Boron trifluoride

(CAS No: 7637-07-2)

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 boron 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 A Wientjes, M.Sc. and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of boron trifluoride has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the on-line databases Medline, Toxline, Chemical Abstracts, and NIOSHTIC covering the period 1966 to 26 April 1999 (19990426/UP), 1965 to 29 January 1999 (19990129/ED), 1967 to 24 April 1999 (19990424/ED), and 1973 to 16 July 1998 (19980716/ED), respectively, and using the following key words: 7637-07-2, boron fluoride, BF_3, boron trifluoride, trifluoroborane, and trifluoroboron. HSDB and RTECS, databases available from CD-ROM, were consulted as well (NIO00, NLM00). The final literature search has been carried out in April 1999.

In April 2001, the President of the Health Council released a draft of the document for public review. Comments were received from the following individuals and organisations: L Whitford (Health and Safety Executive, London, United Kingdom). These comments were taken into account in deciding on the final version of the document.

An additional search in Medline and Toxline in September 2003 did not result in information changing the committee's conclusions.

2 Identity

name	:	boron trifluoride
synonyms	:	boron fluoride; trifluoroborane; trifluoroboron
molecular formula	:	BF_3
molecular structure	:	-

Data from HSE99, Ric92.

3 Physical and chemical properties

molecular weight	:	67,82
boiling point	:	-99.9)ºC
melting point	:	-126.7ºC
flash point	:	-
vapour pressure	:	at 20ºC: 1.13kPa
solubility in water	:	very soluble in cold water, decomposes in hot water
log $P_{octanol/water}$	:	0.22 (estimated)
conversion factors	:	at 20ºC, 101.3 kPa): 1 ppm = 2.8 mg/m^3 1 mg/m^3 = 0.35 ppm

Data from ACG99, Cul94, Tor61, http://esc.syres.com.

Boron trifluoride is a colourless, nonflammable gas with a pungent, suffocating odour. The odour threshold of boron trifluoride has not been determined but a concentration of 1.5 ppm (6 mg/m^3) was found to be detectable by smell (Tor61). It hydrolyses in moist air to both boric and fluoboric acids and, possibly, hydrofluoric acid (ACG99).

4 Uses

Being a Lewis acid (electron acceptor), boron trifluoride is mainly used as a catalyst in chemical reactions (Friedel-Craft reactions, polymerisations, esterifications, alkylations). It further finds it use in magnesium industry (because of its flame-retardant and antioxidant properties), in nuclear applications, and as a fumigant (ACG99, NIO76). As far as the committee

knows, the compound is not permitted to be used as a fumigant in the Netherlands.

5 Biotransformation and kinetics

The committee did not find studies on the toxicokinetics of boron trifluoride per se.

Boron trifluoride will hydrolyse on contact with mucous membranes into boric, fluoboric, and, possibly, hydrofluoric acids.

In 6-month inhalation studies, increased average fluorine concentrations were found in teeth and bone of rats and guinea pigs and in blood of guinea pigs. Contents in lung and liver were similar to those found in control animals (no Standard deviations or statistical analyses were presented) (Tor61).

6 Effects and mechanism of action

Human data

Human data are limited to one case report and 2 studies on workers occupationally exposed to boron trifluoride and were discussed in the NIOSH criteria document. In the limitedly reported case study, acid burns were found upon placing cotton soaked with boron trifluoride in water on the skin for some days. According to an abstract of one study, 51 workers exposed to not reported levels of ethylene, isobutylene, and quite high, but unspecified concentrations of boron trifluoride for 10 to 15 years had experienced irritability, insomnia, headache, excessive fatigue, effects on the respiratory tract (dryness and bleeding of mucosa, bronchitis, emphysema) and the skin (exanthema, dryness), joint pain, and increased fragility of tooth enamel. In the other study, minimally to severely lowered pulmonary function was seen in 8 out of 13 workers with present or past exposure to boron trifluoride and other fluorides for one to 27 years. A maximum concentration of 1.8 ppm (5 mg/m^3) was measured at two 24-hour measurement periods during the study. However, according to NIOSH, the accuracy and precision of the method were unknown and the figures are, therefore, not reliable (NIO76).

Animal data

Skin and eye irritation

The committee did not find data on the (potential) eye and skin irritation and sensitisation of boron trifluoride.

Acute exposure

In rats (Fischer 344; n=5/sex/group) exposed to aerosols of boron trifluoride dihydrate with actual concentrations of 1010, 1222, 1320, 1540 mg/m^3 (mass median aerodynamic diameter - MMAD -: ca. 1.8 µm; geometric standard deviation - GSD -: 1.9), for 4 hours, mortality rates were 3/10, 2/10, 8/10, and 9/10, respectively. The 4-hour LC_{50} was calculated to be 1210 mg/m^3. In-life and post-mortem observations showed respiratory distress, oral and nasal irritation, decreased body weight gain, and increased liver and kidney weights (Rus86). In another report, a 4-hour $LC_{50}$for rats of 413 ppm (1180 mg/m^3) was listed (Izm82). Following 1-hour exposures, LC_{50}s of 387 and 371 ppm (1084, 1039 mg/m^3) were calculated for male and female rats, respectively (Ver77). In mice, the 2-hour LC_{50} was 1211 ppm (3460 mg/m^3), while for guinea pigs, an LC_{50} of 38 ppm (109 mg/m^3) (duration not given) was listed (Izm82).

In range-finding studies concerning 30-day experiments, 10/10 guinea pigs, 1/10 mice, and 1/10 rats (strain and sex not reported) died during exposure to a calculated concentration of 750 ppm (2100 mg/m^3) for 5.5 hours. At 350 ppm (1000 mg/m^3), 7/10 guinea pigs died within about 1.5 hours,and at 135 ppm (375 mg/m^3), only 1/10 guinea pigs and no mice or rats died during a ca. 11-hour exposure (Spi53).

Subacute exposure

In a 2-week study, rats (Fischer 344; n=5/sex/group) were exposed to aerosols of boron trifluoride to mean concentrations of 0, 24, 66, and 180 mg/m^3 (MMAD: ca. 1.8 µm; GSD: 1.9), 6 hours/day, 5 days/week, with a total of 9 exposures. All 10 rats exposed to 180 mg/m^3 died before the 6th exposure while there was no mortality at 24 and 66 mg/m^3. At these lower concentration levels, animals showed respiratory distress, oral and nasal irritation, body weight gain depressions, increased absolute and relative lung weights, and decreased absolute and relative liver weights while kidney weights were normal. Upon

microscopic evaluation, no lesions were seen in the animals of these groups. The only treatment-related histological lesions observed in this study were necrosis and pyknosis of the proximal tubular epithelium in the kidney of the rats exposed to 180 mg/m^3. However, examination of many tissues from this high-exposure group was hampered due to autolytic changes resulting from the death of these animals (Rus86).

Results from 30-day studies performed during the 1940s were summarised by Spiegl (Spi53) and, more extensively, by NIOSH (NIO76). In the first study, rats (n=100), mice (n=101), guinea pigs (n=40), rabbits (n=12), cats (n=6), and dogs (n=5) were exposed to nominal concentrations of 100 ppm (280 mg/m^3) of boron trifluoride, for 30 days. According to Spiegl, exposure was 6 hours/day, 6 days/week; according to NIOSH, 4-7 hours/day, 5 days/week. Actual exposure concentrations varied between 38.5 and 185 ppm (108-518 mg/m^3) with a mean value of 93.5 ppm (262 mg/m^3), but an accurate method to verify actual concentrations was not available. Exposure caused the death of all animals; the length of exposure necessary to produce mortality varied with the species (on average, from less than 14 hours in guinea pigs to more than 180 hours in dogs). Reduced body weight gain was observed in all animals but was not uniform, and there was no clear correlation with exposure duration. Postmortem macroscopic examination showed moderate to severe lung (haemorrhage and mucus in the bronchioles) and kidney (distortion of the cortical and pyramidal striations) damage in cats, rats, rabbits, mice, and guinea pigs. The exact nature and extent of the changes could not be ascertained because there were no controls or follow-up microscopy. The dogs were examined both macro- and microscopically. They all showed rather severe bronchopneumonia. Minor interstitial renal changes were seen as well but their relation with exposure could not be ascertained. Biochemical and haematology examinations performed in dogs and rabbits only showed decreased serum inorganic phosphate levels immediately prior to death and decreased red and white blood cell counts in the initial phase of the study. Finally, progressive fluorosis was found in rats. At the end, the tooth and bone fluoride levels in the exposed animals were 20 to 25 times higher than those in control animals. Another 34 male rats were concurrently exposed to 100 ppm (280 mg/m^3). On each day, sacrifice of one rat was scheduled for serial examination, but during the 2nd week, 13 rats died from exposure. From the 5th day onwards, lung effects such as pneumonia and peribronchitis were observed but they did not correlate with the length of exposure. In addition, degenerative kidney changes were seen beginning with the 3rd exposure day and peaking on day 8. In the treatment-related deaths, bronchopneumonia (in 6/13), lung congestion and oedema (in 1/13), and renal degeneration (in 11/13) were seen.

Examination of the control animals showed bronchopneumonia in 2/10 and low-grade interstitial nephritis in 1/10. In a second study, these 6 species were exposed similarly to 15 ppm (40 mg/m^3). The actual concentrations varied from 13 to 31 ppm (36-87 mg/m^3) with a mean value of 19.8 ppm (55 mg/m^3). Exposure induced appreciable mortality in mice (18/93) and occasional mortality in the guinea pigs (1/30) and rats (2/100) but not in dogs (n=5), cats (n=6), and rabbits (n=12). The higher mortality in mice was thought to have resulted from accidental exposure to BF_3-contaminated water. Body weight losses of 12% were seen in dogs and cats while the other species gained weight normally throughout the study. No abnormalities were seen in blood samples taken weekly from dogs, rats, and rabbits. At the end of the exposure period, one control and 5 exposed dogs, 10 exposed rabbits (no controls reported), 10 exposed rats (no controls reported), and 5 exposed and 5 control guinea pigs were examined microscopically. No treatment-related lesions or fluorosis were seen in rats. There was lung haemorrhage in 1/5 exposed dogs, low-grade interstitial pneumonia in 2/10 exposed rabbits, bronchopneumonia in 4/5 exposed and 4/5 control guinea pigs, and interstitial nephritis in 3/5 exposed and 4/5 control guinea pigs. An additional group of 45 adult male guinea pigs was concurrently exposed to 15 ppm, and one guinea pig was killed each day for gross lung examination and 2 guinea pigs were killed weekly for gross and microscopic examination of the tongue, cheeks, lungs, kidney, and liver. Of the former animals, 64% showed evidence of abnormal pneumonic processes but not of oedema or haemorrhage characteristically caused by lung irritants. There was no indication for a correlation with the length of exposure. All of the animals weekly sacrificed and 1/5 control animals showed interstitial bronchopneumonia. All other tissues were normal (NIO76, Spi53).

Subchronic exposure

Groups of 20 male and 20 female rats were whole-body exposed to stable boron trifluoride dihydrate aerosols, 6 hours/day, 5 days/week, for 13 weeks. Fifteen rats/sex/group were killed during the 14th week while 5 animals/sex/group were held for a 2-week postexposure observation period. The nominal concentrations were 0, 6.4, 24, 54 mg/m^3, the actual concentrations 0, 2.0, 6.0, and 17 mg/m^3. The MMAD of the aerosols was ca. 1.8 µm (GSD: ca. 3.0). The mean relative humidity was ca. 60%. Treatment-related mortality was limited to one male animal of the high-exposure group. Body weights were not affected in any of the exposed groups. Primarily in the high-concentration groups, increased incidences of dried material around mouth and nose, rales, and excessive

lacrimation were observed. There were exposure-related decreases in mean urinary calcium concentrations being statistically significant in the 2 higher exposure groups and exposure-related increases in the urinary ionic and total fluoride amounts being statistically significant in almost all treated groups. These latter urinary levels were still elevated after the 2-week recovery period. Apart from exposure-related decreases in total protein and globulin concentrations, haematology parameters were not affected. Serum and bone fluorine concentrations were increased in all exposure groups, and, apart from serum levels in low- and mid-concentration female groups, still elevated after the 2-week recovery period. Post-mortem examinations did not show effects on absolute or relative organ weights (brain, lungs with trachea, liver, spleen, heart, kidneys, gonads) or gross lesions. Upon microscopic examination, the most significant findings were necrosis and pyknosis of the proximal tubular epithelium in the kidney seen in 2/20 male rats (among which the treatment-related dead animal) exposed to 17 mg/m^3. No lesions were seen in sections from the lungs, nasal turbinates, and other respiratory tract tissues. The NOAEL was set at 6 mg/m^3 (Rus86).

Another subchronic study has been performed by Torkelson et al. (Tor61). These authors present their concentrations in ppm suggesting vapours were produced. However, they noticed droplet formation. In addition, hydrolysis had occurred and etching compounds were formed as well. Overall, it was not clear to what compounds animals were exposed. In the first part of the study, female rats and male guinea pigs were whole-body exposed to nominal concentrations of 36 mg/m^3 (12.8 ppm), 7 hours/day, 5 days/week. Five guinea pigs and 4/13 rats received 42-45 exposures in 62-65 days. The remaining 9 rats were given 60 exposures in 87 days after which 4 of them were killed and the other 5 were kept unexposed for another month. During the first part of the study, one rat and 7 guinea pigs died. The guinea pigs showed obvious difficulty in breathing and appeared asthmatic, and death was the result of respiratory irritation and asphyxia. Final average body weights were increased in exposed animals (694 g vs. 592 g in controls; no explanation was given for an increase in body weight). Post-mortem examination of the lungs, heart, liver, kidneys, spleen, pancreas, and adrenals showed only effects on the lungs: increased relative lung weights and pneumonitis in the hilar regions. The cause of death of the rat was not determined. No changes as to appearance, mortality, and organ weights were observed in the rats receiving 45 exposures in 65 days. In the lungs, gross and microscopic changes indicative of chemically induced pneumonitis were seen, the hilar regions being most obviously affected. The 4 rats killed after 60 exposures in 87 days also showed pathological changes in the lungs. The amount

of fluoride ion ingested due to licking of the fur and skin may have contributed to the fluorosis seen in the teeth and the increased fluoride content of the tissue. In a second experiment, 5 female rats and 10 male guinea pigs were exposed to a nominal concentration of 22 mg/m^3 (7.7 ppm), 7 hours/day, 5 days/week. The rats received 33 exposures in 51 days, the guinea pigs 28 in 41 days. The actual exposure was 8-11 mg/m^3 (3-4 ppm). The rats were normal in appearance and growth. There was no evidence of fluorosis of the teeth although the teeth were light-coloured and the fluoride content of the teeth and bones was increased. In guinea pigs, exposure caused mortality in 4/10 animals. Death was accompanied by what appeared to be an asthmatic attack. The 6 surviving guinea pigs were obviously uncomfortable and had difficulty in breathing. No more data were presented. In the final part of this study, rats (n=12/sex), guinea pigs (n=10/sex), and rabbits (n=3/sex) were exposed to a nominal concentration of 8 mg/m^3 (3 ppm), 7 hours/day, 5 days/week. The animals received 127-128 exposures in 182-183 days. The actual concentration was 4 mg/m^3 (1.5 ppm). Growth, appearance, and mortality were normal for all groups with the exception of the female guinea pigs. For this group, the final average body weight was decreased (723 g vs. 855 g in controls; p=0.07). At autopsy, neither effects on organ weights nor gross abnormalities were seen in any of the exposed groups. Microscopically, rats showed changes in the lungs characterised by the presence of areas of pneumonitis, peribronchial round cell infiltration and areas of congestion of the capillaries lining the alveolar walls. Guinea pigs had a slightly higher incidence (30%) of pneumonitis. No effects were seen in the rabbits. An increase in the fluoride content of rat bone and teeth was found, but the teeth were not affected when compared to those of controls (Tor61).

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

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for boron trifluoride in the Netherlands is 3 mg/m^3 (1 ppm), as a ceiling value.

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

8 Assessment of health hazard

There are no valid human studies in which well characterised exposure by inhalation of boron trifluoride was related to systemic effects.

The committee did not find data specifically addressing the potential skin and eye irriation or sensitisation of boron trifluoride. From a 4-hour LC_{50} of 1210 mg/m^3 in rats, the committee considers boron trifluoride to be 'toxic following exposure by inhalation'.

Data from inhalation experiments in rodents, cats, and dogs indicate that repeated exposure - for 30 days or more - can cause effects on the eyes, the respiratory tract, body weight, liver, kidneys, and teeth and that the guinea pig is the most sensitive species. Interpretation of the repeated inhalation studies is hampered by flaws such as difficulties in maintaining and monitoring exposure making it not clear to what compounds or levels animals were exposed.

There is no information available on the potential reproduction toxicity, carcinogenicity, or genotoxicity/mutagenicity.

The committee considers the subchronic study performed by Torkelson et al. (Tor61) as the study in which exposure was probably best reflecting occupational exposure conditions. In this study, rats and guinea pigs, but not rabbits, showed changes in the lungs following exposure to 4 mg/m^3 of boron trifluoride, 7 hours/day, 5 days/week, for 26 weeks. The LOAEL of 4 mg/m^3 from this study is taken as a starting point in deriving a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, an overall assessment factor of 24 is established. This factor covers the following aspects: the absence of a NOAEL, intra- and interspecies variation, and differences between experimental conditions and the exposure pattern of the worker. Thus, applying this factor and the preferred value approach, a health-based occupational exposure limit of 0.2 mg/m^3 is recommended for boron trifluoride.

The committee recommends a health-based occupational exposure limit for boron trifluoride of 0.2 mg/m^3 (0.07 ppm), as an 8-hour time-weighted average (TWA).

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Annex

Occupational exposure limits for boron trifluoride in various countries.

	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	1,00	3,00	ceiling	administrative		SZW03
Germany						
- AGS	1,00	3,00	8 h			TRG00
	1,00	3,00	15 min			
- DFG MAK-Kommission	-	-[c]				DFG02
Great Britain						
-HSE	1,00	2,80	15 min	OES		HSE02
Sweden	-	-	-			Swe00
Denmark	1,00	3,00	ceiling			Arb02
USA						
- ACGIH	1,00	-	ceiling	TLV		ACG03b
- OSHA	1,00	3,00	ceiling	PEL		ACG03a
- NIOSH	1,00	3,00	ceiling	REL		ACG03a
European Union						
- SCOEL	-	-				EC03

[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.

[c] Listed among substances for which studies of the effects in man or in experimental animals have yielded insufficient information for the establishment of MAk values.