III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Boron trifluoride, BF_3 (formula weight 67.81), is a colorless gas, which is stable in dry atmospheres. [1-3] Its physical and chemical properties are listed in Table X-1. [2,4]

Boron trifluoride is known to be produced at the present time as a specialty chemical by only one US company whose production figures are not available. [5 (pp 244,278)] Methods used over the years in the commercial manufacture of boron trifluoride generally have involved a boron-containing compound allowed to react with a fluorine-containing compound in the presence of an acid. [2,4] The current method of synthesis involves combining fluorosulfonic acid and boric acid as in the following reaction [5 (p 13)]:

$$3\ HSO_3F + H_3BO_3 \longrightarrow BF_3 + 3\ H_2SO_4$$

Boron trifluoride, a Lewis acid (electron acceptor), is an excellent catalyst for Friedel-Crafts reactions as well as for many reactions that are also catalyzed by the hydrogen ion, H^+. [2,4] Some of these reactions, including polymerizations, esterifications, and alkylations, are presented in Table X-2. [4] As a catalyst, it readily forms a coordinate covalent bond, accepting a pair of electrons donated by a Lewis base and thereby gaining the additional stability of a full complement of eight electrons in the outermost energy level of the boron atom. In practice, boron trifluoride is often first allowed to form a complex with such compounds as phenol, monoethylamine, ethyl ether, and methyl ether, as listed in Table X-3. [6-12] These complexes generally are liquids or solids at room temperature and, therefore, are often easier to handle than the boron trifluoride gas. The applications of the complexes are similar to those of the gas, ie, as catalysts for Friedel-Crafts and other reactions. Some complexes are unstable and may dissociate to release boron trifluoride under certain temperature and pressure conditions. [7] Although many boron trifluoride complexes are synthesized through the formation of a coordinate covalent bond, a surprisingly small number of different atoms, ie, argon, nitrogen, phosphorus, carbon, oxygen, hydrogen, sulfur, fluorine, and chlorine, have been shown to donate an electron pair to boron trifluoride. [4,13,14]

Although the predominant use of boron trifluoride is as a catalyst, that is not its only use. The magnesium industry utilizes the fire-retardant and antioxidant properties of boron trifluoride in casting and heat treating. [15] Nuclear applications of boron trifluoride include neutron detector instruments, [16,17] boron-10 enrichment, [18] and the production of neutron-absorbing salts for molten-salt breeder reactors (US Patent No. 3,809,762). Boron trifluoride has also been identified as having insecticidal properties. [19]

Boron trifluoride is readily absorbed by water through the formation of a coordinate covalent bond with the oxygen atom of the water molecule. Wamser [20] has reported that, in equilibrated solutions of water and boron trifluoride at various concentrations, the following chemical species were tentatively identified by conductance measurements: fluoboric acid (HBF4), monohydroxyfluoboric acid (HBF3OH), dihydroxyfluoboric acid (HBF2(OH)2), boric acid (H3BO3), and trihydroxyfluoboric acid (HBF(OH)3). The latter product, however, has not been isolated and was proposed as a transitory intermediate. The mono- and di-hydroxyfluoboric acids, according to Wamser, equilibrate rapidly, while the boric and fluoboric acids are only slowly formed.

The formation of hydrogen fluoride in a mixture of boron trifluoride and water, although likely to occur, has not been conclusively shown. Wamser [20] suggested that the fluoride ion of hydrogen fluoride was not present in the mixture. He theorized that, although hydrogen fluoride may be released through the dissociation of the fluoboric and hydroxyfluoboric acids, it is immediately complexed with the other species present, contributing to the variety of compounds formed. Further support for this theory is found in Halbedel's report [21] that no penetrating burns like those caused by hydrogen fluoride resulted when a person had skin contact with a boron trifluoride-water mixture. Instead, he noted that the resultant surface burns were characteristic of contact with strong acids such as the hydroxyfluoboric acids.

When boron trifluoride gas comes into contact with air, a dense, white mist is formed. [8] As no mist is formed in dried air, [22] the mist in normal air may be assumed to be the product of the reaction of boron trifluoride and water vapor. It is not known if the reaction of boron trifluoride with water vapor in the air results in the same products as its reaction with liquid water. The relative concentrations of boron trifluoride and water vapor are highly variable, and any attempt at identifying the constituents of the mist is speculative. As indicated above, the mono- and di-hydroxyfluoboric acids are formed very rapidly when boron trifluoride contacts water contained in a vessel, [20] but their presence in the mist has not been verified.

Torkelson et al [22] found that, with an infrared analyzer, boron trifluoride was detectable in dry air but not detectable following its reaction with normal room air. This suggested an extensive conversion of the gas to other physical and chemical forms on contact with water vapor. They determined that the average diameter of the droplets in the mist was initially less than 1 μm. The size increased with time to about 1 μm, presumably with the addition of water from the atmosphere. The physical and chemical properties of the mist may depend on the relative humidity (water vapor content) of the air into which the boron trifluoride is released. A slight etching of the glass used in the boron trifluoride exposure chambers was also noticed. [22] Hydrogen fluoride reacts with silica in glass to form volatile silicon tetrafluoride, thereby etching the glass. This observation suggests that some hydrogen fluoride may have been present, at least long enough to react with the silica; however, it is not known whether other products of boron trifluoride hydration may also etch glass.

Employees with potential exposure to boron trifluoride include the initial manufacturers, magnesium founders, organic synthesizers, neutron detector instrument manufacturers, and fumigant producers. [23] NIOSH estimates that 50,000 employees are potentially exposed to boron trifluoride in the United States.

Historical Reports

The discovery and isolation of boron trifluoride date back to the early 1800's and the work of Davy and of Thenard and Gay-Lussac. [4,24] Initially, boron trifluoride was called "fluoric acid" and was confused with hydrogen fluoride since, like hydrogen fluoride, it was released from a mixture of calcium fluoride and boric acid calcined in an iron tube. Commercial production of boron trifluoride was begun in the 1930's in response to interest in its use as a catalyst for which over 400 patents were granted in the 1940's and 1950's. [4] There are no early reports on the toxicity of boron trifluoride.

Effects on Humans

Specific data relating to the toxic effects of boron trifluoride on humans are not available, although, with the advent of water fluoridation and increased uses of fluorides in industry, there is much information on fluorides in general. There are many reviews of the chemistry of boron trifluoride in which its toxicity is alluded to [2,4,8,21]; however, there is little quantitative information to substantiate these views.

The odor threshold of boron trifluoride has not been determined. Torkelson et al [22] reported that a rather pleasant, acidic odor was detected by personnel handling animals exposed to boron trifluoride metered at a concentration of 3.0 ppm (8.3 mg/cu m). Others [25,26] have said that boron trifluoride had a pungent, suffocating odor, but these reports do not contain data on the environmental concentrations. Because of the inadequate information, the use of odor as an indicator is not a sufficient safeguard against excessive exposure.

Halbedel [21] reported, without giving specific details, an attempt by an individual to assess the irritating effect of boron trifluoride on the skin. Cotton soaked with boron trifluoride in water was placed on the skin for "a day or so." The resultant acid burn, according to the author, was not like a typical hydrogen fluoride burn. Halbedel concluded that although burns like those caused by acid might result from prolonged contact with boron trifuoride gas, there was evidently no danger of the more severe hydrogen fluoride-induced burn occurring, since boron trifluoride has the ability to complex the fluoride ion quite effectively.

Epidemiologic Studies

Kirii, [27] in a study found only as a USSR abstract, attempted to determine the effects of chronic boron trifluoride inhalation on chemical workers. Seventy-eight workers were selected on the basis of the chemical exposures they had received in a 10- to 15-year period. Fifty-one of the workers (Group 1) had been exposed to ethylene, isobutylene, and boron trifluoride; the other 27 workers (Group 2) had been exposed only to ethylene and isobutylene. The author stated that the boron trifluoride concentration was quite high, but did not report any specific concentrations in this abstract. Both groups complained of irritability, insomnia, headache, and excessive fatigue. The workers in Group 1 also complained of dryness and bleeding of the nasal mucosa, bleeding gums, exanthema, dryness and scaling of the skin, pain in the joints, and increased fragility of tooth enamel. Additionally, the following objective findings were reported in both groups: slight nasal mucosal changes, apical systolic murmur, bronchitis, emphysema, dryness and reduced turgor of the skin, and a papular rash. The author reported, without supporting data, that these physical findings were more marked in Group 1, suggesting that overexposure to boron trifluoride resulted in joint disease, atrophic nasal mucosal changes, enhanced tendon reflexes, and changes in vascular permeability. However, in the absence of environmental data, it it is not evident that boron trifluoride produced the added effects, since it is not known whether increases in the concentrations of ethylene or isobutylene would also have contributed. If the fragility of tooth enamel was attributable correctly to exposure to boron trifluoride or its hydrolysis products, it seems likely that the fragility would be the consequence of acid products rather than the deposition of fluoride ion.

Physical examinations given to workers employed in a boron trifluoride-manufacturing plant also provided information on workers' exposures. [28] These examinations, instituted in the latter part of 1974, included chest X-rays, urinalyses for fluoride, and pulmonary function tests for forced vital capacity and 1-second forced expiratory volume. Thirteen workers (average age: 47.6 years) with present (7) or past (6) occupational exposures to boron trifluoride and other fluorides ranging from 1 to 27 years (average: 8.84 years) were examined. The X-rays were negative, and no urinary fluoride concentrations were above the acceptable preshift concentration of 4 mg/liter recommended by NIOSH. [34] Eight of the workers (five of seven currently in boron trifluoride areas and three of six with a previous exposure) showed lower pulmonary function volumes than predicted for a normal population. The lower pulmonary function values were judged as minimal in one, moderate in three, and severe in one of the seven workers currently exposed. These five workers had an average exposure of 13.0 years. In the three previously exposed workers with pulmonary function loss (two minimal and one moderate), the exposures ranged from less than 1 year to 20 years. These losses may be related to boron trifluoride exposure, but the data provided are inadequate, especially with regard to the availability of medical histories, and permit no definite conclusions. An air sampling survey of five points throughout the plant showed boron trifluoride concentrations ranging from 0.27 to 0.69 ppm (0.75-1.9 mg/cu m) during one 24-hour period in May 1974, and from 0.1 to 1.8 ppm (0.27-4.99 mg/cu m) in another 24-hour period in August 1974. A midget impinger was used in sampling; distillation and the fluoride-ion-specific electrode was used for analysis. The accuracy and precision of this method are unknown and therefore the data are not known to be true values.

Animal Toxicity

Several investigators have attempted to assess the toxicity of boron trifluoride with animal inhalation studies. However, no investigator has developed an accurate method of verifying the concentrations at which animals were actually exposed. Therefore, throughout this section, nominal or calculated concentrations based on cylinder settings, airflow measurements, and chamber size are used as a probable upper limit of exposure.

The toxicity to animals of boron trifluoride was first investigated during World War II as part of the Manhattan Project. In 1953, Spiegl [29] summarized these studies. Some of the original reports by Weil et al

[30,31] have been declassified and are available, although unpublished.

The studies were initiated with acute mortality range-finding exposures, followed by two 30-day inhalation tests. [29] The acute exposures involved only a few animals and a wide range of calculated concentrations. All 10 guinea pigs, 1 of 10 rats, and 1 of 10 mice died during a 5.5-hour exposure to boron trifluoride at a calculated concentration of 750 ppm (2,100 mg/cu m). Seven of 10 guinea pigs died in a 1.4-hour exposure to boron trifluoride at 350 ppm (970 mg/cu m). A 10.9-hour exposure at 135 ppm (370 mg/cu m) killed only 1 of 10 guinea pigs, while there were no deaths in 10 rats and 10 mice exposed at this concentration. Based on these results, concentrations of 100 and 15 ppm were selected for 30-day exposure studies.

Rats, cats, mice, guinea pigs, dogs, and rabbits were exposed to boron trifluoride at a nominal concentration of 100 ppm for 4-7 hours daily, 5 days/week, for up to 30 days. [30] Daily analyses of the exposure chamber atmospheres were made, and the mean value was determined to be 93.5 ppm (259 mg/cu m) with a range of 38.5-185 ppm (106-512 mg/cu m). These values may not be a true indication of the boron trifluoride levels since separate boron and fluoride determinations did not agree. However, at the conclusion of the experiment it was determined that unknown amounts of boron may have been leached from the glassware used in the sampling and analysis. Moreover, in only a few instances were the measured fluoride levels more than 2-5% of the calculated value.

Although exposure to boron trifluoride at 100 ppm (277 mg/cu m) killed all the animals exposed, [30] the length of exposure necessary to produce death varied with the species. The periods of exposure that resulted in death are given in Table III-1 for animals listed according to species, sex, age, and group size. The guinea pigs were the most susceptible, all dying within the first 2 days of exposure. All of the animals also showed retarded growth as a response to the treatment. However, the weight response was not uniform, and no correlation with the length of exposure was evident.

TABLE III-1

MORTALITY IN ANIMALS EXPOSED TO
BORON TRIFLUORIDE METERED AT 100 PPM

Species	Sex	Number	Age	Hours of Exposure Until Death	
				Average	Range
Dogs	M	3	Adolescent	181.5*	
	F	2	"	181.5*	
Cats	M	4	Adult	135	47.5-174.5
	F	2	"		
Rabbits	M	6	"	139	19.5-181.5
	F	6	"		
Rats	M	25	"	82.5	33.5-146.5
	M	25	Young	88.5	26.5-146.5
	F	25	Adult	92	33.0-167.5
	F	25	Young	134	33.0-202.5
Mice	M	25	"		5.5- 47.5
	M	26	"	24.4	
	F	25	Adult		
	F	25	Young		
Guinea pigs	M	40	Adult	<14	

*Three of the five dogs were killed in moribund condition.

Adapted from Weil et al [30]

Gross examinations of the lungs and kidneys of representative cats, rats, rabbits, mice, and guinea pigs exposed to boron trifluoride revealed moderate to severe damage. [30] Hemorrhage and mucus were consistently noted in the bronchioles of the lungs, and the kidneys showed distortion of the cortical and pyramidal striations. Since there were no controls or followup microscopy, the exact nature and extent of the damage were not ascertained.

The dogs were examined in greater detail. [30] Two of the dogs died from the exposures, and three moribund dogs were killed. Gross examination of the two dogs that died showed patches of dark red airless areas in the lungs, and microscopic examination showed severe bronchopneumonia extending from the bronchial wall into the alveolar walls. The kidneys of one dog showed degeneration of the tubular epithelium, and both dogs had typical and atypical renal regeneration with some dilated tubules. The three dogs which were killed also had bronchopneumonia, but it was evident only on microscopic examination. Again, the pneumonia extended into the alveolar walls; the alveoli were also filled with exudate. The diagnosis of pneumonia caused by boron trifluoride in one dog was questionable since fibrosis was evident, indicating long-standing disease. The kidneys showed interstitial nephritis, but its relation to the exposure is in doubt since the control dog also evidenced nephritis as well as lung changes which, according to the authors, probably resulted from an old case of interstitial pneumonia.

The dogs and rabbits were also tested weekly for biochemical and hematologic changes. [30] Urine sugar, urine protein, blood urea, blood calcium, and blood nonprotein-nitrogen levels were normal. Both species exhibited decreased serum inorganic phosphate levels immediately prior to death. The mean values for dogs were 7.6 mg% initially and 2.4 mg% finally. For rabbits the mean values were 6.3 mg% initially and 4.0 mg% finally. In both species, red and white blood cell counts dropped in the initial weeks of exposure but returned to normal before the animals died.

The teeth and bones of the exposed rats contained 20-25 times as much fluoride as was present in the teeth and bones of unexposed animals. [30] Marked fluorosis based on an observation of the bleaching of incisor teeth was noted in the first week and increased steadily with the length of exposure.

A concurrent phase of this inhalation study used 34 adult male albino rats exposed to boron trifluoride at 100 ppm. [30] One rat was killed each day for serial examination. However, 13 of them died during the second week from the exposure. Therefore the study was continued for only 22 days, in which time 21 rats were killed and examined. These rats showed anatomic changes which were attributed to boron trifluoride exposure. The changes described by the authors, however, did not correlate with the length of exposure. Effects on the lungs apparently started on the fifth or sixth day as pneumonia and peribronchitis. Pronounced pneumonia and bronchitic changes were reported on the 8th, 13th, and 16th days; mild bronchitis and hemorrhage on the 17th and 22nd days. However, the lungs of the rats killed on the intervening days were normal. The author gave no explanation for this phenomenon. The kidneys of the rats were also affected. Degeneration was seen in both the proximal and distal segments of the convoluted tubules, beginning with the third exposure and peaking on the eighth day of exposure. Associated with the degenerative changes, regeneration, often with mitotic figures, was seen in the cortical, midzonal, and pyramidal regions of the kidneys. Mitotic figures were most evident in the pyramidal portion. The 13 rats that died during the second week of exposure were also examined. Bronchopneumonia was present in 6 of these, congestion and edema of the lungs in 1, and renal epithelial degeneration in the medullary and pyramidal areas in 11. The 10 control rats were judged normal, although 2 showed some bronchopneumonia and another showed low-grade interstitial nephritis.

The second boron trifluoride exposure study conducted by Weil et al [31] used a calculated concentration of 15 ppm (41.5 mg/cu m). Subsequent analysis of the chamber atmosphere by a spot-test method, which was a colorimetric reaction between tumeric solution on filter paper and boron, showed a range of 13-31 ppm (36-86 mg/cu m) and a mean concentration of 19.8 ppm (55 mg/cu m). The data, although only semiquantitative, support the metered value of 15 ppm. This test is suitable for detecting order-of-magnitude variability rather than minor fluctuations. [32]

Six species were exposed 4-7 hours/day, 5 days/week, for a maximum of 31 days and were compared with controls. [31] In Table III-2, the animal species, sex, age, and mortality are recorded. The rats, rabbits, guinea pigs, and mice gained weight normally throughout the experiment; dogs and cats showed a 12% weight loss. This exposure resulted in fewer deaths than the 100-ppm exposure; 1 of 30 guinea pigs, 2 of 100 rats, and 15 of 92 mice died; and no deaths occurred in groups of 6 cats, 5 dogs, or 12 rabbits. The higher mortality in mice was thought to have resulted from their accidental exposure to boron trifluoride-contaminated water from the exhaust air scrubber system.

TABLE III-2

MORTALITY IN LABORATORY ANIMALS
EXPOSED TO BORON TRIFLUORIDE METERED AT 15 PPM

Species	Sex	Number	Age	Deaths	Time to Death (hours of exposure)
Dogs	M	4	Adult	0	
	F	1	"	0	
Cats	F	6	"	0*	
Rabbits	M	6	"	0	
	F	6	"	0	
Guinea pigs	M	30	"	1	147
	M	45	"	**	
Rats	M	25	"	0	
	M	25	Young	2	26, 130
	F	25	Adult	0	
	F	25	Young	0	
Mice	M	58	"	12	12-117 (50.1 av)
	F	34	"	3	7, 7, 154

*One cat died of an extraneous cause.
**Used in serial study

Adapted from Weil et al [31]

Blood samples were taken weekly from the dogs, rats, and rabbits. [31] There were no consistent or significant changes in red blood cell and platelet counts. Serum calcium and phosphorus levels in the dogs and rabbits remained normal throughout the experiment.

At the conclusion of the exposure period, 1 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 grossly and microscopically for tissue damage. [31] One exposed dog showed lung hemorrhage, two rabbits showed low-grade interstitial pneumonia, and eight guinea pigs (four exposed and four control animals) showed bronchopneumonia. Three of five exposed and four of five control guinea pigs had interstitial nephritis. No changes related to the treatment were reported in the rats.

In a concurrent phase of this study, 45 adult male guinea pigs were similarly exposed at the 15-ppm concentration. [31] One guinea pig was killed each day for gross lung study, and two guinea pigs were killed each week for gross and microscopic examination of the tongue, cheeks, lungs, kidneys, and liver. In the animals examined daily for gross lung changes, 64% showed evidence of abnormal pneumonic processes, but there was no indication that length of exposure was a factor. Additionally, there was no evidence of edema or hemorrhage characteristically caused by a lung irritant. All of the exposed guinea pigs examined weekly showed interstitial bronchopneumonia, but only one of five control animals showed a similar lesion. The pneumonic process resembled that commonly seen in infection. All other tissues were normal.

Weil and coworkers [30,31] concluded that boron trifluoride was primarily a respiratory irritant which predisposed the exposed animals to respiratory infection. Exposure at 100 ppm (277 mg/cu m) was fatal to all animals. Physiological responses prior to death included respiratory irritation and infection, kidney damage, retarded growth, and severe progressive fluorosis in rat teeth. Exposure at 15 ppm (41.5 mg/cu m) did not produce fluorosis, but did predispose guinea pigs to a rate of respiratory infection greater than that found in controls. The other species were less affected.

Throughout the studies, [30,31] the incidence of kidney disease in the control animals was high. Although the effect in exposed animals was often more marked, it is inappropriate to draw definite conclusions regarding the renal effects of boron trifluoride from these studies.

In 1961, Torkelson et al [22] reported the results of a boron trifluoride inhalation study in rats, rabbits, and guinea pigs. Although boron trifluoride was administered at calculated concentrations of 12.8, 7.7, and 3.0 ppm, analyses of the air in the exposure chambers during the 7.7- and 3.0-ppm exposures showed actual concentrations of only one-half the nominal amounts.

Exposures at calculated concentrations of 12.8 ppm and 7.7 ppm took place in a 160-liter cubical chamber. [22] The exposures metered as 3.0 ppm were in a 3,700-liter vault. Because the rats moved freely in the chambers, they may have received more variable doses of boron trifluoride than the guinea pigs, which were caged. Even though the chambers were not designed originally for exposure to particles, random samples showed that the mist was reasonably well distributed throughout the chambers. Other than the building's air-conditioning system, no devices were used to control moisture. Although variable, the relative humidity was usually about 30%. Boron trifluoride was released into the exposure chamber in a stream of nitrogen to prevent the formation of hydrolysis products in the ducts.

The analytical method used by Torkelson et al [22] was a spectrophotometric reading of the color produced by the reaction of boron and a carminic acid indicator. Total boron in the chamber was determined, and the equivalent boron trifluoride level was calculated. The authors also used infrared analysis to identify the gas, but as previously discussed, this method was not applicable in normal air due to the extensive reactivity of the gas. No data on the precision or accuracy of this method are available.

Ten male guinea pigs and 14 female rats were exposed to boron trifluoride at a nominal concentration of 12.8 ppm (35 mg/cu m), 7 hours/day, 5 days/week, for up to 3 months. [22] On the 19th exposure, the first guinea pigs died. By the 42d exposure, a total of seven had died of respiratory failure and asphyxia. Only one rat died after 34 exposures in 49 days. The 3 surviving guinea pigs and 4 of the 13 rats were killed after 42-45 exposures in 62-65 days. The 9 remaining rats received a total of 60 exposures in 87 days. Four were then killed and examined; the other five were observed without exposure for another month before they were killed and examined. The guinea pigs had difficulty in breathing and appeared asthmatic. Exposed guinea pigs had increased lung weights averaging 0.80 g/100 g of body weight, compared to lung weights of 0.64 g/100 g of body weight for the control animals (P = 0.01). Gross examination revealed pneumonitis, which suggested chemical damage, in the hilar region of the lungs. Examined microscopically, the lungs showed areas of collapse and emphysema adjacent to the areas of more severe pneumonitis. The vessels in the alveolar walls were distended with blood cells, and the alveolar walls were thickened and separated from the vascular epithelium. Tissue examinations of control guinea pigs were not reported. The exposed rats were considered to have normal appearance and organ weights, but gross and microscopic tissue examination showed pulmonary changes indicating chemical irritation. The hilar regions of the lungs were the most affected and the injuries were manifested as pneumonitis. Although the fluoride content in some tissues increased (see Table III-3), no abnormal effects were seen by X-ray examination, and the rats which were observed for 1 month after their last exposure continued to gain weight normally.

TABLE III-3

FLUORIDE LEVELS IN TISSUES OF RATS
EXPOSED TO BORON TRIFLUORIDE BY INHALATION

Sex	Number	Nominal Concentration (ppm)	Exposure Duration (hours)	Fluoride Levels (ppm)*		
				Teeth	Bones	Lungs
F	4	0	0	502	-	9.9
F	4	12.8	45	738	-	11.9
F	5	0	0	342	996	-
F	5	7.7	33	643	1,154	-
F	4	0	0	580	1,335	-
F	4	3.0	127	867	1,732	-
M	4	0	0	305	735	-
M	4	3.0	127	506	1,109	-

*Statistical tests were not reported.

From Torkelson et al [22]

In the second phase of this study, [22] 10 male guinea pigs and 5 female rats were exposed 7 hours/day, 5 days/week, to boron trifluoride at a calculated concentration of 7.7 ppm (21.3 mg/cu m). One guinea pig died on each of days 2, 5, 6, and 11. The deaths were accompanied by "what appeared to be an asthmatic attack." On the 29th day, the six surviving guinea pigs were killed accidentally when, because of a faulty flowmeter, there was exposure at an undetermined concentration of boron trifluoride and nitrogen. All five rats in the chamber survived the accident and were exposed to boron trifluoride a total of 33 times in 51 days. No effects were noted in gross appearance, nor did overt fluorosis of the teeth result, although the teeth were light-colored and the fluoride content of the teeth and bones did increase (Table III-3).

In the third phase of the study, [22] 24 rats, 20 guinea pigs, and 6 rabbits, evenly divided as to sex, were exposed 7 hours daily, 5 days/week, to boron trifluoride at a nominal concentration of 3 ppm (1.5 ppm or 4.2 mg/cu m by analysis) for up to 6 months. Since four female guinea pigs died of extraneous causes, six additional female guinea pigs were added and then exposed 88 times in 127 days. Growth, appearance, and mortality were normal for all animal groups except the added guinea pigs, whose weights were lower than those of control guinea pigs, although not statistically significant by the authors' definition (723 g vs 855 g, p = 0.073). Microscopic examination of the lungs showed the rats were "very slightly" affected; areas of pneumonitis, peribronchial round cell infiltration, and congestion in the capillaries lining the alveolar walls were evident. Guinea pigs, except for those in the additional group, had a 30% higher incidence of pneumonitis than the rats but exact values were not given. The fluoride content of rat bones and teeth was increased (see Table III-3), although no adverse effects were reported. When examined for microscopic changes, the exposed rabbits did not differ from the controls.

The authors [22] concluded that boron trifluoride was a respiratory irritant to which the guinea pig was the most sensitive of the tested species. Repeated inhalation of boron trifluoride resulted in pneumonitis at all concentrations studied. The earlier mortality of guinea pigs exposed at a nominal concentration of 7.7 ppm than of those exposed at 12.8 ppm was not fully explained in the report. The authors did postulate that since the guinea pigs appeared more uncomfortable on humid days, the uncontrolled humidity may have resulted in varying particle sizes and, therefore, varying lung deposition rates. The authors judged odor threshold an inadequate indicator to provide a safe working environment, and they recommended a TWA concentration of 0.3 ppm.

The most recent boron trifluoride inhalation study found was done in the USSR by Kasparov and Kirii [33] in 1972. Guinea pigs, albino rats, and albino mice were subjected to acute, subacute, and chronic exposures to boron trifluoride. Toxicity was evaluated by mortality rates, body weights, respiratory rates, urine amino acid levels, and radiographic and histologic examinations. Whole blood or serum was tested for total protein content, distribution of protein fractions, levels of cholinesterase and aldolase activities, and pyruvic acid concentration. The authors did not specify whether the air concentrations reported were the results of analysis or calculation. They also did not report how many days each week the animals were exposed, but said only that the animals were exposed daily. They did indicate that dry air was used to deliver the boron trifluoride gas to the chamber, but the moisture generated by the animals' respiration was not measured.

The LC50 was 3,460 mg/cu m (1,245 ppm) for a 2-hour exposure of 70 albino mice, 1,180 mg/cu m (425 ppm) for a 4-hour exposure of 50 albino rats, and 109 mg/cu m (39 ppm) for a 4-hour exposure of 42 guinea pigs. [33] The animals died either during the exposure period or within a few days after exposure, but the exact times were not given. Necropsy of the animals showed cyanosis of mucous membranes and hemorrhage of internal organs, especially the lungs. The lungs also showed increased weight, edema, alveolar-duct destruction, and vascular dilatation. Hemorrhage, edema, and "dystrophy" were seen in the heart and the liver. The kidneys, spleen, and brain were affected with hyperemia and edema. Irritation of the mucous membranes of the eyes was noted.

In subacute tests, 26 guinea pigs and 32 albino rats were exposed to boron trifluoride at a concentration of 32.9 mg/cu m (12 ppm), 4 hours/day, for 15 days. [33] The first guinea pigs died on the 5th day, and all were dead by the 13th day. Examination showed increased hemoglobin levels and pulmonary changes including edema, increased vascular permeability, and dystrophic changes of the parenchyma. All of the rats survived; however, their blood serum protein levels increased significantly. Neuromuscular conductivity (measured by an undescribed method) decreased significantly. Exact test values were not reported. In some rats there were signs of subacute bronchitis and occasional unspecified vascular disturbances. According to the authors, these microscopic changes were not very pronounced.

These researchers [33] also studied the effects of inhalation of boron trifluoride at two concentrations in a 4-month chronic study. Twenty-six guinea pigs and 32 albino rats were exposed 4 hours daily.

Exposure to boron trifluoride at 10 mg/cu m (3.6 ppm) resulted in upper respiratory tract irritation, nose bleeding, and increased serum gamma globulin in rats. Guinea pigs showed a decrease in serum beta globulin levels. Several other results were reported, but the species involved was not identified. These results included leukocytosis, reductions in the levels of serum pyruvic acid and inorganic phosphorus, and fluorosis of the teeth. Respiration also decreased (oxygen consumption was reduced by 36.6%), while signs of chronic bronchitis, sclerosis, moderate alveolar edema, desquamative pneumonia, and emphysema were seen in the lungs. The heart and liver were affected with dystrophy, the spleen with reticuloendothelial-element proliferation, and the brain with pericapillary and pericellular edema.

No signs of toxicity were seen after chronic exposure (4 hour/day, up to 4 months) to boron trifluoride at 3 mg/cu m (1.08 ppm). [33] Guinea pigs showed dysproteinemia, leukocytosis, decreased cholinesterase activity (site of measurement not reported), and subacute bronchitis. These changes were reversible, and no changes were evident 1 month after the last exposure. The internal organs of the exposed rats showed no significant differences from the controls.

Kasparov and Kirii [33] concluded that boron trifluoride was a respiratory irritant, but they also suggested that boron trifluoride caused pathologic changes in other organs such as the kidneys, liver, or heart. The many systemic effects indicated that the compound was absorbed through the lungs. The guinea pig was found to be the most sensitive of the tested species, dying after 5 days of exposure at 32.9 mg/cu m (11.8 ppm) and showing reversible changes at 3 mg/cu m (1.08 ppm).

Correlation of Exposure and Effect

Boron trifluoride exposure in an occupational setting or in an animal inhalation study probably does not usually involve exposure to pure boron trifluoride gas. Boron trifluoride reacts with water vapor in air to form a white mist containing hydration and hydrolysis products. [22]

Sampling and analytical methods are limited to independent measurement of the boron or fluoride levels present in workplace or exposure chamber air, from which the concentration of boron trifluoride gas assumed to have caused their presence is calculated. [22,30] Neither accurate measurement of the gas present nor accurate identification of the products actually inhaled has been possible. For this reason, an accurate correlation of exposure concentration with the resultant effects is not possible at this time.

Kirii [27] compared workers exposed to boron trifluoride, isobutylene, and ethylene with workers exposed only to isobutylene and ethylene. (In the introduction to an animal study by Kasparov and Kirii, [33] it is implied that the boron trifluoride concentration in this study [27] was 18-19 mg/cu m.) Both groups showed nasal mucosal changes, bronchitis, emphysema, insomnia, cardiac effects noted as systolic noise, and dryness of the skin with a fine papulous rash. According to the author, these findings were more marked in workers whose exposure included boron trifluoride. Increased fragility of tooth enamel was also reported, but this is more likely the result of exposure to the acid products than of fluoride deposition. The usefulness of this report is limited because environmental concentrations were not reported; the effects attributed to boron trifluoride are not distinguishable from the potential effects of other chemicals present; and the study was only available in abstract form from which details such as the actual data and statistical analysis of results are missing.

In a boron trifluoride production facility, [28] the environmental concentrations of boron trifluoride were calculated from fluoride levels measured with the fluoride-ion-specific electrode. The 10 determinations made in 1974 showed concentrations ranging from 0.1 to 1.8 ppm (0.27-4.98 mg/cu m). Thirteen workers, with exposures ranging from 1 to 27 years (average, 8.84 years), did not have urinary fluoride levels exceeding the recommended permissable levels, [34] but eight of them showed minimal to severe departures from normal pulmonary function.

The effect of boron trifluoride on the skin of one worker has been reported. [21] A burn similar to that caused by an acid resulted when boron trifluoride (concentration unspecified) in water was placed on the subject's arm for "a day or so."

Animal studies can be used to estimate the effects of boron trifluoride at varying environmental concentrations, but accurate measurement of these concentrations has not been possible. Although animals in these studies were exposed to boron trifluoride and its hydrolysis products by inhalation, it is probable that varying amounts of these products may have been consumed by ingesting the droplets deposited on the cages and their coats. Single-exposure and repeated-exposure effects in animals are summarized in Tables III-4 and III-5.

Single-exposure studies (Table III-4) involved high boron trifluoride concentrations. LC50 values were calculated, [33] as follows: 1,180 mg/cu m (425 ppm) in rats for a 4-hour exposure; 3,460 mg/cu m (1,245 ppm) in mice for a 2-hour exposure; and 109 mg/cu m (39 ppm) in guinea pigs for a 4-hour exposure. The guinea pig, in all mortality studies, was the most sensitive species. [22,29,33]

Repeated-inhalation experiments (Table III-5) involved exposure periods of 1-6 months. [22,30] All the exposed dogs, cats, rats, mice, rabbits, and guinea pigs died in 30 days or less when exposed to boron trifluoride metered at a concentration of 100 ppm (277 mg/cu m) for up to 30 days [30]; all guinea pigs died when exposed at a concentration of 33 mg/cu m (12 ppm) for 15 days; and no rats, guinea pigs, or rabbits died when exposed for up to 6 months to boron trifluoride at concentrations of 3 and 4.2 mg/cu m (1.08-1.5 ppm). [22,33] Lungs and kidneys were adversely affected at all concentrations which caused deaths. Guinea pigs and rats showed pneumonitis and congestion in the lungs after a 6-month exposure to boron trifluoride calculated at a concentration of 3.0 ppm (8.3 mg/cu m), [22] and a 4-month exposure at 3.0 mg/cu m (1.08 ppm) caused reversible tracheitis and bronchitis. [33]

Guinea pigs [31] and rats [30] were killed daily in serial studies performed to determine the time course of adverse respiratory and kidney effects. The variation in response among animals of a single species was extensive. The results indicate that boron trifluoride is a respiratory irritant with no specific progression of effects, since the onset of irritation did not correlate with the length of exposure.

The guinea pig has proved to be the species most sensitive to the effects of boron trifluoride exposure, but rats, mice, rabbits, dogs, and cats also are susceptible. Although the effects of respiratory irritation induced by boron trifluoride have not been adequately demonstrated in humans, animal experiments strongly suggest that the inhalation of boron trifluoride would produce general respiratory irritation in humans.

Carcinogenicity, Mutagenicity, and Teratogenicity

No studies have been found regarding any carcinogenic, mutagenic, or teratogenic potential of this compound.

Summary Tables of Exposure and Effect

The effects on animals from boron trifluoride exposure discussed in detail in Chapter III are summarized in Tables III-4 and III-5.

TABLE III-4

ANIMAL MORTALITY FROM SINGLE ACUTE INHALATION EXPOSURES TO BORON TRIFLUORIDE

Species	Concentration (mg/cu m)*	Exposure Duration (hr)	Mortality Fraction	Reference
Mice	5,570	2	59/70	33
"	3,460	2	35/70	33
"	2,120	2	11/70	33
"	2,078	5.5	1/10	29
Guinea pigs	2,078	5.5	10/10	29
Rats	1,450	4	42/50	33
"	1,180	4	25/50	33
"	1,078	5.5	1/10	29
Guinea pigs	970	1.4	7/10	33
Rats	720	4	8/50	33
Mice	374	10.9	0/10	29
Rats	374	10.9	0/10	29
Guinea pigs	374	10.9	1/10	29
"	149	4	35/42	33
"	109	4	21/42	33
"	40	4	7/41	33

*Converted when expressed as ppm in reference

TABLE III-5

EFFECTS OF REPEATED BORON TRIFLUORIDE INHALATION ON ANIMALS

Species	Nominal Concentration (mg/cu m)*	Exposure Duration**	Effects (including mortality fraction)	Reference
Rats	259	4 - 7 hr/d x 30 d	100/100; 10% weight loss; dental fluorosis; mild renal degeneration; pulmonary edema, hemorrhage, congestion	30
"	55	4 - 7 hr/d x 30 d	2/100; normal growth in others, slight coloring of "incisor enamel"	31
"	35	7 hr/d x 60 d	1/14; pneumonitis, increased fluoride in tissues, dental fluorosis normal whole-body X-ray	22
"	10	4 hr/day for 4 mo	0/32; epistaxis; upper respiratory tract irritation, edema, bronchitis; dental fluorosis	33
"	8.3 - 11	7 hr/d x 33 d	0/5; increased fluoride in teeth and bones	33
"	8.3	7 hr/d x 128 d	0/24; congestion in alveolar capillaries, slight pneumonitis, light-colored teeth	22
"	3	4 hr/d for 4 mo	0/32; no microscopic changes reported	33

TABLE III-5 (CONTINUED)

EFFECTS OF REPEATED BORON TRIFLUORIDE INHALATION ON ANIMALS

Species	Nominal Concentration (mg/cu m)*	Exposure Duration**	Effects (including mortality fraction)	Reference
Mice	259	4 - 7 hr/d x 30 d	101/101; blood and mucus in bronchioles, gross kidney changes	30
"	55	4 - 7 hr/d x 30 d	15/92; high mortality from accidental exposure	30
Guinea pigs	259	4 - 7 hr/d x 30 d	40/40; subnormal weight, blood and mucus in bronchioles	30
"	55	4 - 7 hr/d x 30 d	1/30; bronchopneumonia and interstitial nephritis in control and exposed animals	31
"	35	7 hr/d x 42 - 45 d	7/10; pneumonitis, high lung weight, areas of emphysema	22
"	10	4 hr/d for 4 mo	0/26; low serum inorganic phosphorus levels, bronchitis, emphysema	33
"	8.3 - 11	7 hr/d x 29 d	4/10; asthama-type attacks prior to death; death of remaining animals day 29 from faulty flowmeter	22
"	8.3	7 hr/d x 128 d	4/20; pneumonitis 30% higher than in rats	22
"	8.3	7 hr/d x 88 d	0/6; slight decrease in body weights	22

TABLE III-5 (CONTINUED)

EFFECTS OF REPEATED BORON TRIFLUORIDE INHALATION ON ANIMALS

Species	Nominal Concentration (mg/cu m)*	Exposure Duration**	Effects (including mortality fraction)	Reference
Guinea pigs	3.0	4 hr/day for 4 months	0/26; subacute bronchitis, decreased cholinesterase	33
Rabbits	259	4 - 7 hr/d x 30 d	12/12; decreased serum inorganic phosphorus (from 6.3 to 4.0 mg%)	30
"	55	4 - 7 hr/d x 30 d	0/12; low-grade interstitial pneumonia	31
"	8.3	7 hr/d x 128 d	0/6; no microscopic changes observed	22
Cats	259	4 - 7 hr/d x 30 d	6/6; blood and mucus in bronchioles, mild renal changes	30
"	55	4 - 7 hr/d x 30 d	0/5; 12% body weight loss	31
Dogs	259	4 - 7 hr/d x 30 d	5/5; pneumonia in all, decreased serum inorganic phosphorus (from 7.6 to 2.4 mg%)	30
"	55	4 - 7 hr/day x 30 d	0/5; 12% weight loss	31

*Converted to mg/cu m when expressed as ppm in reference
**Exposures were 5 days/week by Torkelson et al [22] and by Weil et al [30,31] and unspecified by Kasparov and Kirii. [33]