



Hydrogen Fluoride and Hydrofluoric Acid (HF)

Toxicological Overview

Key Points

Kinetics and metabolism

- it is readily absorbed following inhalation or dermal contact
- the main route of excretion is via the urine

Health effects of acute exposure

- hydrogen fluoride dissolves in water/moisture to form corrosive hydrofluoric acid
- effects from exposure may be localised and systemic
- inhalation can cause irritation of the eyes, nose and throat, chest tightness and pulmonary oedema
- dermal contact can cause severe burns
- ingestion of dissolved hydrofluoric acid may cause burns to the mouth and throat
- systemic effects include convulsions, CNS depression and cardiac conduction disturbances can occur secondary to electrolyte disturbances

Health effects of chronic exposure

- hydrogen fluoride is not considered to be carcinogenic
- there are no data available on the developmental or reproductive effects of hydrogen fluoride

Summary of Health Effects

Hydrogen fluoride can cause both local and severe systemic effects. It readily dissolves in water or moisture to form corrosive hydrofluoric acid. Following exposure fluoride ions are readily released from hydrogen fluoride and are almost completely absorbed. Fluoride ions are responsible for the systemic effects of hydrogen fluoride.

Inhalation of hydrogen fluoride can lead to upper respiratory tract symptoms such as shortness of breath, sore throat and coughing. Effects from low doses are usually restricted to the upper respiratory tract as hydrogen fluoride is absorbed by mucous membranes. In the case of exposure to high concentrations, hydrogen fluoride may also affect the lower respiratory tract causing pulmonary oedema which may take up to 36 hours to develop.

Ingestion of hydrofluoric acid can cause burning of the mouth and throat, nausea, vomiting and abdominal pain. In severe cases oesophageal or gastric perforation can occur.

Dermal exposure can cause severe and deep burns. There may be a blue-green discolouration of the skin in severe cases. Eye contact may cause conjunctivitis, chemosis and necrosis.

Acute exposure by any route can cause systemic effects including electrolyte disturbances that can lead to convulsions, CNS depression and cardiac conduction abnormalities.

There are limited data available on the effects of long-term exposure to hydrogen fluoride.

Kinetics and Metabolism

Hydrogen fluoride is water soluble and forms corrosive hydrofluoric acid when in contact with moisture [1, 2].

Fluoride ions are readily released from water soluble fluoride compounds including hydrogen fluoride and are almost completely absorbed. A study in rats reported that the majority of inhaled hydrogen fluoride was absorbed by the lining of the upper respiratory tract [3]. Hydrogen fluoride readily penetrates intact skin, nails and deep tissue layers [4].

Following absorption fluoride is distributed to the intracellular and extracellular water of tissues and organs [5]. However, it accumulates in calcified tissues, approximately 50% of absorbed fluoride is deposited into the bones [3].

The main route of excretion of fluoride ions is via the urine; small amounts are excreted in the faeces, urine and sweat [2, 3, 5].

Sources and Route of Human Exposure

Hydrogen fluoride is a corrosive gas or liquid with a boiling point of 19.5 °C. It readily dissolves in water to form hydrofluoric acid. Inhalation and dermal contact are the main routes of exposure [3].

Hydrogen fluoride may be released into the environment from both natural sources and anthropogenic activities. Natural sources of hydrogen fluoride include volcanoes, weathering of minerals and marine aerosols [3]. Volcanic activity is a major source of naturally occurring hydrogen fluoride in the atmosphere [2, 6]. Hydrogen fluoride is formed as a by-product during various industrial processes including the production of phosphate fertiliser, aluminium and steel production, and the ceramic industry [3].

Environmental exposure to hydrogen fluoride is expected to be minimal as it does not persist; it is rapidly transformed into other fluoride compounds [2, 3].

Exposure to hydrogen fluoride is more likely to occur in the workplace where it is produced or used [3]. Examples of occupations where exposure may occur include metal extracting, refining, polishing and glass etching [2-4]. However, there are workplace exposure limits set by the Health and Safety Executive to protect the health of workers. The 8-hr long-term exposure limit for hydrogen fluoride is 1.5 mg/m³ and the 15 minute short-term exposure limit is 2.5 mg/m³ [7].

Health Effects of Acute/Single Exposure

Human data

General toxicity

Hydrogen fluoride is corrosive to tissues. Systemic effects caused by exposure to hydrogen fluoride include hypocalcaemia, hypomagnesaemia, metabolic acidosis and hyperkalaemia. Myoclonus, tetany, convulsions, CNS depression, cardiac conduction abnormalities and arrhythmias may occur secondary to electrolyte disturbances [4]. Fluoride ions are responsible for the systemic effects of hydrogen fluoride. The effects of fluoride ions within the body will not be discussed within this document unless it is evidenced as a direct result of exposure to hydrogen fluoride.

Inhalation

Exposure can arise from both the inhalation of hydrogen fluoride gas directly, or from the fumes emitted by concentrated hydrofluoric acid [4]. Inhalation of hydrogen fluoride may cause irritation of the eyes and nose with sore throat, cough, chest tightness, headache, ataxia and confusion [4]. Slight irritation to the eyes and nose could arise following exposure to hydrogen fluoride at a concentration as low as 1.16 mg/m³ [3]. Dyspnoea and stridor due to laryngeal oedema can also occur [4, 8]. Acute exposure to hydrogen fluoride can be fatal and is usually as a result of pulmonary oedema [1, 4, 8].

In a volunteer study 20 male volunteers were exposed for 1 hour to a constant concentration of hydrogen fluoride within 3 groups: 0.17-0.58 mg/m³, (n=9); 0.71-2.4 mg/m³, (n=7); and 2.5-5.2 mg/m³, (n=7). They were asked to rate respiratory parameters using a questionnaire and undertake a lung function test. At concentrations ≥ 2.5 mg/m³, increased symptom scores of the upper airways (nose and throat) were recorded. Only mild symptoms were reported at the lower exposure concentrations. No other significant differences were found between the concentration groups. None of the subjects had obvious signs reflecting bronchial constrictions. Almost all symptoms had disappeared 4 hours after the end of the exposure [9].

In a second volunteer study, 10 volunteers were exposed for 1 hour to hydrogen fluoride 3.3-3.9 mg/m³. Nasal lavage was performed on the subjects immediately and 1.5 hours after end of exposure. A change in neutrophil numbers correlated significantly with reported airway symptoms and there was an increase in tumour necrosis factor- α (TNF α) and the total protein content of nasal lavage fluid [10].

Two volunteers exposed to hydrogen fluoride for several minutes or shorter experienced smarting in the nose, eyes and respiratory tract irritation at concentrations of 26 mg/m³, marked conjunctival and nasal mucosae irritation at 50 mg/m³, and pain to exposed skin and respiratory irritation at 100 mg/m³ [3].

Following accidental dermal contact with hydrofluoric acid, patients have experienced concurrent inhalation following off gassing from dermal exposure. These individuals went on

to develop respiratory problems such as pulmonary oedema, pulmonary haemorrhagic oedema and tracheobronchitis. Exposure concentrations were not reported [3].

Following accidental exposure of 13 workers to hydrofluoric acid mist at a maximum concentration of 125-170 mg/m³ for 2 minutes, workers were treated immediately with 4 mL of 2.5% calcium gluconate through a nebuliser. Workers reported no dermal or ocular burns, only minor upper respiratory tract irritation and none developed pulmonary oedema [11].

In 2012, an accidental spill of 8-12 tons of 100% hydrogen fluoride, at a fluoride manufacturing plant in South Korea, resulted in exposure of industrial workers and local residents (with a 2 km radius). Five workers at the site died following the release and many workers and residents received treatment in hospitals. The main symptoms reported were: respiratory issues such as haemoptysis and dyspnoea, gastrointestinal symptoms including nausea and indigestion, neurological symptoms such as headache and numbness, and sore throat and lip pain. Gastrointestinal symptoms were suggested to have occurred due to large volumes of the gas being inhaled and the hydrogen fluoride being absorbed into the lower respiratory system [12].

Ingestion

Ingestion of dissolved hydrogen fluoride (as hydrofluoric acid) is likely to cause burns to the mouth, throat with retrosternal and abdominal pain. The larynx may also be affected causing oedema, airway obstruction and difficulty in clearing bronchial secretions. There is often hypersalivation, vomiting, haematemesis and hypotension. Oesophageal or gastric perforation may occur which may develop over weeks or months [4].

Ingestion of hydrofluoric acid can also produce systemic effects and may be fatal [13].

Dermal/ocular exposure

Dermal contact with hydrofluoric acid can cause severe and deep burns that are extremely painful and difficult to heal [4]. In severe cases there may be whitish discoloration, or a blue-grey discoloration to the skin followed by rapid tissue destruction and necrosis [3]. Hydrofluoric acid solutions as low as 2% may cause burns if they remain in contact with the skin for long enough [4].

Hydrogen fluoride can be absorbed through the skin with the fluoride ion penetrating tissues deeply. This can cause cellular and systemic effects [13]. Decalcification of underlying bone can occur [8].

Changes in electrocardiograms have been reported following dermal exposure, which were reversible within 3 days [3, 6, 14].

Ocular exposure to hydrogen fluoride can result in conjunctivitis, conjunctival oedema, corneal epithelial coagulation and necrosis [4]. The severity of eye burns caused by hydrogen fluoride is due to the pH and the toxicity of the F⁻ ion. The initial damage caused by the acidity of the hydrogen fluoride enables the fluoride ion to penetrate into deeper layers of tissue where it causes severe eye lesions [3].

Delayed effects following acute exposure

Development of dermal burns may be delayed from time of exposure. Anhydrous or hydrogen fluoride/hydrofluoric acid solutions of greater than 50% may have immediate symptom onset; for solutions between 20-50% onset of symptoms may take up to 8 hours, while solutions less than 20% onset may take up to 24 hours [4, 8, 15].

Following inhalation, haemorrhagic pulmonary oedema with increasing breathlessness, wheeze, hypoxia and cyanosis may take up to 36 hours to develop [4].

Animal and in-vitro data

Inhalation

A number of studies and reviews have been conducted on the effects of acute inhalation of hydrogen fluoride in a range of laboratory animals [1-3, 8]. Table 1 provides a summary of reported inhalation LC₅₀ values.

Table 1: Reported inhalation LC₅₀ values for laboratory animals *.

Species	Duration (min)	mg/m ³ HF
Rat	5	4075
Rat	15	2205
Guinea pig	15	3548
Rat	30	1674
Rat	60	1061-1160
Mouse	5	5196
Mouse	60	379-417
Rhesus monkey	60	1476
References [1-3, 8, 16]		

Rats exposed to hydrogen fluoride for 5 minutes displayed moderate eye and nasal irritation at concentrations of 614 mg/m^{3*}, severe eye and nasal irritation at 1,179 mg/m^{3*}, and respiratory distress and weakness at 1,994 mg/m^{3*}. Thirty minutes of exposure at 820 mg/m^{3*} caused nasal fibrinonecrotic rhinitis and fibrin thrombi in the submucosa and haemorrhage. At 1,066 mg/m^{3*} nasal lesions and necrosis and inflammation, and at 1,129 mg/m^{3*} increased activity, respiratory distress and severe eye and nasal irritation was reported. After one hour of exposure, eye and nasal irritation in the rat increased in severity with increasing concentrations from occasional eye irritation at 84 mg/m^{3*}, to moderate irritation at 239 mg/m^{3*} [2, 16].

Exposure of rats to 1,100 mg/m³ of hydrogen fluoride gas for 30 minutes resulted in decreased ventilation rates of 27%, during and 24 hours after exposure and a 10% reduction in body weight after 24 hours [2]

Studies in mice reported that exposure to hydrogen fluoride at concentrations of 110-123 mg/m³ resulted in respiratory depression in 50% of animals [3].

*Converted from ppm to mg/m³ using 0.82 as the conversion factor [17]. Protective Action Criteria, *Table 1: Chemicals of Concern and Associated Chemical Information*. 2012.

Ingestion

There are no data available on the acute ingestion of hydrofluoric acid in animals.

Dermal/ocular exposure

Severe skin damage including blistering, oedema and coagulative necrosis down to the dermal muscular junction, was seen in rats following the application of 50 μ L of a 70% solution of hydrogen fluoride to shaved skin for 1 minute. The wounds took between 35-56 days to heal [3].

In a study conducted according to OECD test guideline 404 for skin irritation, rabbits exposed to 5 ml of a 5% hydrogen fluoride solution for 4 hours showed marked eschar formation and destruction of the underlying tissue after 24 hours. The lesions did not recover within 14 days [3].

In a study using rabbits, a 100 μ L of a 0.13 % or 1.06 % aqueous solution of hydrogen fluoride was applied to the eye. The 1.06 % solution caused corneal opacity, iritis, conjunctival oedema and redness. In another study in rabbits hydrogen fluoride solutions from 0.5 up to 20% (quantity unknown) were administered to the rabbit's eye, the 20% solution caused immediate and extensive ocular damage [3].

Health Effects of Chronic/Repeated Exposure

Inhalation

Data are limited on the repeated or prolonged exposure to hydrogen fluoride.

In a sub-chronic volunteer study with exposure to hydrogen fluoride for 6 hours/day for 15-50 days: eye, nose and skin irritation was reported at 1.7 mg/m³ [2].

Pulmonary function was not affected in individuals occupationally exposed to an average hydrogen fluoride concentration of 0.82 mg/m³ and no increase in respiratory complaints was reported in workers exposed to concentrations below 2.5 mg/m³. However, a minimal increase in bone density was overserved in workers exposed to less than 3.5 mg/m³ hydrogen fluoride [3].

Skeletal fluorosis has been reported in workers chronically exposed to hydrogen fluoride. However, exposures are usually to both hydrogen fluoride and fluoride dusts and the exposure concentrations are not reported or were estimated [1,2]. Therefore, it is not possible to draw any definitive conclusions.

Ingestion

There are currently no data available on the effects of chronic ingestion of hydrogen fluoride in humans.

Dermal/ocular exposure

In a volunteer study five individuals were exposed to hydrogen fluoride for 6 hours/day at concentrations ranging from 1.2–3.9 mg/m³ for between 10-50 days. At below 1.6 mg/m^{3*} volunteers experienced symptoms of discomfort slight stinging to the eyes and facial skin, and slight irritation of the nasal mucosa. At concentrations of on average of 2.78 mg/m³ and above, erythema and desquamation of the superficial epithelium of the facial skin were observed. Symptoms of discomfort disappeared following discontinuation of the study and redness persisted for only short while after [3, 18].

Genotoxicity

There are currently no data available on the genotoxicity of hydrogen fluoride/hydrofluoric acid in humans.

Carcinogenicity

Hydrogen fluoride and hydrofluoric acid are not considered to be a carcinogen [8].

Reproductive and developmental toxicity

There are currently no data available on the reproductive and developmental effects of hydrogen fluoride/hydrofluoric acid in humans.

* Converted from ppm to mg/m³ using 0.82 as the conversion factor [19]

Animal and in-vitro data

Inhalation

Changes in dental enamel, airways and formation of irregular shaped bone cavities were reported in rats following inhalation of hydrogen fluoride at 1 mg/m³ for 6 hours/day for 1 month [3].

In a sub-chronic study male and female rats (20 per group) were exposed to 0, 0.082, 0.816 and 8.16 mg HF/m³ (nominal values; actual concentrations were 0.098, 0.72 and 7.52 mg/m³) for 6 hours/day 5 days/week. Haematological changes, clinical signs, changes in body and organ weight and death (5 males, 1 female) were observed in the 8.16 mg/m³ dose group. The reported nominal NOAEL for this study is 0.816 mg/m³ (actual value 0.72 mg/m³) [3].

Ingestion

There is currently no data available on the effects of chronic ingestion of hydrogen fluoride in animals.

Genotoxicity

The data available on the genotoxicity of hydrogen fluoride is very limited therefore it is not possible to draw any definitive conclusions [3].

Carcinogenicity

Hydrogen fluoride is not considered to be a carcinogen [8].

Reproductive and developmental toxicity

There are currently no data available on the reproductive and developmental effects of hydrogen fluoride.

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