Toxicology of Substances in Relation to Major Hazards

Hydrogen fluoride

By R M Turner and S Fairhurst

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Tables

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SUMMARY

This paper examines the 'dangerous toxic load' (DTL) for hydrogen fluoride, in accordance with the principles of toxicological assessment described in the recent HSE publication *Assessment of the Toxicity of Major Hazard Substances*.

There are no quantitative data on the exposure conditions producing severe toxicity in humans. From the available animal studies, it is suggested that for risk analyses the following relationship is used:

$$DTL = 2\,400\,000\ ppm^2\ min$$

INTRODUCTION

This paper is a review of the available toxicological data on hydrogen fluoride, in order to establish the most appropriate toxicity values for land-use planning decision making. It should be read in conjunction with the above-mentioned HSE publication which provides the general framework within which this evaluation of the toxicity of hydrogen fluoride was performed [1].

Hydrogen fluoride (HF), at atmospheric pressure, is a corrosive, fuming liquid at temperatures below 292 K, and a gas at higher temperatures[2]. It shows complex association behaviour (oligomerisation) in the vapour phase. This behaviour has been extensively studied but there is still disagreement as to the number and type of the oligomeric forms[3]. Association up to the hexamer and possibly the octamer would, however, seem to be generally accepted[4-6]. On release into dry air dilution with the air would lead to dissociation of the oligomers which would be an endothermic process. However, if water vapour was present a strong interaction with hydrogen fluoride would occur and this would be a highly exothermic process. It is therefore clear that the nature and dispersion characteristics of any hydrogen fluoride released to the atmosphere would be very complex.

Some physicochemical properties of hydrogen fluoride are shown below[2,7]:

Property	*Value*
Molecular weight	20.01
Boiling point at 1.0133×10^5 Pa	292.5 K
Freezing point at 1.0133×10^5 Pa	190 K
Vapour pressure at 290 K	6.01×10^3 Pa
Density at 273 K	liquid 0.987 gas 0.921
Water solubility at 273 K, 1.0133×10^5 Pa	infinite
Conversion factor at 273 K, 1.0133×10^5 Pa	1 ppm = 0.83 mg/m^3

TOXICOLOGICAL DATA AVAILABLE IN HUMANS

Two human volunteers were exposed to different atmospheric concentrations of hydrogen fluoride gas for up to three minutes, in controlled experiments[8]. A concentration of 32 ppm was tolerated for three minutes, although a flat, sour taste and mild sensory irritation of the eyes, nose and upper respiratory tract were apparent. Sensory irritation was more pronounced at 61 ppm and was marked at 122 ppm, with additional 'smarting' of the skin.

Although there are several reports of accidental human exposure to hydrogen fluoride, as a gas, anhydrous liquid, or in the form of hydrofluoric acid, none of these reports contains quantitative exposure data suitable for the purposes of this paper. Single exposures to hydrogen fluoride gas have produced sensory irritation of the skin, eyes and respiratory tract, and inflammation and congestion of the lungs[2,8]. Skin contact with anhydrous hydrogen fluoride liquid produces severe painful skin burns.

The toxicological properties of hydrogen fluoride in liquid form suggest the possibility of disfigurement with skin burns or permanent eye damage. No information is available on other potential long-term sequelae in humans arising from a single exposure to hydrogen fluoride.

TOXICOLOGICAL DATA AVAILABLE IN ANIMALS

The toxicity of hydrogen fluoride following a single inhalation exposure has been studied in several animal species[8-14]. These studies are summarised in Table 2. Some indication of species variation in susceptibility to hydrogen fluoride is given by the LC_{50} values and associated exposure times in Table 1. In addition, sensory irritation of the skin, eyes, nose and respiratory tract, but no deaths, was observed in rabbits exposed to up to 1247 ppm hydrogen fluoride for 15 minutes, or in dogs exposed to up to 686 ppm for 15 minutes or 243 ppm for 60 minutes[9].

The principal effects observed following a single exposure of animals to hydrogen fluoride gas were sensory irritation of the eyes, nose and respiratory tract, and pathological lesions of the skin (inflammation), eyes (corneal opacity and erosion), nasal mucosa (inflammation, necrosis) and lungs (inflammation, oedema, congestion, haemorrhage, emphysema)[8-11]. There was also some evidence for systemic effects, with congestion, oedema or necrosis in the liver, kidneys, heart, spleen and thymus[8,9,11]. Deaths, due principally to lung damage, were seen mainly within 24 hours post-exposure, although some occurred after several days.

DERIVATION OF 'DANGEROUS TOXIC LOAD'

Estimation of one set of exposure conditions producing the HSE land-use planning SLOT (Specified Level of Toxicity)

The available data on the human response to inhalation of hydrogen fluoride are insufficient to provide a basis for establishing a 'dangerous toxic load' (DTL). Therefore it is necessary to use the available animal data to establish a model for the response in humans.

Although it might be anticipated that from the species tested, the response in monkeys would be more closely related than that of other species to the response in humans, the data available in monkeys are very limited. In fact from the information available there is no clear indication as to which of the animal species and strains used is the most reliable model for the human response. In these circumstances it is considered prudent to use the most sensitive animal species of those tested to represent human responsiveness to hydrogen fluoride vapour[1].

From the data available the mouse appears to be the most sensitive of the species tested. The various studies in mice have produced results indicating a 5-minute LC_{50} of 6247 ppm and 60-minute LC_{50} values ranging from 342 ppm to 501 ppm. There are no grounds for considering the findings of these mouse studies to be unreliable or unsuitable in the context of this assessment. Consequently the most sensitive response observed, yielding a 60-minute LC_{50} value of 342 ppm, has been used as the basis for deriving the dangerous toxic load[11].

The results of this mouse study can be used to estimate the 60-minute exposure concentration producing a level of toxicity in mice comparable to the land-use planning SLOT. Analysis of the data using the probit approach[15] gives the values LC_1 = 205 ppm, LC_5 = 230 ppm. In the study itself, in groups of 10 animals, no deaths were observed at 260 ppm and one death at 278 ppm[11]. Sensory irritation of the skin, eyes, nose and upper respiratory tract has been reported in animals (and in humans) exposed to hydrogen fluoride concentrations in the range 25-125 ppm[8,9]. However, in animal studies signs of severe toxicity and pathological damage to the skin, eyes, respiratory tract and internal organs were reported only under exposure conditions close to or within the range producing lethality. Consideration of these factors, in conjunction with the other information available, suggests that a suitable estimate of one set of exposure conditions predicted to produce the land-use planning SLOT in humans is:

200 ppm for 60 minutes.

Derivation of a dangerous toxic load equation

Exposure to hydrogen fluoride could occur over a continuum of combinations of airborne concentration and exposure time. Consequently, the available data were evaluated to determine whether a relationship exists between the airborne concentration of hydrogen fluoride, exposure time and a toxic load constant.

From the animal studies on hydrogen fluoride, only one report presents adequate data with which to investigate this issue. In this study rats were exposed to various concentrations of hydrogen fluoride for periods of between 5 and 60 minutes[9]. Examination of these data by a graphical plot of the LC_{50} values from each exposure period indicates a value of approximately 2 for the exponent *n*, producing the expression

toxic load = c^2t.

In the only other study in which variable exposure periods were used, the mortality data were poorly presented and represented the combined results from two species[8]. Such data are unsuitable for the investigation of the toxic load relationship, as species variation will also exert an unknown degree of influence on the derived relationship between c and t[11].

Therefore, from the available data the most appropriate toxic load equation for hydrogen fluoride is:

toxic load = c^2t.

Dangerous toxic load value for hydrogen fluoride

Using the toxic load relationship c^2t and the prediction of 200 ppm for 60 minutes as one set of exposure conditions producing the land-use planning SLOT, the dangerous toxic load (DTL) is:

DTL = 2 400 000 ppm^2 min.

Some examples of exposure conditions producing this DTL are given below:

	Exposure period (min)				
	5	10	30	60	120
Atmospheric concentration (ppm)	693	490	283	200	141

Table 1 LC_{50} values for hydrogen fluoride in animals

Species	*Duration of exposure (min)*	*LC_{50} (ppm)*	*Reference*
Rat	5	18200	10
		4970	9
	15	2689	9
	30	2042	9
	60	1395	11
		1307	9
		1276	14
		966	12,13
Mouse	5	6247	10
	60	501	14
		456	12,13
		342	11
Guinea pig	15	4327	9
Monkey	60	1774	14

TABLE 2 SINGLE EXPOSURE INHALATION STUDIES IN ANIMALS

Species characteristics	Exposure conditions	Observations
Rat[9] Wistar-derived male 100-120 g 10-20 per group	Groups exposed to various concentrations of HF for periods of between 5 and 60 minutes.	For exposure conditions producing deaths, rats were observed for up to 14 days. At sublethal exposures the observation period was up to 150 days. The following LC_{50} values were reported:- exposure period min / LC_{50} (ppm) 5 — 4970 15 — 2689 30 — 2042 60 — 1307 The probit lines for each exposure period had steep slopes (8-14), and exposure concentrations of up to 68% of the LC_{50} values produced no deaths. Exposures within the lethal range produced irritation of the eyes and nose, body weight loss, respiratory distress and some deaths. Pathological findings were severe necrosis and inflammation of the nasal turbinates, liver sinusoidal congestion, kidney proximal convoluted tubule damage, and skin inflammation with altered collagen structure. However, no substance-related effects were reported in the lungs, which is very questionable in view of other studies on HF. For each exposure period, concentrations of 6%, 12.5%, 25%, 50% and 68% of the LC_{50} produced concentration-dependent irritation of the eyes, nose and respiratory tract, but no deaths and little or no indication of histopathological damage. The LC_{50} values given above fit the relationship: toxic load = $c^n t$ where n = 1.9, ie approximately 2.

TABLE 2 SINGLE EXPOSURE INHALATION STUDIES IN ANIMALS

Species characteristics	Exposure conditions	Observations
Rat [12, 13] Sprague-Dawley male 250-300 g 5 per group	Exposure to 848-1576 ppm for 60 minutes.	Rats were exposed for 14 days. The mortality results were:- 848 ppm 0/5 1087 ppm 3/5 1576 ppm 5/5 The LC_{50}, with 95% confidence limits, was: 966 (785-1188) ppm The signs of toxicity reported were eye and nose irritation, lacrimation, corneal opacity, rhinorrhoea, salivation, respiratory distress and skin erythema. Deaths occurred at up to 6 days post-exposure. Histopathological examination of the lungs of survivors at 14 days revealed vascular congestion, multiple areas of intraalveolar haemorrhage, and peribronchiolar lymphoid hyperplasia. No lesions were noted in other major organs.
Rat [10] Wistar 250-275 g 10 per group	Groups exposed to 11550-25 690 ppm for 6 minutes	Rats were observed for 7 days. The mortality results were:- 12440 ppm 1/10 17615 ppm 5/10 18580 ppm 8/10 20730 ppm 7/10 25800 ppm 10/10 The LC_{50} with 95% confidence limits, was: 18200 (15 965-20 748) ppm Most deaths occurred within 24 hours post-exposure, although some deaths occurred at 3-4 days. Pulmonary oedema and haemorrhage were commonly observed at necropsy.
Rat [11] Sprague-Dawley derived CFE 250-325 g 10 per group	Groups exposed to 1087-1765 ppm for 60 minutes	Rats were observed for up to 14 days. The mortality results were: 1087 ppm 0/10 1108 ppm 2/10 1405 ppm 3/10 1565 ppm 8/10 1765 ppm 10/10

TABLE 2 SINGLE EXPOSURE INHALATION STUDIES IN ANIMALS

Species characteristics	Exposure conditions	Observations
		The LC_{50}, with 95% confidence limits, was: 1395 (1302-1495) ppm The signs of toxicity reported were eye and mucous membrane irritation, corneal opacity, skin erythema and respiratory distress. Necropsy revealed pulmonary congestion and oedema, and thymic haemorrhage.
Rat[14] Sprague-Dawley male 10 per group	Several groups exposed to different concentrations for 60 minutes.	Rats were observed for 14 days. The only data given was an LC_{50} value of 1278 ppm.
Mouse[12,13] CF-1 female 30-35 g 10 per group	Exposure to unspecified concentrations for 60 minutes.	Mice were observed for 14 days. The mortality results were:- 351 ppm 0/10 438 ppm 5/10 505 ppm 9/10 518 ppm 8/10 633 ppm 10/10 The LC_{50}, with 95% confidence limits, was: 456 (426-489) ppm The signs of toxicity reported were eye and nose irritation, skin erythema and respiratory distress. Deaths occurred at up to 6 days post-exposure. Histopathological examination of the lungs of survivors at 14 days revealed scattered areas of intraalveolar haemorrhage, with diffuse pulmonary congestion at the higher concentrations.
Mouse[10] ICR 30-35 g 15 per group	Groups exposed to 2430-11 010 ppm for 5 minutes.	Mice were observed for 7 days. The mortality results were:- 2430 ppm 0/15 4500 ppm 5/15 7615 ppm 10/15 8140 ppm 8/15 11010 ppm 15/15

TABLE 2 SINGLE EXPOSURE INHALATION STUDIES IN ANIMALS

Species characteristics	Exposure conditions	Observations
		The LC_{50}, with 95% confidence limits, was: 6247 (4769-8149) ppm Most deaths occurred within 24 hours post-exposure, although some deaths occurred at 3-4 days. Pulmonary oedema and haemorrhage were commonly observed at necropsy.
Mouse[11] ICR-derived CF-1 female 25-32 g 10 per group	Groups exposed to 263-458 ppm for 60 minutes.	Mice were observed for up to 14 days. The mortality results were:- 263 ppm 0/10 278 ppm 1/10 324 ppm 7/10 381 ppm 8/10 458 ppm 9/10 The LC_{50}, with 95% confidence limits, was: 342 (315-372) ppm The signs of toxicity reported were eye and mucous membrane irritation, corneal opacity, skin erythema and respiratory distress. Necropsy revealed pulmonary congestion and haemorrhage.
Mouse[14] ICR male 10 per group	Several groups exposed to different concentrations for 60 minutes.	Mice were observed for 14 days. The only data given was an LC_{50} value of 501 ppm.
Guinea pig[9] Hartley-derived male 340-360 g 10 per group	Groups exposed to various concentrations for 15 minutes.	Guinea pigs observed for 14 days. The LC_{50}, with 95% confidence limits, was:- 4327 (4006-4672) ppm The probit line had a steep slope of 15.5. At exposure levels producing some deaths, toxic signs were irritation of the eyes and nose, body weight loss and respiratory distress. Another group of 10 guinea pigs were exposed to 1377 ppm for 30 minutes. No deaths occurred.

TABLE 7 SINGLE EXPOSURE INHALATION STUDIES IN ANIMALS

Species characteristics	Exposure conditions	Observations
Rabbit[8] New Zealand White 4-6 months old 1.8-3.9 kg and Guinea pig 0.5-1.3 kg 3 rabbits and 3 guinea pigs per group	This study involved both single and repeated exposures. The experiments of particular interest involved exposing groups of 3 rabbits plus 3 guinea pigs to varying concentrations of HF for periods of 5 minutes to 8 hours.	This study was not well reported, in that it is difficult to relate precisely the severity of effects and mortality to particular exposure conditions. Mortality data are presented in graphical form only, and in terms of no deaths, a proportional number of deaths, and total deaths within the group, with no clear separation of deaths in rabbits from those in guinea pigs. For each exposure period, the lowest concentrations tested which produced some deaths were:- 5 minutes @ 2000 ppm 15 minutes @ 1500 ppm 30 minutes @ 2000 ppm 60 minutes @ 700 ppm 120 minutes @ 250 ppm Concentration-dependent irritation of the eyes, nose and respiratory tract was evident at 25 ppm and above. Higher concentrations, particularly those producing severe systemic toxicity and some deaths after the shorter exposure periods used, produced corneal erosion and necrosis of the nasal turbinates. Severe systemic toxic effects were seen under the exposure conditions producing some deaths (listed above), but also at somewhat lower values, examples being 800 ppm and above for 5 minutes, and 54 ppm and above for 6 hours. These effects consisted of lung congestion, haemorrhage, oedema, emphysema, and inflammation of the trachea and bronchi, and congestion, oedema and necrosis of several other organs: liver, kidneys, heart, spleen.
Rabbit[9] 5 per group	634 or 1247 ppm for 15 minutes.	Rabbits were observed for 45 days. Irritation of the eyes, nose and respiratory tract was observed, persisting for several hours post-exposure. At 1247 ppm the animals appeared subdued and weak for up to 2 days post-exposure. No deaths occurred.

TABLE 2 SINGLE EXPOSURE INHALATION STUDIES IN ANIMALS

Species characteristics	Exposure conditions	Observations
Dog[9] congrel 2 per group	460 or 666 ppm for 15 minutes, or 157 or 243 ppm for 60 minutes.	Dogs were observed for 7-21 days post-exposure. Sensory irritation of the skin, eyes, nose and respiratory tract was apperent, and coughing persisted for a few days post exposure. No deaths occurred.
Monkey[14] Rhesus males and females 4 per group	Several groups exposed to different concentrations for 60 minutes	Monkeys were observed for 14 days. The only data given was an LC_{50} value of 1774 ppm.

REFERENCES

1 Turner R M and Fairhurst S. Assessment of the toxicity of Major Hazard substances. *HSE Specialist Inspector Report* No 21. 1989.

2 Clayton G D and Clayton F E (Eds). *Patty's Industrial Hygiene and Toxicology*. Third Revised Edition. Volume 2B. John Wiley and Sons, New York. 1981. pp 2945-2948.

3 Rushmore J D. The self-association of hydrogen fluoride. A short review of the published literature. *SCS TN-31*. 1954.

4 Schotte W. Fog formation of hydrogen fluoride in air. *Ind Eng Chem Res* 1987 **26** 300.

5 Clough P N, Grist D R and Wheatley C J. Thermodynamics of mixing and final state of a cloud formed by the dilution of anhydrous hydrogen fluoride with moist air. *SRD report R306*.

6 Maclean J N et al. The self-association of hydrogen fluoride vapour. *J Inorg Nucl Chem* 1962 **24** 1549.

7 Weast R C (Ed). *CRC Handbook of Chemistry and Physics*. 60th Edition. CRC Press, Florida, USA, 1979.

8 Machle W, Thomann F, Kitzmiller K and Cholak J. The effects of the inhalation of hydrogen fluoride. I. The response following exposure to high concentrations. *J Ind Hyg Toxicol* 1934 **16** 129-145.

9 Rosenholtz M J, Carson T R, Weeks M H, Wilinski F, Ford D F and Oberst F W. A toxicopathological study in animals after brief single exposures to hydrogen fluoride. *Am Ind Hyg Assoc J* 1963 **24** 253-261.

10 Higgins E A, Fierce V, Thomas A A and Davis H V. Acute toxicity of brief exposures to HF, HCl, NO_2 and HCN with and without CO. *Fire Technol* 1972 **8** 120-130.

11 Wohlslagel J, Dipasquale L C and Vernot, E H. Toxicity of solid rocket motor exhaust: effects of HCl, HF and alumina on rodents. *J Combust Toxicol* 1976 **3** 61-70.

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

13 MacEwan J D and Vernot E H. *Toxic Hazards Research Unit Annual Technical Report*. AMRL Report No AD-A031-860. 1976.

14 Darmer K I, Haun C C and MacEwan J D. The acute inhalation toxicology of chlorine pentafluoride. *Am Ind Hyg Assoc J* 1972 **33** 661-668.

15 Finney D J. *Probit Analysis*. Cambridge University Press, London. 1977.

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