Toxicology Letters 248 (2016) 25–33

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

Dermal absorption and skin damage following hydrofluoric acid exposure in an *ex vivo* human skin model

Kathrin Dennerlein[a,*], Franklin Kiesewetter[b], Sonja Kilo[a], Thomas Jäger[a], Thomas Göen[a], Gintautas Korinth[a,1], Hans Drexler[a,1]

[a] Institute and Out-Patient Clinic of Occupational, Social and Environmental Medicine Friedrich-Alexander University Erlangen-Nürnberg (FAU), Schillerstrasse 25/29, 91054 Erlangen, Germany
[b] Department of Dermatology, University Hospital Erlangen, Ulmenweg 18, 91054 Erlangen, Germany

HIGHLIGHTS

- The dermal absorption and skin damaging potential of HF was assessed *ex vivo*.
- Fluoride rapidly penetrates human skin under formation of a notable skin reservoir.
- Epidermal alterations are obvious already after exposure to 5% HF for 3 min.
- HF concentration is the main factor determining absorption and skin damage.

ARTICLE INFO

Article history:
Received 23 October 2015
Received in revised form 4 December 2015
Accepted 26 February 2016
Available online 27 February 2016

Keywords:
Hydrofluoric acid
Ex vivo human skin model
Diffusion cell
Percutaneous absorption
Skin damage

ABSTRACT

The wide industrial use of hydrofluoric acid (HF) poses a high risk for accidental dermal exposure. Despite local and systemic hazards associated with HF, information on percutaneous penetration and tissue damage is rare. In the present *ex vivo* study, the dermal absorption of HF (detected in terms of fluoride ions) was quantified and the skin damaging potential as a function of concentration and exposure duration was assessed. Percutaneous penetration of HF (c = 5, 30, and 50%) at 3 exposure durations (3, 5, and 10 min) was investigated in a static diffusion cell model using freshly excised human skin. Alterations of skin were histologically evaluated. HF rapidly penetrated through skin under formation of a considerable intradermal reservoir (~13–67% of total absorbed fluoride). Histologically, epidermal alterations were detected already after exposure to 5% HF for 3 min. The degree of skin damage increased with rising concentration and exposure duration leading to coagulation necrosis. For HF concentrations of ≥30%, skin damage progressed into deeper skin layers. Topically applied HF concentration was the principal parameter determining HF induced skin effects. The intradermal HF retention capacity associated with progression and prolongation of HF induced skin effects must be considered in the review of skin decontamination procedures.

1. Introduction

Dermal contact to acidic solutions might cause skin irritation and corrosion of varying severity and occasionally permanent damage. Characteristic for hydrofluoric acid (HF, CAS 7664-39-3) is the combination of the local acidic corrosiveness and the concurrent local as well as systemic toxicity. Due to this dual mode of action particular caution is warranted in dealing with HF.

Primarily, HF is used in the chemical industry, *e.g.* in the manufacture of fluorocarbons and fluoropolymers. The petrochemical industry needs aqueous solution of hydrogen fluoride as a catalyst in the fuel production (EUROFLUOR, 2015). The etching

Abbreviations: CAS, chemical abstract service; HF, hydrofluoric acid; KOH, potassium hydroxide; LC-ICP-MS, liquid chromatography linked with inductively coupled plasma-mass spectrometry; NaCl, sodium chloride; pK_a, negative decadic logarithm of the ionisation constant of an acid; SD, standard deviation; SEM, standard error of the mean.

* Corresponding author.
E-mail address: Kathrin.Dennerlein@ipasum.med.uni-erlangen.de (K. Dennerlein).

[1] These authors contribute equally to this work.

http://dx.doi.org/10.1016/j.toxlet.2016.02.015
0378-4274/

properties of HF are widely used in the semiconductor device fabrication and other fields of electronic as well as glass and metalworking industries (IPCS, 1990; EUROFLUOR, 2015). To a small extent, low concentrated HF is also being used in commercial products, *e.g.* pesticides, rust remover (Bennion and Franzblau, 1997; Perry, 2001) or aluminium cleanser (Wong et al., 2012). In 2012, the production of HF in Europe amounted to 240,000 tons with more than 50,000 workers involved in the fluoride industry (EUROFLUOR, 2015). Despite enormous efforts in the area of occupational health and safety, the rise in production and use of HF increases the risk of accidental exposure, mainly by dermal contact or inhalation. Occupational exposure limits for hydrogen fluoride and other fluoride-containing compounds focus on respective air concentrations and do not incorporate a potential dermal route of uptake for the lipophilic HF (SCOEL, 1998). However, dermal exposure and uptake of fluoride contributes to the internal burden and therefore to the extent of health effects caused by HF. Furthermore, accidental exposure to HF usually involves the skin resulting in dermal fluoride uptake. According to the Taiwan Poison Control Center, 80% of 324 workplace-related incidents between 1991 and 2010 associated with HF have been caused by dermal contact (Wu et al., 2013).

Following dermal exposure to lipophilic HF, the systemic toxicity of fluoride is a serious hazard since fluoride is known to act as calcium scavenger. A lack of endogenous calcium, which is essential for the maintenance of several physiological as well as biochemical processes in the human organism can cause electrolyte imbalances and eventually fatal heart rhythm disturbances (Dalamaga et al., 2008). Lethal accidents have been reported in workers at different workplace settings following burns of as little as 2.5–8% of their skin surface with high concentrated HF (≥70%) leading to ventricular fibrillation, metabolic acidosis and multiple organ failure (Tepperman, 1980; Gubbay and Fitzpatrick, 1997; Blodgett et al., 2001).

Although HF is a weak acid ($pK_a = 3.19$; dissociation constant = 4×10^{-4} mol/l), dermal absorption may lead to damage of deeper tissue. Dependent on the concentration of HF, skin surface damage and pain might occur delayed (NIH, 1943). HF-induced skin damage was investigated in several histological studies in different species (Dunn et al., 1992; Seyb et al., 1995; Burgher et al., 2011a, 2011b). In rabbits, occlusive application of HF at concentrations up to 2% for up to 4 h only led to slight skin irritation within the first hour of exposure, but subsequently to subcutaneous edema, ulceration and necrosis within 96 h (Derelanko et al., 1985). In contrast, high concentrated HF immediately damaged the skin. Already 5 min after a 60 s exposure to 70% HF, necrosis of skin tissue was evident in rats (Bracken et al., 1985).

Although the danger of HF exposure is widely known the serious consequences of the systemic toxicity are still difficult to control. The systemic effects of HF (*e.g.* electrolyte imbalances) can last or even getting worse over days. Therefore information on the pattern of percutaneous absorption, in particular the time course of HF penetration is of particular importance, providing a basis for the assessment of decontamination strategies and the improvement of intensive care management.

So far, the amount of fluoride taken up dermally after exposure to HF was assessed in the blood serum (Kono et al., 1982; Derelanko et al., 1985; Bordelon et al., 1993). However, these studies do not permit qualitative and only to a limited extent quantitative statements regarding the dermal penetration patterns of HF. Due to the health hazards associated with the exposure to HF *in vivo* studies cannot be justified. Since animal skin shows significant differences compared to human skin (Bronaugh et al., 1982; ECETOC, 1993) which restricts the transfer of results from animal-studies to humans, the implementation of reliable *ex vivo* human skin models is crucial (Williams, 2006). In the present study the kinetics of dermal fluoride absorption as well as the extent of histological skin damage was investigated after exposure to different HF concentrations for 3–10 min by an *ex vivo* model using freshly excised viable human skin.

2. Materials and methods

2.1. Test compound

Hydrofluoric acid (HF) was selected as test compound for the experiments. 5% (w/w) and 50% HF (w/w) (both VLSI Selectipur®) were obtained from BASF (Ludwigshafen, Germany), 30% HF (w/w) was purchased from AppliChem (Darmstadt, Germany).

2.2. Skin preparation

Freshly excised human skin was anonymously obtained from a local clinic after plastic reduction surgery. Subsequently the skin was stripped from subcutaneous fat tissue using a scalpel. For dermal absorption studies, full-thickness abdominal skin (~2.5 mm) from 2 female and one male donor (age: 20–36 years) was used immediately after excision.

Histological studies were carried out with freshly excised, full-thickness thigh skin (female, age: 55 years). The integrity of skin was visually assessed prior to mounting on diffusion cells and after the experiments by inspection of every single kinetic penetration curve.

2.3. Dermal penetration studies

For percutaneous penetration experiments, the skin was fixed between exposure and receptor chambers of static PermeGear® diffusion cells (flat flange joint vertical system; 9 mm orifice; exposure area 0.64 cm^2; receptor chamber volume ~5 ml) (SES GmbH, Bechenheim, Germany), which are similar to the cells described by Franz (1975). The receptor chambers were filled with 0.9% aqueous NaCl solution and equipped with magnetic Teflon® stirring bars (500 rpm). Since HF is a parent substance in the manufacture of Teflon® products the background contamination potential of the stirring bars was assessed in preliminary experiments. Blank sample analysis did not indicate any migration of HF from the stirring bars. However, new stirring bars were taken for each experiment to avoid any transfer contamination from previous experiments. The receptor chambers were heated to 35 °C during experiments by a circulating thermostatic water bath (MV-4; Julabo GmbH, Seelbach, Germany). After 1 h skin surface temperature was measured by a digital precision thermometer (GMH 1160 with GOF 500 universal probe, type K; Greisinger electronic GmbH, Regenstauf, Germany). This procedure assures a skin surface temperature of about 32 ± 1 °C. For control of background contamination, blank receptor fluid samples (500 µl) were taken from selected receptor chambers prior to HF exposure. Since higher concentrated HF fumes on air as observed in preliminary tests with 50% HF a volume of 160 µl/0.64 cm^2 HF was chosen to avoid diminishing of the applied concentration by the emission of hydrogen fluoride into the ambient air. The volume for 5 and 30% HF was adjusted accordingly. Percutaneous penetration of HF was assessed for each exposure scenario using 2 membranes of a skin donor in parallel. Following equilibration 160 µl (250 µl/cm^2) of 5, 30, and 50% HF were applied as single doses (12.1, 78.6, and 138.8 mg fluoride/cm^2, respectively) on the epidermal side of the skin. After 3, 5, or 10 min of exposure, the skin surface was gently wiped using dry cotton swabs to remove the excess of HF. The exposure chambers of diffusion cells were left open until the end of experiments. Experiments with 5 and 30% HF were carried out using skin of 3 donors, studies with 50% HF using skin of 2 donors.