Nitrogen trifluoride

(CAS No: 7783-54-2)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of nitrogen trifluoride by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands).

In November 1999, literature was searched in the databases Toxline, Medline, and Chemical Abstracts, starting from 1981, 1966, and 1937, respectively, and using the following key words: nitrogen trifluoride, nitrogen fluoride (NF_3), and 7783-54-2.

In February 2001, the President of the Health Council released a draft of the document for public review. No comments were received.

An additional search in Toxline and Medline in January 2004 did not result in information changing the committee's conclusions.

2 Identity

name	:	nitrogen trifluoride
synonyms	:	nitrogen fluoride; trifluoroamine; trifluoroammonia; perfluoroammonia
molecular formula	:	NF_3
CAS number	:	7783-54-2

3 Physical and chemical properties

molecular weight	:	71.0
boiling point	:	-129°C
melting point	:	-208.5°C
flash point	:	-
vapour pressure	:	at 20°C: >100 kPa
solubility in water	:	very slightly soluble
log $P_{octanol/water}$	:	-1.60
conversion factors	:	at 20°C, 101.3 kPa: 1 mg/m^3 = 0.34 ppm 1 ppm = 2.96 mg/m^3

Data from ACG91, NLM04, http://esc.syrres.com.

Nitrogen trifluoride is a colourless, stable gas with a mouldy odour (ACG91).

The gas is heavier than air. It decomposes upon combustion or after contact with a hot surface, forming toxic vapours (i.e., hydrogen fluoride). The compound is a strong oxidiser and reacts vigorously with flammable and reducing agents. In the presence of water, it corrodes many metals. It reacts vigorously with many compounds, upon heating and electric discharge, with a chance for fire and explosion (NIA98).

None out of 5 volunteers could detect any odour at 100 ppm (2960 mg/m^3) and one of them thought he could detect the odour at 500 ppm (14,800 mg/m^3) (Tor62).

4 Uses

Nitrogen trifluoride is an oxidiser for high-energy fuels and is used in chemical synthesis (ACG91). It is used as a fluorine source for the hydrogen fluoride and deuterium fluoride (HF/DF) high-energy chemical lasers (Woy80).

5 Biotransformation and kinetics

A generalised moderate increase in rat tissue fluoride levels appeared at the end of a 50-minute exposure to NF_3 concentrations of 14,750 mg/m^3 (5000 ppm) and disappeared in one day. However, in erythrocytes, high concentrations of fluoride persisted up to 48 hours after exposure (no statistical calculation). Appreciable amounts of fluoride appeared in the spleens of some animals during 48 hours after exposure, possibly reflecting high concentrations in erythrocytes. There was no accumulation of fluorine in the adrenals and thyroid gland or in the testes (no quantitative data) (Dos70b).

6 Effects and mechanism of action

Human data

The committee did not find data on effects in humans following (occupational) exposure to nitrogen trifluoride.

Animal data

The committee did not find data on local effects, e.g., on skin, eyes, and mucous membranes, of nitrogen trifluoride.

Using groups of 10 male rats and mice, 15-minute LC_{50} values of 26,700 and 19,300 ppm (79,000 and 57,128 mg/m^3) were calculated for rats and mice, respectively, while 1-hour LC_{50} values were 6,700 and 7,500 ppm (19,832 and 22200 mg/m^3), respectively. Using groups of 2-3 dogs and monkeys, approximate 15-minute LC_{50} values were 38,000 and 24,000 ppm (112,480 and 70140 mg/m^3) for dogs and monkeys, respectively, and 1-hour LC_{50}s 9,600 and 10,000 ppm (28,416 and 29,600 mg/m^3), respectively. All animals died because of extensive methaemoglobin formation and resulting anoxia. Although the dog was the most resistant species tested to the lethal effects of NF_3, dog blood exhibited much more severe decreases in haematology parameters after exposure to this material. Dogs surviving exposure to 9600 ppm (28,416 mg/m^3) for 60 min exhibited Heinz-body anaemia with red blood cell count, haemoglobin, and haematocrit decreasing 33% to minimum values by the end of the second week post-exposure. Recovery of haematological values to pre-exposure levels was attained in 40 days (Ver73). For mice, a 4-hour LC_{50} value of 2000 ppm (5920 mg/m^3) was listed (NIO04). All male rats (n=4-8/group) survived exposures to 20,000, 10,000, 5000, 2500, and 1000 ppm (59,200-9600 mg/m^3) for 0.2, 0.5, 1, 2, and 7 hours, respectively. Concentrations of 20,000 and 10,000 ppm were lethal to all rats within 0.5 and 1 hour, respectively, while exposure to 5000 and 2500 ppm resulted in the death of 75% of the animals within 2 and 7 hours, respectively. The cause of death was excessive methaemoglobinaemia (Tor62).

In rats, NF_3 did not apparently influence the rate at which high concentrations of methaemoglobin (MetHb) were reduced, but residual concentrations of MetHb or a derivative spectrally similar to MetHb persisted at concentrations of as much as 5% for several days (Dos70a).

Rabbits were much less affected by an intraperitoneal injection of NF_3 than were rats. Not only did the rabbits survive after much larger doses, moreover, they did not develop the cyanotic appearance that was seen in rats. In rabbits, slight to moderate cyanosis was observed after an injection of 20.0 mL/kg bw; in rats, an injection of 7.95 mL/kg bw induced cyanosis within 20 minutes (Tor62).

Inhalation of NF_3 concentrations of 100 ppm (296 mg/m^3), 7 hours/day, 5 days/week, for 4.5 months, did not induce methaemoglobinaemia in rats (n=12/sex; controls: n=6/sex). Organ weights of the female rats were normal but the average relative liver, kidney, and spleen weights of the male rats were increased (p=0.005, p=0.01, and p=0.06, respectively) compared with a control group. Microscopically, degenerative changes were seen in the livers and kidneys of both male and female rats. The changes in the livers were described as generalised cloudy swelling of the parenchymal cells with some round cell filtration and some proliferation of the bile duct epithelium in the portal areas. In

the kidneys of both sexes, interstitial and slight tubular nephritis were seen. No evidence of fluorosis of the teeth or deposition of fluorine in the teeth and bone was observed although a very slight increase in total fluorine in the urine was detected (Tor62).

Both *in vitro* and *in vivo* data indicate, that 1 mol of NF_3 mediates or participates in the oxidation of 3 haem equivalents. The *in vivo* experiments used anaesthetised dogs, given an initial concentration of 0.6-1.0% (6000-10,000 ppm or 17,760-29,600 mg/m^3) endotracheally. The maximum rate of MetHb formation under these circumstances was in the order of 1% of total Hb per minute (Dos71).

The committee did not find data on the potential carcinogenicity, mutagenicity, genotoxicity, or reproduction toxicity of nitrogen trifluoride.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for nitrogen trifluoride in the Netherlands of is 29 mg/m^3 (10 ppm), 8-hour TWA.

Existing occupational exposure limits for nitrogen trifluoride in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

Nitrogen trifluoride is a strong oxidiser and reacts vigorously with a variety of chemicals. In the body, NF_3 splits off a fluoride ion and its target is the erythrocyte, reacting with haemoglobin to form methaemoglobin (MetHb). At high, lethal concentrations, methaemoglobinaemia is the cause of death in rats, mice, dogs, and monkeys.

In a 4.5-month study in rats (Tor62), exposure to NF_3 concentrations of 296 mg/m^3, 7 hours/day, 5 days/week, did not induce methaemoglobinaemia. However, this concentration induced an increase in relative liver, kidney, and spleen weights in male rats and, microscopically, degenerative changes in the livers and kidneys of both male and female rats. Since only one concentration was used in this study, the committee is of the opinion that this study cannot be used as a starting point for deriving a health-based occupational exposure limit. The committee considers the liver, kidneys, and spleen to be the target organs for toxicity of nitrogen trifluoride.

The committee considers the toxicological database on nitrogen trifluoride too poor to justify recommendation of a health-based occupational exposure limit.

Given the effects observed in the inhalation study with rats (Tor62), the committee concludes that the current MAC-value of 29 mg/m^3 (10 ppm), 8-hour TWA, is too high.

References

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ACG03 American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2003. Cincinnati OH, USA: ACGIH®, 2003: 97.

ACG04 American Conference of Governmental Industrial Hygienists (ACGIH). 2004 TLVs® and BEIs® based on the documentation of the Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, 2004: 42.

Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002: 33 (At-vejledning C.0.1).

DFG03 Deutsche Forschungsgemeinschaft (DFG): Commisson for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2003. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH Verlag & Co. KGaA, 2003; rep no 39.

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Dos70b Dost FN, Reed DJ, Cooper TD, et al. Fluorine distribution in rats following acute intoxication with nitrogen and halogen fluorides and with sodium fluoride. Toxicol Appl Pharmacol 1970; 17: 573-84.

Dos71 Dost FN, Reed DJ, Johnson DE, et al. Stoichiometry of the reaction of hemoglobin with nitrogen trifluoride in vitro and in vivo. J Pharmacol Exp Ther 1971; 176: 448-54.

EC04 European Commission: Directorate General of Employment and Social Affairs. Occupational exposure limits (OELs); http://europe.eu.int/comm/employment_social/health_safety/areas/oels_en.htm.

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational Exposure Limits 2002. Sudbury (Suffolk), England: HSE Books, 2002: 22.

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NIO04 US National Institute for Occupational Safety and Health (NIOSH), ed. Nitrogen trifluoride. In: The Registry of Toxic Effects of Chemical Substances (RTECS) (last update nitrogen trifluoride file: October 2002); http://www.cdc.gov/niosh.

NLM04 US National Library of Medicine (NLM), ed. Nitrogen trifluoride. In: The Hazardous Substances Data Bank (HSDB) (last revision data nitrogen trifluoride file: November 2002; last review date: September 1994); http://toxnet.nlm.nih.gov.

Swe00 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000; Ordinance AFS 2000:3.

SZW04 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2004. The Hague, the Netherlands: Sdu Uitgevers, 2004: 40.

Tor62 Torkelson TR, Oyen F, Sadek SE, et al. Preliminary toxicologic studies on nitrogen trifluoride. Toxicol Appl Pharmacol 1962; 4: 770-81.

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Ver73 Vernot EH, Haun CC, MacEwen JD, et al. Acute inhalation toxicology and proposed emergency exposure limits of nitrogen trifluoride. Toxicol Appl Pharmacol 1973; 26: 1-13.

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Annex

Occupational exposure limits for nitrogen trifluoride in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	10	29		administrative		SZW04
Germany						
- AGS	-	-				TRG03
- DFG MAK-Kommission	-	-				DFG03
Great Britain						
- HSE	10	30	8 h	OES		HSE02
	15	44	15 min			
Sweden	-	-				Swe00
Denmark	10	29	8 h			Arb02
USA						
- ACGIH	10	-	8 h	TLV		ACG04
- OSHA	10	29	8 h	PEL		ACG03
- NIOSH	10	29	10 h	REL		ACG03
European Union						
- SCOEL	-	-				EC04

[a] S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.