats, 5000 ppm for 50 minutes, resulted in a moderate increase in tissue fluoride at the end of the exposure that resolved in one day (Dost et al. 1970b). A high erythrocyte fluoride content, 15-28 µg/gram tissue wet weight, persisted during the 0 to 48-hour recovery period. A control value was not provided, but exposures to other fluorides that were not taken up to a great degree showed erythrocyte fluoride levels of 2.1-3.3 µg/gram tissue wet weight. Fluorine exposure was associated with an ammonium sulfate precipitate of erythrocyte proteins including Hb and MetHb (Dost et al. 1970a). Spectral examination indicated that this complex was not fluoromethemoglobin.

4.2. Mechanism of Toxicity

The acute inhalation toxicity of NF_3 is due to formation of MetHb, with death ensuing from the resulting anoxia (Ruff 1931; Torkelson et al. 1962; Dost et al. 1970a). Methemoglobin is incapable of carrying oxygen to the tissues. The exact mechanism for the reaction with Hb is unknown. Reaction of NF_3 with Hb, both *in vitro* and *in vivo* with anesthetized dogs indicates that one mole of NF_3 oxidizes three heme equivalents (Dost et al. 1971). Death in monkeys, dogs, rats, and mice following acute exposures was attributed to MetHb formation or conversely, the amount of oxyhemoglobin remaining in the blood as measured immediately after exposure (Vernot et al. 1973). A decrease in oxyhemoglobin to less than 4 g/100 mL (i.e., >75% MetHb) invariably resulted in death of the animals. Oxyhemoglobin values in surviving animals returned to pre-exposure values at 5-10 hours post-exposure.

The concentration of MetHb in the blood is generally less than 1% (Bloom and Brandt 2008). Most individuals tolerate levels less than 10%, but cyanosis may be obvious when MetHb concentration exceeds 5-10%. Levels above 20% are considered clinically significant. Signs and symptoms associated with MetHb concentrations in humans are summarized in Table 9 (Kiese 1974; Seger 1992). The classifications in Table 9 are based on acute clinical methemoglobinemia. Methemoglobinemia is usually accompanied by the presence of Heinz bodies. Heinz bodies are precipitates of proteins in erythrocytes that develop after oxidation of Hb. Erythrocytes with Heinz bodies are removed by the spleen.

Dogs may develop anemia following acute exposure to NF_3. Dogs that inhaled 2000 ppm for 60 minutes had Hb, hematocrit, and erythrocyte count reduced by approximately 16% (Vernot et al. 1973). Dogs that survived a 60-minute exposure to 9600 ppm showed a 33% decrease in these parameters, attaining maximum reductions at about 2 weeks. Hematologic changes then recovered slowly, attaining normal values by 40 days post-exposure.

A one-minute intra-tracheal instillation of male Sprague-Dawley rats with 100% NF_3 caused a rapid, sharp drop in blood pressure and a decrease in heart rate (Foster 1970). Blood pressure and heart rate recovered slowly, but were still below pre-exposure values at 60 minutes after treatment.

TABLE 9. Signs and Symptoms Associated with Methemoglobin Concentrations in Humans

Methemoglobin Concentration (%)	Signs and Symptoms
1.1	Normal level
1-15	None
15-20	Clinical cyanosis (chocolate brown blood); no hypoxic symptoms
30	Fatigue; recovery without treatment
20-45	Anxiety, exertional dyspnea, weakness, fatigue, dizziness, lethargy, headache, syncope, tachycardia
45-55	Decreased level of consciousness
55-70	Hypoxic symptoms: semistupor, lethargy, seizures, coma, bradycardia, cardiac arrhythmias
>70	Heart failure from hypoxia; high incidence of mortality
>85	Lethal

Sources: Kiese 1974; Seger 1992.

4.3. Structure-Activity Relationships

Other fluorides including chlorine trifluoride and bromine pentafluoride have been tested (Dost et al. 1970b); however, the mode of action for non-nitrogen fluorides does not involve formation of MetHb. Therefore, structure-activity relationships between these other fluorides and NF_3 are not relevant to development of AEGL values. The related chemical, nitrogen trichloride, is a thick, oily liquid (O'Neil et al. 2001). No toxicity information for nitrogen trichloride was available in the open literature.

4.4. Other Relevant Information

4.4.1. Species Variability

Compared with the rat and mouse, the monkey and dog are more similar to humans regarding hematopoiesis and blood cell kinetics (Bloom and Brandt 2008). Results of some *in vitro* studies in which nitrates were incubated with erythrocytes from humans and the dog, cat, mouse, and rabbit, show that spontaneous methemoglobin reductase activity is similar in the dog, cat, and human (Stolk and Smith 1966; Smith 1996). *In vitro* studies with acetanilide show that the rat, mouse, rabbit, guinea pig, and monkey are less sensitive to MetHb formation and

generally have a faster reduction of the induced MetHb than humans, dogs, and cats (Blom 2000). *In vivo*, differences in sensitivity are due to several species-specific factors including rate of metabolism of the inhaled chemical to the methemoglobin-inducing form and activity of methemoglobin reductase and other reducing components of the blood. Nitrogen trifluoride is presumably a direct-acting chemical and metabolism is not involved in formation of MetHb. Humans, dogs, and cats are more sensitive than rodents or rabbits to chemically-induced methemoglobinemia due in part to the reduced activity of erythrocytic methemoglobin reductase. *In vitro* studies show that the erythrocytes of beagle dogs are comparatively poor in methemoglobin reductase (Srivastava et al. 2002). This differential sensitivity did not affect lethality values (Table 6), but was associated with reductions in hematology parameters in the dog.

Based on 60-minute LC_{50} values (Table 6; Vernot et al. 1973) monkeys, dogs, rats and mice showed similar sensitivity to the effects of inhaled NF_3. The 60-minute LC_{50} values ranged from to 6700 for the rat to 10,000 ppm for the monkey. At concentration-exposure duration combinations that resulted in 15% MetHb formation, i.e., 120,000 ppm-minute, monkeys and dogs showed similar sensitivity (Table 7). After beagle dogs inhaled 9600 ppm NF_3, pre-exposure MetHb values were attained in <10 hours (Vernot et al. 1973). However, hematology values required longer to recover in dogs compared with monkeys. Exposure of dogs to approximately 31,000 ppm-min (510 ppm for 60 minutes) resulted in no change in baseline hematology values.

4.4.2. Susceptible Populations

There are individuals who are sensitive to chemicals that oxidize Hb to MetHb (Eaton and Gilbert 2008). Individuals with an inherited deficiency of NADH-methemoglobin reductase have 10-15% of their circulating blood pigment in the form of MetHb. This condition is inherited as an autosomal recessive trait and is characterized by a deficiency in NADH-cytochrome b5 reductase activity. The effect is primarily cosmetic as these individuals have a compensatory polycythemia, although symptoms may occur during exercise. Other individuals may have a deficiency of erythrocyte NADPH-glucose-6-phosphate dehydrogenase, an enzyme responsible, via the pentose phosphate shunt, for generating an alternate source of energy for the cell; these individuals do not have elevated levels of MetHb as this is a minor MetHb reducing system (Kiese 1974; Seger 1992). The Hb of individuals with defective Hb M or H is more susceptible to autooxidation of the ferric iron (Seger 1992; Smith 1996). Individuals with Hb M maintain MetHb levels of 25-30% and are clinically cyanotic. Individuals with Hb H suffer from chronic hemolytic anemia (thalassemia). Individuals with anemia may be more sensitive to MetHb-forming chemicals than healthy individuals.

NADH-methemoglobin reductase is deficient in neonates making them especially sensitive to chemicals that cause methemoglobinemia (Gregus and Klaassen 2001). NADH lacks full activity until infants are four months of age.

4.4.3. Concentration-Exposure Duration Relationship

The concentration-time relationship for a single endpoint for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$. A computer program

developed by ten Berge (2006) and based on probit analysis integrates all concentration and time information for a range of lethality data. Concentration, exposure duration, and response, including the number of animals responding, are considered simultaneously in a linear regression equation, with the Maximum Likelihood statistical method used to find the closest estimates of the regression coefficients for each parameter. The probit-analysis dose-response program of ten Berge was applied to the animal lethality data sets of Vernot et al. (1973) and Dost et al. (1970a) to estimate the threshold for lethality at each AEGL exposure duration (with confidence limits of 95%). For the monkey, dog and rat (single and combined data sets), the calculated values of n in $C^n \times t = k$ were 1.5, 1.0, and 1.2, respectively.

4.4.4. Concurrent Exposure Issues

No information relevant to concurrent exposure issues was located.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No clinical studies appropriate for the derivation of AEGL-1 values for NF_3 were available.

5.2. Summary of Animal Data Relevant to AEGL-1

Methemoglobin formation under varying conditions of NF_3 exposure is summarized in Table 7 (Vernot et al. 1973). Hematology parameters in monkeys and dogs exposed to 30,000 ppm-minutes (presumably 2000 ppm for 15 minutes, 1000 ppm for 30 minutes, or 500 ppm for 60 minutes) remained unaffected, and MetHb (2.2%) in dogs was within the analytical limits of the control value. Exposure to 64,500 ppm-minutes (1075 ppm for 60 minutes) oxidized 9.7% of circulation Hb to MetHb in dogs. Exposure to NF_3 at 105,000 to 120,000 ppm-minutes (7000 ppm for 15 minutes, 3500 ppm for 30 minutes, or 2000 ppm for 60 minutes) induced 15% MetHb in monkeys and dogs (Vernot et al. 1973). There were no clinical signs of anoxia at these levels. Hematology parameters were affected only in dogs (average 16% reduction in erythrocyte count, Hb and hematocrit).

5.3. Derivation of AEGL-1

AEGL-1 values were based on an exposure of monkeys and dogs to 2000 ppm NF_3 for 60 minutes (total administered dose of 120,000 ppm-minutes) (Vernot et al. 1973). This concentration-exposure duration resulted in 15% MetHb formation in dogs and 10% in monkeys. A MetHb concentration of ≤15% is without clinical signs or symptoms. Hematology changes (decreases in erythrocyte count, Hb, and hematocrit of approximately 16%), seen only in dogs, were reversible. An interspecies uncertainty factor of 1 was applied because LC_{50} values were similar for all four species and because the dog is the most sensitive species for effects on hematology parameters. Furthermore, compared with rodents, the dog is more hematologically similar to humans regarding hematopoiesis and blood cell kinetics. An intraspecies uncertainty factor of 10 was applied because infants, lacking the NADH cofactor for methemoglobin reductase, are especially sensitive to MetHb-forming chemicals. In addition, some humans may be anemic, have hereditary methemoglobinemia, or have defective hemoglobins. The resulting

60-minute 200 ppm value was time-scaled using an n value of 1.0 from the dog lethality studies. The same endpoint of methemoglobinemia was the basis for time-scaling in the lethality studies. Calculations are in Appendix A and AEGL-1 values are summarized in Table 10. A category graph of the AEGL values in relation to the toxicity data is in Appendix B.

TABLE 10. AEGL-1 Values for Nitrogen Trifluoride

10-min	30-min	1-h	4-h	8-hour
1200 ppm (3500 mg/m^3)	400 ppm (1200 mg/m^3)	200 ppm (580 mg/m^3)	50 ppm (150 mg/m^3)	25 ppm (73 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human studies appropriate for the derivation of AEGL-2 values for NF_3 were available.

6.2. Summary of Animal Data Relevant to AEGL-2

No data on an NF_3 concentration that would result in effects consistent with the definition of an AEGL-2 were available in the open literature. A MetHb concentration of approximately 45% is the threshold for loss of consciousness (Table 9). AEGL-values for aniline were also based on MetHb formation (NRC 2000). A MetHb concentration of 41% in rats that inhaled 150 ppm aniline for 8 hours was the point of departure for the AEGL-2 values for aniline.

6.3. Derivation of AEGL-2

A MetHb concentration of 40-45% is predicted to induce weakness, fatigue, dizziness, and lethargy in humans (Kiese 1974; Seger 1992). These symptoms are the threshold for an impaired ability to escape and meet the definition of an AEGL-2. Responses to MetHb-forming chemicals are similar in dogs and humans. Data on an atmospheric concentration of NF_3 that would result in a MetHb concentration of approximately 43% in the dog were unavailable. The relationship between the atmospheric concentration of NF_3 and MetHb formation is linear (Figure 1). Therefore, a concentration of NF_3 of 43% was estimated as the midpoint between the 15% MetHb concentration that defines the AEGL-1 and the 70% MetHb predicted threshold value for lethality as cited in several reviews (Kiese 1974; Seger 1992) and referenced in the key and supporting studies (Dost et al. 1970a; Vernot et al. 1973). The AEGL-2 values for each exposure duration were calculated as the midpoint concentration between each AEGL-1 and AEGL-3 value. Inter- and intraspecies uncertainty factors are already accounted for in derivation of the AEGL-1 and AEGL-3 values. Calculations are in Appendix A and AEGL-2 values are summarized in Table 11. A category graph of the AEGL values in relation to the toxicity data is in Appendix B.

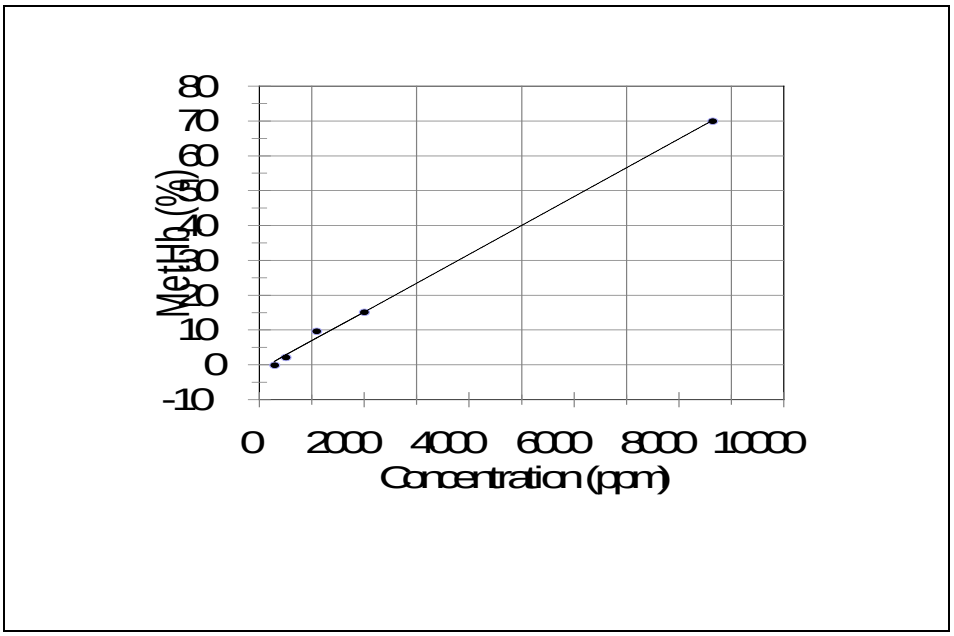

FIGURE 1. Measured and projected methemoglobin levels in dogs exposed to NF_3 for 60 minutes. Measured (solid line); projected (dashed line). The projected value is based on a 60-minute threshold for lethality in dogs of 8646 ppm resulting in formation of 70% MetHb.

TABLE 11. AEGL-2 Values for Nitrogen Trifluoride

10-min	30-min	1-h	4-h	8-h
3100 ppm (9000 mg/m^3)	1100 ppm (3200 mg/m^3)	530 ppm (1500 mg/m^3)	140 ppm (400 mg/m^3)	68 ppm (200 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human studies appropriate for the derivation of AEGL-3 values for NF_3 were available.

7.2. Summary of Animal Data Relevant to AEGL-3

Several NF_3 studies addressed lethality. Mortality values for monkeys, dogs, rats, and mice were reported at various concentrations over exposure durations from 15 to 60 minutes (Dost et al. 1970a; Vernot et al. 1973; see Tables 2, 3, 4, and 5). Rats and mice were also exposed to a single concentration for 120 minutes. At the same exposure duration, LC_{50} values for the four species differed by no more than a factor of 2 (Table 6). Dost et al. (1970a) reported lethality values in rats following exposure to 4000 ppm for 180 or 225 minutes or exposure to 10,000 ppm for 63.5 minutes. Respective mortalities were 0/10, 10/10, and 30/35.

7.3. Derivation of AEGL-3

The AEGL-3 values were based on the threshold for lethality in the dog (Vernot et al. 1973). The dog was chosen because, compared with rodents, the dog is more similar to humans regarding MetHb reductase activity and hematopoiesis. Furthermore, the dog was the most sensitive species concerning post-exposure anemia. The threshold for lethality at each AEGL-3 exposure duration was calculated using the probit-based, dose-response program of ten Berge (2006). The threshold for lethality was set at 1% (NRC 2001). This value is similar to the benchmark dose BMC_{01}. The data indicated a time-scaling value of 1.0 ($C^{1.0} \times t = k$). An interspecies uncertainty factor of 1 was applied because mortality for four species exposed under identical conditions differed by less no more than a factor of 2, and the dog was considered an appropriate model for humans. An intraspecies uncertainty factor of 10 was applied because infants, lacking the NADH cofactor for methemoglobin reductase, are especially sensitive to MetHb-forming chemicals. Furthermore, humans who are anemic, deficient in MetHb reductase, or have abnormal Hb are more sensitive to MetHb-generating chemicals. Output data from the ten Berge program are in Appendix A and AEGL-3 values are summarized in Table 12. The monkey and rat data were also analyzed and results are summarized in Appendix A. A category graph of the AEGL values in relation to NF_3 toxicity data is in Appendix B.

TABLE 12. AEGL-3 Values for Nitrogen Trifluoride

10-min	30-min	1-h	4-h	8-h
5000 ppm (15,000 mg/m^3)	1700 ppm (4900 mg/m^3)	860 ppm (2500 mg/m^3)	220 ppm (640 mg/m^3)	110 ppm (320 mg/m^3)

The 8-hour AEGL-3 value of 110 ppm may be considered conservative. Rats exposed to 100 ppm for 6 hours/day, 5 days/week for two weeks showed marginal to moderate reductions in erythrocyte count, Hb, and hematocrit (Bamberger 1998), and rats exposed to 100 ppm for 7 hours/day, 5 days/week for 19 weeks showed no changes in hematology parameters (Torkelson et al. 1962).

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

AEGL values are summarized in Table 13. Derivations are summarized in Appendix C.

TABLE 13. Summary of AEGL Values

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	1200 ppm (3500 mg/m^3)	400 ppm (1200 mg/m^3)	200 ppm (580 mg/m^3)	50 ppm (150 mg/m^3)	25 ppm (73 mg/m^3)
AEGL-2 (Disabling)	3100 ppm (9000 mg/m^3)	1100 ppm (3200 mg/m^3)	530 ppm (1500 mg/m^3)	140 ppm (400 mg/m^3)	68 ppm (200 mg/m^3)
AEGL-3 (Lethal)	5000 ppm (15,000 mg/m^3)	1700 ppm (4900 mg/m^3)	860 ppm (2500 mg/m^3)	220 ppm (640 mg/m^3)	110 ppm (320 mg/m^3)

8.2. Comparison with Other Standards and Guidelines

Standards and guidelines for NF_3 are listed in Table 14.

Based on the absence of an odor warning property at concentrations that are toxic, the American Industrial Hygiene Association (AIHA) did not develop a level 1 Emergency Response Planning Guideline (ERPG-1) for airborne NF_3 (AIHA 2005). The 1-hour ERPG-2 is based on a 1-hour exposure of mice, rats, dogs, and monkeys to 2000 ppm NF_3 (Vernot et al. 1973). Monkeys experienced 10.3% MetHb at this exposure concentration-duration. A reduction to 400 ppm for 1-hour was expected to result in <10% MetHb formation. The ERPG-3 was based on the 1-hour LC_{50} values of 10,000 ppm and 9600 ppm in monkeys and dogs, respectively (Vernot et al. 1973). A reduction to 800 ppm for 1 hour was not expected to be fatal to most people.

The National Institute for Occupational Safety and Health (NIOSH) Immediately Dangerous to Life and Health (IDLH) 30-minute value of 1000 ppm is based on the 60-minute lethality studies of Vernot et al. (1973) with four species of animals (NIOSH 1996). The one-LC_{50} hour values (6700-9600 ppm) were adjusted to 30 minutes by multiplying by a factor of 1.25, averaged, and then reduced 10-fold.

The National Academy of Sciences/National Research Council Committee on Toxicology recommended 10-, 30-, and 60-minute Emergency Exposure Limits (EELs) of 2250, 750, and 375 ppm (Dinman 1974). These values were intended for healthy adult military or space personnel only. The values were based on the study of Vernot et al. (1973), but the basis was not provided.

The American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value – Time Weighted Average (TLV-TWA) of 10 ppm (ACGIH 2001) is a 10-fold reduction of the 19-week 100 ppm value that resulted in mild to moderate hepatic and renal changes in rats (Torkelson et al. 1962). The NIOSH REL, OSHA PEL, and Dutch MAC are 10 ppm. Germany has not set workplace values for NF_3.

TABLE 14. Standards and Guidelines for Nitrogen Trifluoride

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	1200 ppm	400 ppm	200 ppm	50 ppm	25 ppm
AEGL-2	3100 ppm	1100 ppm	530 ppm	140 ppm	68 ppm
AEGL-3	5000 ppm	1700 ppm	860 ppm	220 ppm	110 ppm
ERPG-1 (AIHA)[a]			NA		
ERPG-2 (AIHA)			400 ppm		
ERPG-3 (AIHA)			800 ppm		
EEL (Dinman 1974)[b]	2250 ppm	750 ppm	375 ppm	—	—
IDLH (NIOSH)[c]		1000 ppm			
REL-TWA (NIOSH)[d]					10 ppm
OSHA PEL (NIOSH)[e]					10 ppm
TLV-TWA (ACGIH)[f]					10 ppm
MAK (Germany)[g]					Not determined
MAC (The Netherlands)[h]					10 ppm

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2005)
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 protective 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]**EELs (Emergency Exposure Limits)** (Dinman 1974) are for the designated time periods and apply to emergency situations with military and space personnel only.

[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 2008) is defined analogous to the ACGIH-TLV-TWA.

[e]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** (NIOSH 2008) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[f]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2001) 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]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] 2007) is defined analogous to the ACGIH-TLV-TWA.

[h]**MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined similar to the ACGIH TLV.

8.3. Data Adequacy and Research Needs

9. REFERENCES

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APPENDIX A: Derivation of Nitrogen Trifluoride AEGLs

Derivation of AEGL-1 Values

Key Study:	Vernot, E.H., C.C. Haun, J.D. MacEwen and G.F. Egan. 1973. Acute inhalation toxicology and proposed emergency exposure limits of nitrogen trifluoride. Toxicol. Appl. Pharmacol. 26:1-13.
Toxicity endpoint:	Methemoglobin formation of ≤15% in dogs and monkeys at a dose of 120,000 ppm-minutes (2000 ppm for 60 minutes) in the key study.
Time scaling:	$C^n \times t = k$ where n = 1.0 based on the threshold for lethality in dogs in the key study.
Uncertainty factors:	Total uncertainty factor: 10 Interspecies: 1 – Methemoglobin values were similar at identical NF_3 atmospheric concentrations for four species (monkey, dog, rat, and mouse). Healthy humans are expected to react similarly. Humans and dogs have similar erythrocyte MetHb reductase activity. Dogs were more sensitive than rodents for reductions in hematology parameters. Intraspecies: 10 – Infants are more susceptible to methemoglobin-forming chemicals as they lack NADH, the cofactor for methemoglobin reductase until four months of age. Individuals with congenital methemoglobinemia including abnormal hemoglobins are more susceptible to methemoglobinemia.
Modifying factor:	None applied
Calculations:	$(C/10)^n \times t = k$; n = 1.0 $(2000 \text{ ppm/UF of } 10)^{1.0} \times 60 \text{ minutes} = 12{,}000 \text{ ppm•min}$
10-min AEGL-1:	$C^{1.0} = 12{,}000 \text{ ppm•min}/10 \text{ min}$ C = 1200 ppm
30-min AEGL-1:	$C^{1.0} = 12{,}000 \text{ ppm•min}/30 \text{ min}$ C = 400 ppm
1-h AEGL-1:	C = 200 ppm
4-h AEGL-1:	$C^{1.0} = 12{,}000 \text{ ppm•min}/240 \text{ min}$ C = 50 ppm
8-h AEGL-1:	$C^{1.0} = 12{,}000 \text{ ppm•min}/480 \text{ min}$ C = 25 ppm

Derivation of AEGL-2 Values

Key Study:	Vernot, E.H., C.C. Haun, J.D. MacEwen and G.F. Egan. 1973. Acute inhalation toxicology and proposed emergency exposure limits of nitrogen trifluoride. Toxicol. Appl. Pharmacol. 26:1-13.
Toxicity endpoint:	Estimated 43% MetHb in the dog calculated as the mid-point between AEGL-1 (15% MetHb) and AEGL-3 (70% MetHb).
Time scaling	$C^n \times t = k$ where n = 1.0 on time scaling for the threshold for lethality in dogs in the key study.
Uncertainty factors:	Total uncertainty factor: 10 Interspecies: 1 – Methemoglobin values were similar at similar atmospheric concentrations for four species (monkey, dog, rat, and mouse). Healthy humans are expected to react similarly. The dog was the most sensitive species for changes in hematology parameters. Intraspecies: 10 – Infants are more susceptible to methemoglobin-forming chemicals as they lack NADH, the cofactor for methemoglobin reductase, until four months of age. Individuals with congenital methemoglobinemia including abnormal hemoglobins are more susceptible to methemoglobinemia.
Calculations:	Midpoint between respective AEGL-1 and AEGL-3 values
10-min AEGL-2:	C = (1200 ppm + 5000 ppm)/2 C = 3100 ppm
30-min AEGL-2:	C = (400 ppm + 1100 ppm)/2 C = 1100 ppm
1-h AEGL-2:	C = (200 ppm + 860 ppm)/2 C = 530 ppm
4-h AEGL-2:	C = 50 ppm + 220 ppm)/2 C = 140 ppm
8-h AEGL-2:	C = 25 ppm + 110 ppm/2 C = 68 ppm

Derivation of AEGL-3 Values

Key Studies: Vernot, E.H., C.C. Haun, J.D. MacEwen and G.F. Egan. 1973. Acute inhalation toxicology and proposed emergency exposure limits of nitrogen trifluoride. Toxicol. Appl. Pharmacol. 26:1-13.

Toxicity endpoint: Threshold for lethality in dogs at the 1% response calculated with the regression-analysis dose-response program of ten Berge (2006).

Time scaling: Values automatically scaled by ten Berge (2006) program: $C^n \times t = k$ where $n = 1.0$

Uncertainty factors: Total uncertainty factor: 10
Interspecies: 1 – Methemoglobin values were similar at similar atmospheric concentrations for four species (monkey, dog, rat, and mouse). Healthy humans are expected to react similarly. The dog was the most sensitive species for changes in hematology parameters.
Intraspecies: 10 – Infants are more susceptible to methemoglobin-forming chemicals as they lack NADH, the cofactor for methemoglobin reductase, until four months of age. Individuals with congenital methemoglobinemia including abnormal hemoglobins are more susceptible to methemoglobinemia.

Modifying factor: None applied

Program output (with total uncertainty factor of 10 applied)

Exposure Duration	AEGL-3 Value
10 minutes	5000 ppm
30 minutes	1700 ppm
60 minutes	860 ppm
4 hours	220 ppm
8 hours	110 ppm

Summary Data – ten Berge Program.

Summary Data Output – ten Berge Program					
	Exposure Duration				
Species	10-min	30-min	1-h	4-h	8-h
Monkey[a]	26,240 ppm	13,000 ppm	8350 ppm	3443 ppm	2211 ppm
Dog[a]	50,200 ppm	17,070 ppm	8646 ppm	2217 ppm	1123 ppm
Rat[b]	16,550 ppm	6714 ppm	3799 ppm	1217 ppm	689 ppm
Rat[c]	17,880 ppm	7317 ppm	4164 ppm	1349 ppm	768 ppm

Values are not rounded and no uncertainty factor has been applied.

[a] Data from Vernot et al. 1973 (monkey: n = 1.5; dog: n = 1.0).

[b] Combined data of Vernot et al. 1973 and Dost et al. 1970a (n = 1.2).

[c] Combined data of Vernot et al. 1973, Dost et al. 1970a, and Torkelson et al. 1962 (n = 1.2).

```
Filename: NF3: Monkey, Log Probit Model (Data of Vernot et al. 1973)
Date: 17 October 2008      Time: 10:09:03

Seq.Nr        conc ppm    minutes       exposed       responded
  1              21250           15          3             0
  2              23490           15          2             1
  3              25026           15          2             1
  4              27150           15          3             3
  5              13038           30          3             0
  6              15170           30          3             3
  7               8519           60          2             0
  8               9390           60          3             1
  9               9947           60          3             1
 10              11273           60          3             3


Observations  1 through  10 considered!

Seq.nr        conc ppm    minutes       exposed       responded

  1              21250           15          3             0
  2              23490           15          2             1
  3              25026           15          2             1
  4              27150           15          3             3
  5              13038           30          3             0
  6              15170           30          3             3
  7               8519           60          2             0
  8               9390           60          3             1
  9               9947           60          3             1
 10              11273           60          3             3

Used Probit Equation  Y = B0 + B1*X1 + B2*X2
X1 = conc ppm, ln-transformed
X2 = minutes, ln-transformed

ChiSquare          =        5.67
Degrees of freedom =        7
Probability Model  =    5.79E-01

Ln(Likelihood)    =  -6.44

B 0  = -1.7265E+02     Student t  =   -2.7869
B 1  =  1.5053E+01     Student t  =    2.8737
B 2  =  9.6211E+00     Student t  =    2.8086
```

```
  variance B 0  0  =  3.8380E+03
covariance B 0  1  = -3.2438E+02
covariance B 0  2  = -2.1052E+02
  variance B 1  1  =  2.7440E+01
covariance B 1  2  =  1.7725E+01
  variance B 2  2  =  1.1734E+01

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate       =   1.565
Lower limit (95% CL) =   1.394
Upper limit (95% CL) =   1.735

Estimation of conc ppm at response of  1  %
minutes        =  10
Point estimate       conc ppm =  2.624E+04 for response of  1  %
Lower limit (95% CL) conc ppm =  1.803E+04 for response of  1  %
Upper limit (95% CL) conc ppm =  2.899E+04 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  30
Point estimate       conc ppm =  1.300E+04 for response of  1  %
Lower limit (95% CL) conc ppm =  9.325E+03 for response of  1  %
Upper limit (95% CL) conc ppm =  1.395E+04 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  60
Point estimate       conc ppm =  8.350E+03 for response of  1  %
Lower limit (95% CL) conc ppm =  5.992E+03 for response of  1  %
Upper limit (95% CL) conc ppm =  9.020E+03 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  120
Point estimate       conc ppm =  5.362E+03 for response of  1  %
Lower limit (95% CL) conc ppm =  3.774E+03 for response of  1  %
Upper limit (95% CL) conc ppm =  5.953E+03 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  240
Point estimate       conc ppm =  3.443E+03 for response of  1  %
Lower limit (95% CL) conc ppm =  2.342E+03 for response of  1  %
Upper limit (95% CL) conc ppm =  3.988E+03 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  480
Point estimate       conc ppm =  2.211E+03 for response of  1  %
Lower limit (95% CL) conc ppm =  1.440E+03 for response of  1  %
Upper limit (95% CL) conc ppm =  2.696E+03 for response of  1  %
```

Filename: **NF3: Dog, Log Probit Model (Data of Vernot et al. 1973)**
Date: 04 December 2008 Time: 10:58:33

Seq.Nr	Conc ppm	Minutes	Exposed	Responded
1	31816	15	3	0
2	37600	15	5	2
3	41410	15	3	2
4	43460	15	3	3
5	19434	30	3	0
6	20779	30	3	2
7	24026	30	3	3
8	8550	60	2	0
9	9947	60	3	2
10	11450	60	2	2
11	9600	60	18	4

Observations 1 through 11 considered!

Seq.nr	Conc ppm	Minutes	exposed	responded
1	31816	15	3	0
2	37600	15	5	2
3	41410	15	3	2
4	43460	15	3	3
5	19434	30	3	0
6	20779	30	3	2
7	24026	30	3	3
8	8550	60	2	0
9	9947	60	3	2
10	11450	60	2	2
11	9600	60	18	4

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = Conc ppm, ln-transformed
X2 = Minutes, ln-transformed

ChiSquare = 3.65
Degrees of freedom = 8
Probability Model = 8.88E-01 (89%)

Ln(Likelihood) = -7.40

B 0 = -1.9566E+02 Student t = -2.8621
B 1 = 1.5159E+01 Student t = 2.9610
B 2 = 1.4881E+01 Student t = 2.8473

variance B 0 0 = 4.6736E+03
covariance B 0 1 = -3.4991E+02
covariance B 0 2 = -3.5679E+02
variance B 1 1 = 2.6209E+01
covariance B 1 2 = 2.6686E+01
variance B 2 2 = 2.7314E+01

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 1.019 (n= 1.0)
Lower limit (95% CL) = 0.962
Upper limit (95% CL) = 1.075

Estimation of Conc ppm at response of 1 %

```
Minutes        =  10
Point estimate       Conc ppm =  5.020E+04 for response of  1  %
Lower limit (95% CL) Conc ppm =  3.442E+04 for response of  1  %
Upper limit (95% CL) Conc ppm =  5.508E+04 for response of  1  %


Estimation of Conc ppm at response of  1  %
Minutes        =  30
Point estimate       Conc ppm =  1.707E+04 for response of  1  %
Lower limit (95% CL) Conc ppm =  1.285E+04 for response of  1  %
Upper limit (95% CL) Conc ppm =  1.816E+04 for response of  1  %


Estimation of Conc ppm at response of  1  %
Minutes        =  60
Point estimate       Conc ppm =  8.646E+03 for response of  1  %
Lower limit (95% CL) Conc ppm =  6.816E+03 for response of  1  %
Upper limit (95% CL) Conc ppm =  9.136E+03 for response of  1  %


Estimation of Conc ppm at response of  1  %
Minutes        =  120
Point estimate       Conc ppm =  4.378E+03 for response of  1  %
Lower limit (95% CL) Conc ppm =  3.552E+03 for response of  1  %
Upper limit (95% CL) Conc ppm =  4.677E+03 for response of  1  %


Estimation of Conc ppm at response of  1  %
Minutes        =  240
Point estimate       Conc ppm =  2.217E+03 for response of  1  %
Lower limit (95% CL) Conc ppm =  1.813E+03 for response of  1  %
Upper limit (95% CL) Conc ppm =  2.444E+03 for response of  1  %


Estimation of Conc ppm at response of  1  %
Minutes        =  480
Point estimate       Conc ppm =  1.123E+03 for response of  1  %
Lower limit (95% CL) Conc ppm =  9.103E+02 for response of  1  %
Upper limit (95% CL) Conc ppm =  1.298E+03 for response of  1  %


Estimation of Conc ppm at response of  5  %
Minutes        =  10
Point estimate       Conc ppm =  5.251E+04 for response of  5  %
Lower limit (95% CL) Conc ppm =  3.909E+04 for response of  5  %
Upper limit (95% CL) Conc ppm =  5.691E+04 for response of  5  %


Estimation of Conc ppm at response of  5  %
Minutes        =  30
Point estimate       Conc ppm =  1.786E+04 for response of  5  %
Lower limit (95% CL) Conc ppm =  1.465E+04 for response of  5  %
Upper limit (95% CL) Conc ppm =  1.870E+04 for response of  5  %


Estimation of Conc ppm at response of  5  %
Minutes        =  60
Point estimate       Conc ppm =  9.044E+03 for response of  5  %
Lower limit (95% CL) Conc ppm =  7.749E+03 for response of  5  %
Upper limit (95% CL) Conc ppm =  9.430E+03 for response of  5  %


Estimation of Conc ppm at response of  5  %
```

```
Minutes        =  120
Point estimate       Conc ppm =  4.580E+03 for response of  5  %
Lower limit (95% CL) Conc ppm =  3.990E+03 for response of  5  %
Upper limit (95% CL) Conc ppm =  4.886E+03 for response of  5  %


Estimation of Conc ppm at response of  5  %
Minutes        =  240
Point estimate       Conc ppm =  2.319E+03 for response of  5  %
Lower limit (95% CL) Conc ppm =  2.003E+03 for response of  5  %
Upper limit (95% CL) Conc ppm =  2.596E+03 for response of  5  %


Estimation of Conc ppm at response of  5  %
Minutes        =  480
Point estimate       Conc ppm =  1.174E+03 for response of  5  %
Lower limit (95% CL) Conc ppm =  9.928E+02 for response of  5  %
Upper limit (95% CL) Conc ppm =  1.397E+03 for response of  5  %
```

Filename: **NF3: rat, Log Probit Model (Vernot et al. 1973; Dost et al. 1970a)**
Date: 17 October 2008 Time: 11:08:39

Seq.Nr	conc ppm	minutes	exposed	responded
1	19316	15	10	0
2	21430	15	10	0
3	25200	15	10	3
4	28257	15	10	7
5	28930	15	10	8
6	30714	15	10	10
7	8204	30	10	0
8	10250	30	10	3
9	11257	30	10	1
10	12281	30	10	7
11	13226	30	10	9
12	4118	60	10	0
13	5117	60	10	1
14	6121	60	10	4
15	7190	60	10	5
16	8204	60	10	9
17	4500	120	10	9
18	4000	180	10	0
19	4000	225	10	10
20	10000	53	35	30

Observations 1 through 20 considered!

Seq.nr	conc ppm	minutes	exposed	responded
1	19316	15	10	0
2	21430	15	10	0
3	25200	15	10	3
4	28257	15	10	7
5	28930	15	10	8
6	30714	15	10	10
7	8204	30	10	0
8	10250	30	10	3
9	11257	30	10	1
10	12281	30	10	7
11	13226	30	10	9
12	4118	60	10	0
13	5117	60	10	1
14	6121	60	10	4
15	7190	60	10	5
16	8204	60	10	9
17	4500	120	10	9
18	4000	180	10	0
19	4000	225	10	10
20	10000	53	35	30

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = conc ppm, ln-transformed
X2 = minutes, ln-transformed

ChiSquare = 90.95
Degrees of freedom = 17
Probability Model = 4.09E-12

Ln(Likelihood) = -59.66

B 0 = -3.7503E+01 Student t = -2.8589
B 1 = 3.4618E+00 Student t = 3.2115

```
B 2  =  2.8434E+00     Student t  =    3.2187

  variance B 0  0  =  1.7209E+02
covariance B 0  1  = -1.4093E+01
covariance B 0  2  = -1.1211E+01
  variance B 1  1  =  1.1620E+00
covariance B 1  2  =  8.9898E-01
  variance B 2  2  =  7.8036E-01

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate       =   1.218
Lower limit (95% CL) =   0.950
Upper limit (95% CL) =   1.485

Estimation of conc ppm at response of  1  %
minutes        =  10
Point estimate       conc ppm =  1.655E+04 for response of  1  %
Lower limit (95% CL) conc ppm =  4.536E+03 for response of  1  %
Upper limit (95% CL) conc ppm =  2.310E+04 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  30
Point estimate       conc ppm =  6.714E+03 for response of  1  %
Lower limit (95% CL) conc ppm =  1.770E+03 for response of  1  %
Upper limit (95% CL) conc ppm =  8.996E+03 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  60
Point estimate       conc ppm =  3.799E+03 for response of  1  %
Lower limit (95% CL) conc ppm =  9.357E+02 for response of  1  %
Upper limit (95% CL) conc ppm =  5.183E+03 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  120
Point estimate       conc ppm =  2.150E+03 for response of  1  %
Lower limit (95% CL) conc ppm =  4.806E+02 for response of  1  %
Upper limit (95% CL) conc ppm =  3.073E+03 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  240
Point estimate       conc ppm =  1.217E+03 for response of  1  %
Lower limit (95% CL) conc ppm =  2.414E+02 for response of  1  %
Upper limit (95% CL) conc ppm =  1.864E+03 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  480
Point estimate       conc ppm =  6.886E+02 for response of  1  %
Lower limit (95% CL) conc ppm =  1.191E+02 for response of  1  %
Upper limit (95% CL) conc ppm =  1.150E+03 for response of  1  %
```

Filename: **NF3: rat, Log Probit Model**
Data of Vernot et al. 1973; Dost et al. 1970a; Torkelson et al. 1962
Date: 17 October 2008 Time: 11:11:40
(note: Torkelson used 4-8 rats/experiment; average of 6 was used)

Seq.Nr	conc ppm	minutes	exposed	responded
1	19316	15	10	0
2	21430	15	10	0
3	25200	15	10	3
4	28257	15	10	7
5	28930	15	10	8
6	30714	15	10	10
7	8204	30	10	0
8	10250	30	10	3
9	11257	30	10	1
10	12281	30	10	7
11	13226	30	10	9
12	4118	60	10	0
13	5117	60	10	1
14	6121	60	10	4
15	7190	60	10	5
16	8204	60	10	9
17	4500	120	10	9
18	4000	180	10	0
19	4000	225	10	10
20	10000	53	35	30
21	20000	12	6	0
22	20000	30	6	6
23	10000	30	6	0
24	5000	60	6	0
25	2500	120	6	0
26	1000	420	6	0

Observations 1 through 26 considered!

Seq.nr	conc ppm	minutes	exposed	responded
1	19316	15	10	0
2	21430	15	10	0
3	25200	15	10	3
4	28257	15	10	7
5	28930	15	10	8
6	30714	15	10	10
7	8204	30	10	0
8	10250	30	10	3
9	11257	30	10	1
10	12281	30	10	7
11	13226	30	10	9
12	4118	60	10	0
13	5117	60	10	1
14	6121	60	10	4
15	7190	60	10	5
16	8204	60	10	9
17	4500	120	10	9
18	4000	180	10	0
19	4000	225	10	10
20	10000	53	35	30
21	20000	12	6	0
22	20000	30	6	6
23	10000	30	6	0
24	5000	60	6	0
25	2500	120	6	0
26	1000	420	6	0

```
Used Probit Equation  Y = B0 + B1*X1 + B2*X2
X1 = conc ppm, ln-transformed
X2 = minutes, ln-transformed

ChiSquare          =       98.32
Degrees of freedom =       23
Probability Model  =    2.74E-11

Ln(Likelihood)    =  -62.64

B 0  = -4.2892E+01     Student t  =   -3.9213
B 1  =  3.9065E+00     Student t  =    4.3689
B 2  =  3.1769E+00     Student t  =    4.2296

  variance B 0  0  =  1.1964E+02
covariance B 0  1  = -9.7464E+00
covariance B 0  2  = -7.9581E+00
  variance B 1  1  =  7.9951E-01
covariance B 1  2  =  6.3498E-01
  variance B 2  2  =  5.6416E-01

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate       =   1.230
Lower limit (95% CL) =   1.034
Upper limit (95% CL) =   1.425

Estimation of conc ppm at response of  1  %
minutes        =  10
Point estimate       conc ppm =  1.788E+04 for response of  1  %
Lower limit (95% CL) conc ppm =  1.005E+04 for response of  1  %
Upper limit (95% CL) conc ppm =  2.295E+04 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  30
Point estimate       conc ppm =  7.317E+03 for response of  1  %
Lower limit (95% CL) conc ppm =  4.234E+03 for response of  1  %
Upper limit (95% CL) conc ppm =  9.016E+03 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  60
Point estimate       conc ppm =  4.164E+03 for response of  1  %
Lower limit (95% CL) conc ppm =  2.372E+03 for response of  1  %
Upper limit (95% CL) conc ppm =  5.173E+03 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  120
Point estimate       conc ppm =  2.370E+03 for response of  1  %
Lower limit (95% CL) conc ppm =  1.296E+03 for response of  1  %
Upper limit (95% CL) conc ppm =  3.043E+03 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  240
Point estimate       conc ppm =  1.349E+03 for response of  1  %
Lower limit (95% CL) conc ppm =  6.952E+02 for response of  1  %
Upper limit (95% CL) conc ppm =  1.824E+03 for response of  1  %

Estimation of conc ppm at response of  1  %
minutes        =  480
Point estimate       conc ppm =  7.675E+02 for response of  1  %
Lower limit (95% CL) conc ppm =  3.678E+02 for response of  1  %
       Upper limit (95% CL) conc ppm =  1.108E+03 for response of  1  %
```

APPENDIX B: Category Graph of AEGL Values and Toxicity Data

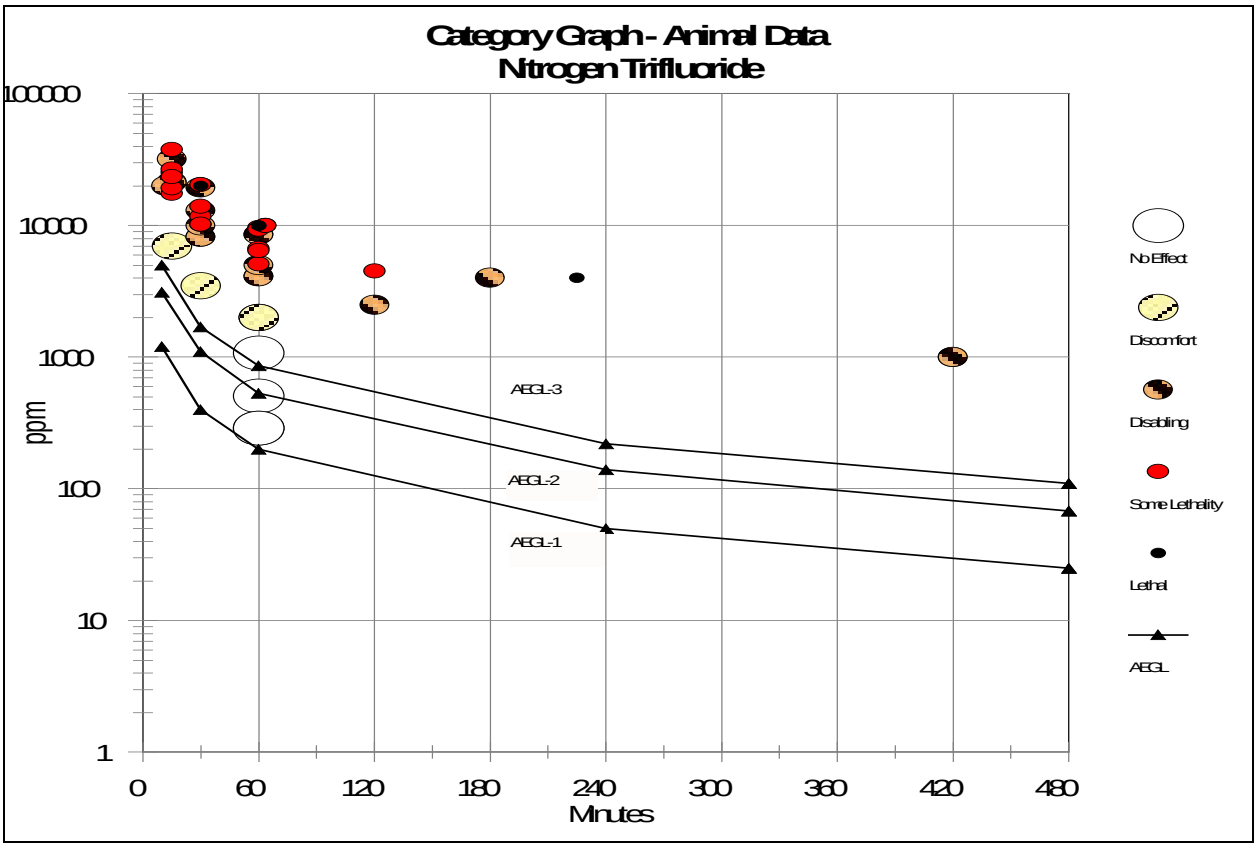

Figure 2. Category Graph of AEGL Values and Animal Toxicity Data

Data:

For Category: 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal				
Source	**Species**	**ppm**	**Minutes**	**Category**
NAC/AEGL-1		1200	10	AEGL
NAC/AEGL-1		400	30	AEGL
NAC/AEGL-1		200	60	AEGL
NAC/AEGL-1		50	240	AEGL
NAC/AEGL-1		25	480	AEGL
NAC/AEGL-2		3100	10	AEGL
NAC/AEGL-2		1100	30	AEGL
NAC/AEGL-2		530	60	AEGL
NAC/AEGL-2		140	240	AEGL
NAC/AEGL-2		68	480	AEGL
NAC/AEGL-3		5000	10	AEGL
NAC/AEGL-3		1700	30	AEGL
NAC/AEGL-3		860	60	AEGL
NAC/AEGL-3		220	240	AEGL
NAC/AEGL-3		110	480	AEGL

Vernot et al. 1973	rat	21,430	15	2: no mortality
	rat	25,200	15	SL: mortality 3/10
	rat	26,700	15	SL: calculated LC_{50}
	rat	8204	30	2: no mortality
	rat	10,250	30	SL: mortality 3/10
	rat	11,700	30	SL: calculated LC_{50}
	rat	4118	60	2: no mortality
	rat	5117	60	SL: mortality 1/10
	rat	6700	60	SL: calculated LC_{50}
	dog, monkey	7000	15	1: 16.5-19.2% MetHb
	dog, monkey	3500	30	1: 10.3-15.0% MetHb
	dog, monkey	2000	60	1: 10.3-15.2% MetHb
	dog	1075	60	0: 9.7% MetHb
	dog	510	60	0: 2.2% MetHb
	dog	290	60	0: 0.0% MetHb
	mouse	17,515	15	SL: mortality 3/10
	mouse	19,300	15	SL: calculated LC_{50}
	mouse	8212	30	2: no mortality
	mouse	10,222	30	SL: mortality 1/10
	mouse	4112	60	2: no mortality
	mouse	6469	60	SL: mortality 3/10
	mouse, rat	4500	120	SL: mortality 2/10 and 9/10, respectively
	dog	31,816	15	2: no mortality
	dog	37,600	15	SL: mortality 2/5
	dog	19,434	30	2: no mortality
	dog	20,400	30	SL: calculated LC_{50}
	dog	8550	60	2: no mortality
	dog	9600	60	SL: calculated LC_{50}
	monkey	21,250	15	2: no mortality
	monkey	23,490	15	SL: mortality 1/2
	monkey	13,038	30	2: no mortality
	monkey	14,000	30	SL: calculated LC_{50}
	monkey	8519	60	2: no mortality
	monkey	9390	60	SL: mortality 1/3
Dost et al. 1970a	rat	4000	180	2: no mortality
	rat	4000	225	3: mortality 10/10
	rat	10,000	63.5	SL: mortality 30/35
Torkelson et al. 1962	rat	20,000	12	2: no mortality
	rat	20.000	30	3: 100% mortality
	rat	10,000	30	2: no mortality
	rat	10,000	60	3: 100% mortality
	rat	5000	60	2: no mortality
	rat	2500	120	2: no mortality
	rat	1000	420	2: no mortality

Signs for all animals at Category 2 included eye irritation, tachypnea, gasping, and cyanosis.

1

APPENDIX C: Derivation Summary for Nitrogen Trifluoride AEGLs

Acute Exposure Guideline Levels For Nitrogen Trifluoride (CAS Reg. No. 7783-54-2)

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
1200 ppm	**400 ppm**	**200 ppm**	**50 ppm**	**25 ppm**

Key Reference: Vernot, E.H., C.C. Haun, J.D. MacEwen, and G.F. Egan. 1973. Acute inhalation toxicology and proposed emergency exposure limits of nitrogen trifluoride. Toxicol. Appl. Pharmacol. 26:1-13.

Test Species/Strain/Sex/Number: Dogs/beagle/male and female/3; monkey/rhesus/male and female/2-3

Exposure Route/Concentration/Duration: Inhalation/2000 ppm/60 minutes

Effects: Blood methemoglobin of ≤15%

Endpoint/Concentration/Rationale: 60-minute exposure to 2000 ppm – reversible methemoglobinemia, no clinical signs

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 1, For similar exposure durations and concentrations, methemoglobin and lethality values were similar among the monkey, dog, and rat. Healthy humans are expected to react similarly. The dog was the most sensitive species for changes in hematology parameters.

Intraspecies: 10, infants lack the NADH cofactor for methemoglobin reductase until 4 months of age, making them more vulnerable than adults to methemoglobinemia. Some individuals may be anemic or have abnormal hemoglobins that are sensitive to oxidation.

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n \times t = k$, where n = 1.0 (based on lethality studies with the dog)

Data Adequacy: Data were available from several laboratories. Data addressed both methemoglobin formation in the dog and monkey and lethality in the monkey, dog, rat, and mouse.

1

AEGL-2 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
3100 ppm	**1100 ppm**	**530 ppm**	**140 ppm**	**68 ppm**

Key Reference: Vernot, E.H., C.C. Haun, J.D. MacEwen, and G.F. Egan. 1973. Acute inhalation toxicology and proposed emergency exposure limits of nitrogen trifluoride. Toxicol. Appl. Pharmacol. 26:1-13.

Test Species/Strain/Number: Dogs/beagle/male and female/3

Exposure Route/Concentration/Duration: Inhalation/Concentrations that cause 43% methemoglobin in the dog were estimated as mid-point of AEGL-1 (15% methemoglobin) and AEGL-3 (70% methemoglobin) values.

Effects: 43% methemoglobin formation in dogs, estimated as midpoint of AEGL-1 (15% methemoglobin) and AEGL-3 (70% methemoglobin) values.

Endpoint/Concentration/Rationale: 43% methemoglobin formation in dogs, estimated as midpoint of AEGL-1 (15% methemoglobin) and AEGL-3 (70% methemoglobin)

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 1, For similar exposure durations and concentrations, methemoglobin and lethality values were similar among the monkey, dog, rat, and mouse. The human is expected to react similarly. The dog was the most sensitive species for changes in hematology parameters.

Intraspecies: 10, infants lack the NADH cofactor for methemoglobin reductase until 4 months of age, making them more vulnerable than adults to methemoglobinemia. Some individuals may be anemic or have abnormal hemoglobins that are sensitive to oxidation.

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n \times t = k$, where n = 1. 0

Data Adequacy: Data were available from several laboratories. Data addressed methemoglobin formation in the monkey and dog and lethality in the monkey, dog, rat, and mouse.

2
3
4
5

1

AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
5000 ppm	**1700 ppm**	**860 ppm**	**220 ppm**	**110 ppm**

Key References: (1) Vernot, E.H., C.C. Haun, J.D. MacEwen, and G.F. Egan. 1973. Acute inhalation toxicology and proposed emergency exposure limits of nitrogen trifluoride. Toxicol. Appl. Pharmacol. 26:1-13.

Test Species/Strain/Number: Dogs/beagle/male and female/3

Exposure Route/Concentration/Duration: Inhalation/Concentrations were calculated using regression analysis of all dog lethality data over exposure durations of 15, 30, and 60 min.

Effect: Lethality and non-lethality

Endpoint/Concentration/Rationale: ten Berge (2006) probit analysis, dose-response program applied to the dog data set of the key study (see data summarized under category graph in Appendix B)

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 1, For similar exposure durations and concentrations, methemoglobin and lethality values were similar among the monkey, dog, rat, and mouse. The human is expected to react similarly. The dog was the most sensitive species for changes in hematology parameters.

Intraspecies: 10, infants lack the NADH cofactor for methemoglobin reductase until 4 months of age, making them more vulnerable than adults to methemoglobinemia. Some individuals may be anemic or have abnormal hemoglobins that are sensitive to oxidation.

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Calculated using the ten Berge (2006) program (n in $C^n \times t = 1.0$)

Data Adequacy: Data addressed methemoglobin formation in the monkey and dog and lethality in the monkey, dog, rat, and mouse.

2