HEXAFLUORINE®
SOLUTION

Emergency washing solution for ocular and cutaneous splashes of **hydrofluoric acid**

Updated review of current knowledge of **hydrofluoric acid** injuries

Version July 2015

Hexafluorine® Solution
- Toxicological data
- Comparative studies of washing effectiveness
- User feedback
- Recommendations

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PREVOR
ANTICIPATE AND SAVE
Toxicology Laboratory & Chemical Risk Management

Hexafluorine® Solution Dossier

This dossier is a collection of data about hydrofluoric acid (HF) burns and Hexafluorine® solution. It is a compilation of toxicological data, *in vitro* studies and *in vivo* development of the HF burn and comparison of decontamination solutions' efficacy. Cases of ocular or cutaneous splashes by pure or mixed hydrofluoric acid having occured in industry and been washed with water or Hexafluorine® solution, followed in some case reports by calcium gluconate application, are reported and analysed.

There is a glossary in chapter 7 where you will find the detailed definitions of the technical words used herein. Each term which appears in the glossary is written in blue in the dossier.

The authors would like to thank all health and safety professionals who have been involved in this project by sharing their experience or rereading this new edition.

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July 2015 edition

- Summary -

Introduction

Developed by Prevor, Hexafluorine® solution is an emergency rinsing solution for washing ocular and cutaneous splashes of hydrofluoric acid (HF) and fluoride ions in an acidic medium.

Objective

This file summarizes data showing the efficacy of Hexafluorine® solution in the decontamination of HF splashes, when used as a primary care.

Methodology

In vitro, *ex vivo* and *in vivo* comparative experiments compare the efficacy of various protocols: water, water followed by calcium gluconate application and Hexafluorine® solution or Hexafluorine® solution followed by calcium gluconate application. Case reports of use of these washing protocols for ocular and cutaneous splashes of hydrofluoric acid occurred in the industrial environment are also reported in this dossier.

Results

The *in vitro*, *ex vivo* and *in vivo* experiments have highlighted the efficacy of Hexafluorine® solution in the decontamination of HF splashes in comparison with rinsing with water only and rinsing with water followed by one application of calcium gluconate.

An *ex vivo* model of human skin explants has been used to study the tissular impact of 70 % hydrofluoric acid and to estimate the efficacy of decontaminating protocols.

A similar *ex vivo* model using enucleated rabbit eyes in association with the OCT-HR (*Optical Coherence Tomography – High Resolution*) technique, has enabled the modeling of HF penetration into the eye and of the Hexafluorine® solution efficacy *versus* water or 2.5 % calcium gluconate solution which is the current controversial standard.

32 cases of ocular and cutaneous splashes of hydrofluoric acid washed with Hexafluorine® solution have been reported in the industrial environment.

Five isolated cases

A worker fell into a tank containing 30 liters of concentrated hydrochloric acid (HCl), 233 liters of 59 % hydrofluoric acid in 1505 liters of water. He was completely immersed in this bath. Another operator was hit by an ocular 40 % hydrofluoric acid splash while filling a stainless steel stripping bath. Two workers had cutaneous 5 % hydrofluoric acid splashes. In a glasswork plant, an operator was splashed on the cheek by a 70 % hydrofluoric acid vapour.

Two series of cases

- 11 cases of hydrofluoric acid ocular and cutaneous splashes have occurred in a German metalworking unit: 6 workers were hit by ocular and cutaneous 40 % hydrofluoric acid splashes and 5 operators were victims of 6 % HF / 15 % nitric acid (HNO_3) mixture splashes. A 40 % HF splash targeted more than 16 % of the total body surface area.

- In a Swedish metalworking company, 16 ocular and cutaneous splashes occurred between 1998 and 1999, two of which were 70 % HF splashes onto the left forearm and in the buccal cavity and the other 14 involving a pH 1 HF/HNO_3 mixture.

Those 32 workers were washed with Hexafluorine® solution as primary care. There was no occurrence of severe injury in any case. The worker whose cheek was splashed by 70 % HF vapour only developed a painless erythema. The operator who fell into a HCl/HF bath only had a minor injury on the abdomen, whereas his left eye that was washed with water developed a severe ocular lesion. No secondary intensive extended treatment was necessary in any case. Most of those workers did not require lost work time. 3 of them were kept in hospital for 2 to 3 days for observation.

In these series, five potentially lethal cases of HF splashes generated no local lesion or general clinical signs.

Recently, an isolated case, initially washed with water, then later decontaminated with Hexafluorine® solution and having benefited from a secondary treatment with calcium gluconate, did not develop systemic effects and favorably evolved within 90 days with grafting.

Conclusion

Setting emergency protocols for hydrofluoric splashes and initial rinsing with Hexafluorine® solution have enabled either preventing the occurrence of HF-induced lesions or to significantly lessen their severity. Washing with Hexafluorine® solution can be followed by calcium gluconate treatment if it is required by the company's medical protocol or in cases of delayed use of Hexafluorine® solution.

Hexafluorine® solution

Emergency rinsing solution for the decontamination
of ocular and cutaneous splashes of hydrofluoric acid

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Introduction

In industrial environment, hydrofluoric acid (HF) is extensively used for fluoration of organic compounds (fluorocarbons including cooling agents) and inorganic compounds (such as uranium in the nuclear industry), in processing fluoropolymers and their derivatives, in metalworking industry for surface treatment of numerous metals including stainless steel, in the oil industry - specifically for refining operations, in glass and crystal industry for engraving and polishing, in the ceramics and semiconductors industry for its action on the quartz, in the building industry for surface cleaning and obviously HF is used in chemistry labs.

In lower concentrations and smaller volumes, HF is also present in cleaning products (polishing of aluminium wheel rims, rust removing agent in laundries, wood cleaning products…).

The world production is increasing and exceeds one million tons annually.

It's therefore easy to understand that hazardous situations are numerous and diverse. While typically hands and other uncovered body parts are the targeted cutaneous surfaces, some much more extensive burns occur combining ocular and respiratory injuries with potentially lethal consequences.

Nevertheless, hydrofluoric acid is dangerous whatever its concentration. Its action is both corrosive and toxic, and it can be immediate or delayed, painful or painless, depending on concentration of the involved product. It leads to severe local burns, and also to general alterations, particularly respiratory lesions or heart deseases that can be life threatening.

All people involved in prevention in industrial environment have the experience of hazards due to handling of hydrofluoric acid. Therefore, the first responsibility is to set up a hazard recognition, training and prevention policy for all operators exposed to HF, in accordance with the regulation for chemical risk assessment and management in the workplace. However, despite such care, ocular or skin splashes can occur during common operations or in critical conditions: stripping, polishing, grease-removing, immersion in baths, facilities cleaning, maintenance operations, pipe repairing, changing gates, and decanting operations…

In the 1996 International Meeting about Chemical Burns in La Baule, France, Dr Gouet illustrated the severity of HF exposure with a presentation of the evolution of a cutaneous 70 % HF injury (Fig.1).

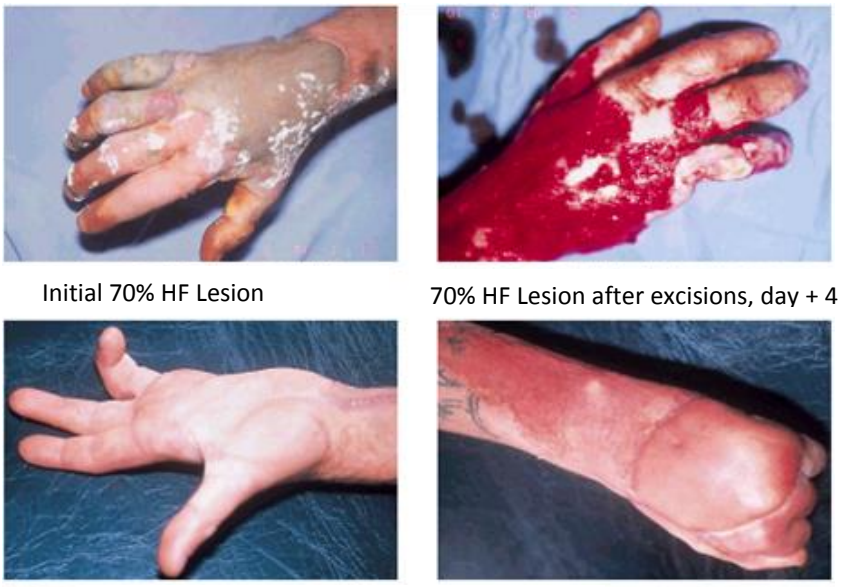


Figure 1: Evolution of a cutaneous 70 % HF lesion

This example shows that an effective decontamination device must be set up, on the accident scene itself.

Numerous works have aimed at developing an effective decontamination of hydrofluoric acid injuries. The most widely used is water rinsing, combined with secondary local applications of calcium gluconate gel or gauzes, and sometimes completed with localy subcutaneous, intravenous and or intra-arterial infusions of calcium gluconate.

However, both epidemiological studies and *in vivo* experiments show that the achieved results are not always satisfactory, particularly when HF concentrations are high. Even with early intervention there is often a lesion. The situation may require surgical operations: excision of necrotic tissues, amputation of limb extremities (hands are the most oftenly exposed parts)[1]. There are few studies on deeper lesions. As for eyes, lesions induced by concentrated HF lead to rapid opacification and ulceration of the cornea[2].

In such conditions, severe psychological consequences may be combined with functional sequelae. Finally, some accidents due to concentrated hydrofluoric acid splashes are lethal.

The incidence of lesions due to hydrofluoric acid can represent 50 % of all injuries due to acids admitted to a burn center[3].

Because of HF hazards and handling risks, PREVOR Laboratory, specialized in chemical risk, has developed a specific emergency rinsing solution, named Hexafluorine® solution, which can effectively decontaminate ocular or cutaneous hydrofluoric acid splashes. Rinsing with Hexafluorine® solution limits or stops the diffusion of hydrofluoric acid into the skin or the eye and brings both its corrosive potential and its toxic action under control. Thus it prevents severe alterations of the biological balances of cells constituting the living tissues due to this acid.

This dossier gathers:

- *In vitro*, *ex vivo* and *in vivo* experiments supporting the comparison of the efficacy of Hexafluorine® solution rinsing to that of the following common protocols respectively: water, water followed by calcium gluconate…

- Clinical cases decontaminated with Hexafluorine® solution in the industrial environment. Companies using hydrofluoric acid share their experience of emergency rinsing with Hexafluorine® solution, either by a general account of benefits observed by exposed staff when used, by information concerning isolated cases, or through a series of splash cases. Splashes may be ocular or cutaneous and due to hot or cold and diluted or concentrated hydrofluoric acid. Hydrofluoric acid can also be mixed with other acids. Globally, more than 30 cases of ocular or cutaneous splashes washed with Hexafluorine® solution are described herein, three of which are cutaneous splashes with 70 % hydrofluoric acid.

1 Hydrofluoric Acid induced Lesions: a lethal risk

1.1 Mechanism of hydrofluoric acid lesions

Hydrofluoric acid has a double action[4,5]: corrosive and toxic (Fig.2)

Figure 2: Pictograms associated with hydrofluoric acid

- Corrosive action due to acid ions (H^+), which can attack superficial tissues (corneal epithelium or epidermis).
- Toxic action due to fluoride ions (F^-), which, due to the destruction of eye or skin superficial layers by the acid, can penetrate deeply, chelate calcium and magnesium, and thus disrupt the biological balances and lead to more or less severe biochemical, cellular and tissular disorders (Fig. 3). The disruption of various metabolic cycles is the cause of a variety of clinical signs observed: muscular, neurological, cardiac symptoms…

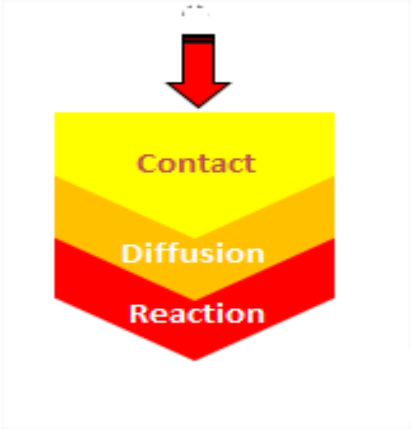


Figure 3: Process of reactivity of a chemical product

Systemic diffusion can be life threatening[6] depending on the concentration of HF solution and the percentage of altered body surface (Fig. 4).

Route of exposure	Body surface	HF concentration
Skin	1 %	Anhydrous
	5 %	> 70 %
	7 %	50-70 %
	10 %	20-50 %
	20 %	< 20 %
Ingestion		> 5 %
Inhalation		

Figure 4: Lethal systemic risk following a HF burn
depending on route of exposure concentration and affected body surface

McCulley[7] has proved the role of H^+ ions and F^- ions in the mechanism of ocular lesions formation. He compared lesions induced by:

- various concentrations of HF, which generates an epithelial ulceration before damaging deeper layers,
- pure hydrochloric acid, which destroys the epithelium,
- sodium and potassium chlorides and fluorides, which remain almost harmless to a safe epithelium though they are highly corrosive when put on an eye when the protecting layer of the epithelium is not present,
- fluoride ions in acidic medium (mixture of hydrochloric acid and sodium fluoride), which cause lesions that are similar to those due to HF.

McCulley proved that the acid's action mainly destroys superficial layers, whereas the fluoride ion only slightly operates on these layers. Then the destruction of these superficial layers allows the penetration and the diffusion of HF and fluoride ions released by HF into deeper tissues which develop liquefactive necrosis. This specific mechanism differentiates HF and other acids, particularly strong acids, which generates a coagulative necrosis with precipitation of tissue proteins[8] (see page 27 paragraph 2.1.2.2).

These various pathophysiological mechanisms due to hydrofluoric exposure can be extrapolated and pictured as follows for skin (Fig.5):

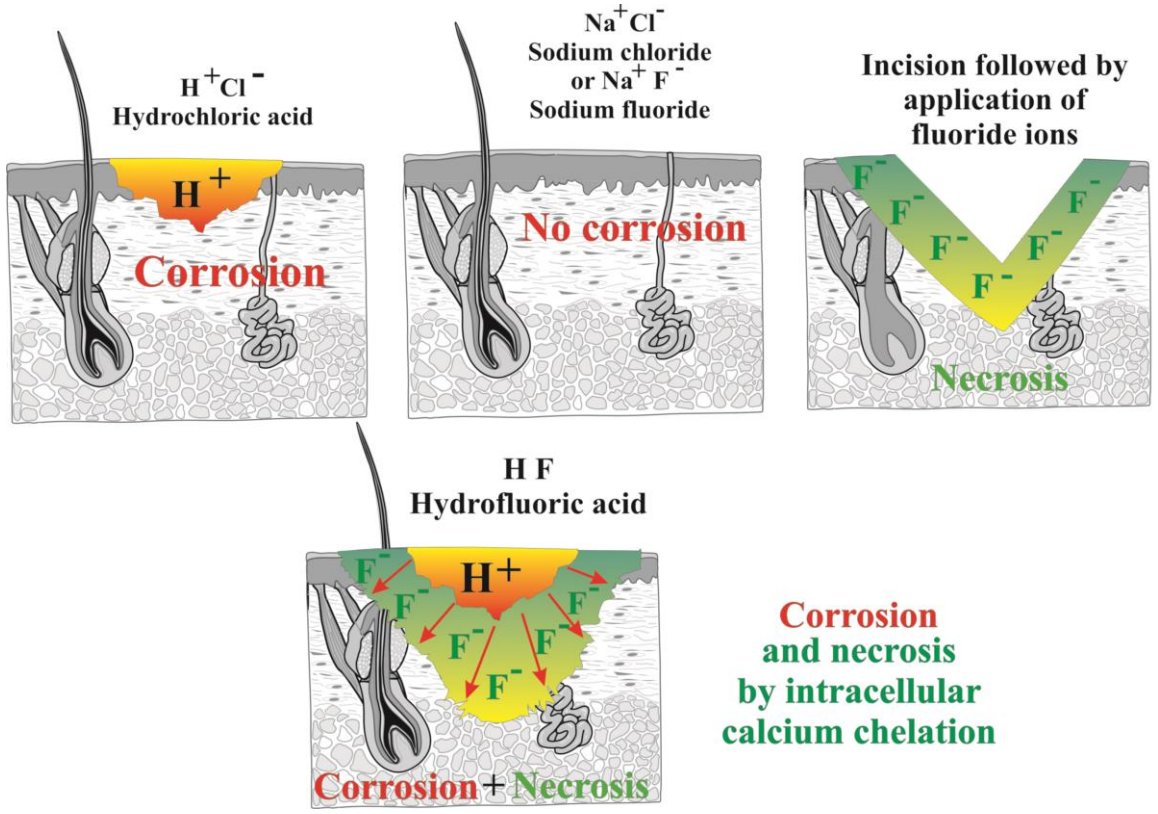


Figure 5: Mechanism of chemical lesion due to HF

Boink *et al* made similar observations[9].

The attack of H^+ ions on superficial layers stops when all the aggressive ions are consumed. When there is no acid function in the chemical in contact with skin, like with fluorides (for instance sodium fluoride, NaF), there is no ulceration. Penetration of fluoride ions into the epidermis remains limited and local lesions are negligible. Any penetration route, such as an incision, shows the intrinsic action of F^- ions. Helped by a rupture of the epithelial barrier, the velocity of penetration of fluoride ions is then proportional to the chemical concentration. A tissular necrosis progressively develops, and is inexorable as long as the F^- ions are free and reactive.

When fluoride ions are in an acid solution, their toxicity is hidden - which does not appear with fluorides in a non acidic solution. The toxicity of fluoride ions is revealed with the concomitant H^+ ions presence in the same solution ; specific lesions are generated that are identical to those due to HF.

The major attacks by HF can moreover necrotize the subjacent muscular masses and even cause a decalcification of deep bone structures.

Finally, the specific severity of lesions induced by hydrofluoric acid is definitely due to the synergic action of acid and the fluoride ions.

What are the pathophysiological mechanisms underlying the toxicity of fluoride ions?

- The chelation of fluoride ions by calcium and magnesium ions is responsible for metabolic disorders[10,11,12] leading to a secondary death of cells which progressively form tissular necrosis.
- Fluoride ions also damage cellular enzymes, and particularly metalloproteinases.
- Fluoride ions increase the permeability of cytoplasmic membranes[13] releasing potassium ions from intracellular compartment.

Whereas potassium is essentially an intracellular ion, its release into the external medium might be the cause of the strong stimulation of local nerve endings, which is at the origin of particularly intense pain of HF burns[14,15,16]. Another explanation might be that the initial corrosive action generates a secondary action of degeneration of the conjunctival tissue around vessels and nerves, thus causing painful stimulation[17]. Whatever the explanation, pain is a characteristic element and a good indication of lesions' evolution and the efficacy of decontamination during the course of an HF cutaneous lesion.

1.1.1 Cutaneous splashes

The appearance delay and the intensity of pain are relative to HF concentration. For very concentrated solutions, pain is immediate. For low concentration solutions, pain may be delayed by a few hours to one day or more.

The Division of Industrial Hygiene of the U.S.A. National Institute of Health[18] has classified HF injuries according to three classes of concentration (Fig. 6):

Concentration	Pain
50 % and more	Immediate, associated by tissue destruction that is visible rapidly
From 20 to 50 %	Delayed by 1 to 8 hours after contact (with erythema developing within the same timeframe)
Less than 20 %	Delayed by 24 hours or more (with erythema developing within the same timeframe)

Figure 6 : Time to onset of pain after contact with HF, depending on concentration

Whether the concentration is high or low, the splashed surface rapidly becomes erythematous and slightly edematous. Then, there is a whitish or greyish discoloration in the middle surrounded by a purplish ring (Fig. 7), such as observed in animal experimentation by Rusch et al[19].

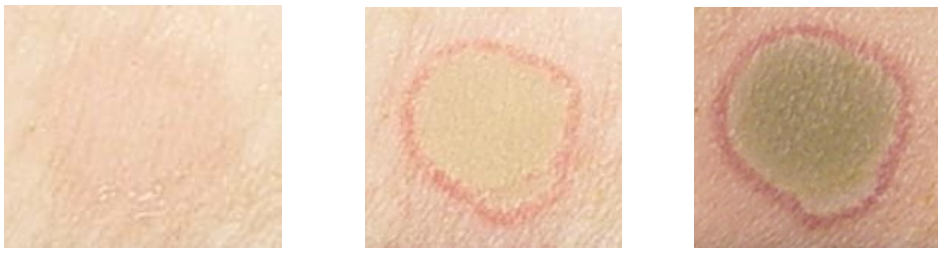


Figure 7 : Aspect of a 60 % HF lesion contact time 60 seconds
After the end of exposure, 15 minutes and 2 hours after the end of exposure (pig)

If the contact time increases, the damaged skin becomes red, then turns from grayish purple to blackish purple with important edema (Fig.7) and intense pain. The burn's evolution leads to blisters (phlyctenae), which may develop over 9 or 10 days. The excision of these blisters releases a brown liquid or a well organized blackish blue coagulate.

The 70 % HF penetration into skin has been experimentally observed on skin sections for the first time[20,21] with the use of an *ex vivo* model of human skin explants.

This work has enabled the real time observation of the kinetics of the appearance of cellular damages on histological sections by optical microscopy.

The diagram below is a reminder of different layers of normal skin as observed in low magnification optical microscopy (X40) (Fig.8).

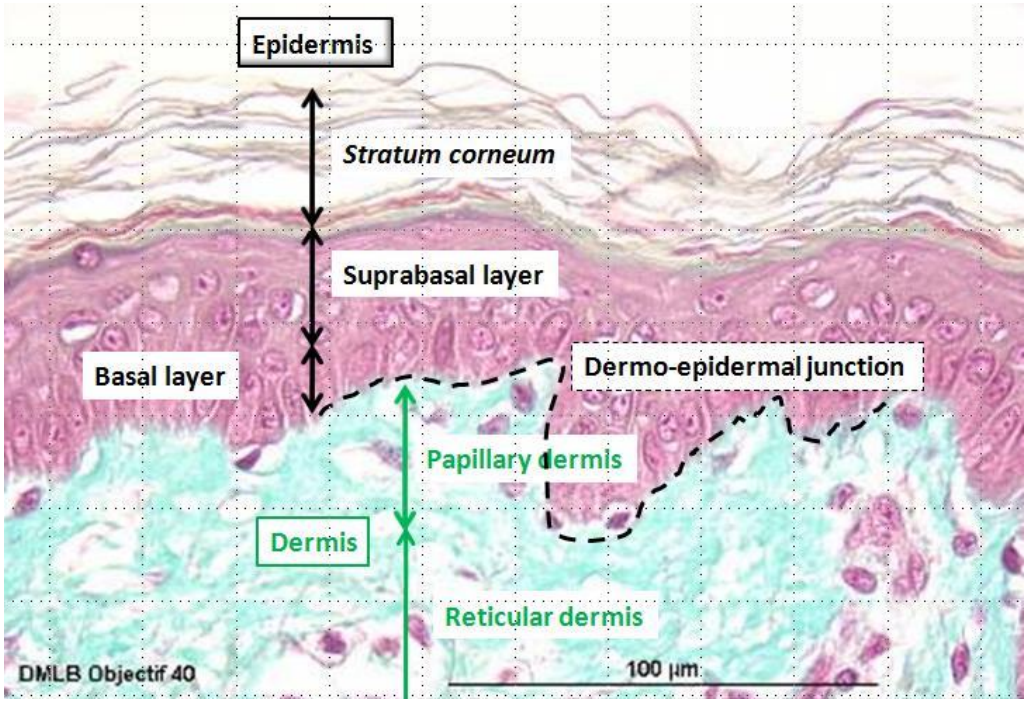


Figure 8 : The different layers of normal skin (PREVOR/BIO-EC Experiment)

Histological analysis of explants exposed to HF shows that penetration (Fig. 9) into the superficial layers of epidermis starts in the first minute of contact.

It definitely increases after 2 minutes of contact, with presence of a clear acidophilic (orange-colored) cytoplasm.

Lesions are greater after 3 minutes of contact with appearance of edematous cells in the epidermis and of slightly pyknotic cells nuclei in the papillary dermis.

After 4 minutes of contact, epidermal lesions are clear with clearly pyknotic nuclei in the papillary dermis (Fig. 10).

After 5 minutes of contact, lesions are marked in the epidermis and in the papillary dermis. They remain weak in the lower reticular dermis.

Therefore lesions spread step by step after 20 seconds of contact until they reach the deep layer of dermis after 5 minutes.

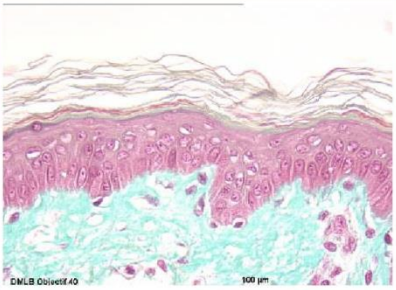
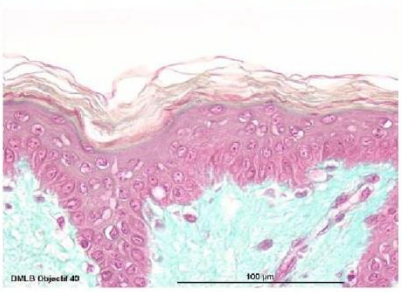
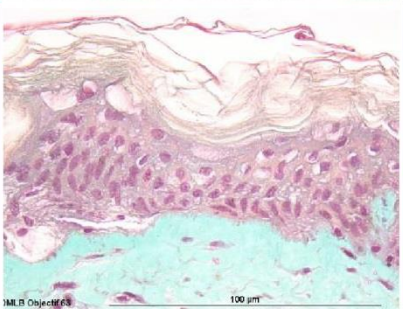
Explant exposure	Histological aspect	Comments
Not exposed		The morphology of the cellular structures of all the superficial layers of the skin (epidermis and dermis) is good.
Exposure to 70% HF for 1 minute		There are some morphological damages starting only in the upper layers of the epidermis.
Exposure to 70% HF for 5 minutes		The epidermis presents a very damaged morphology: pyknosis of nuclei, perinuclear edema, cytoplasmic alterations (acidophilia). Same kind of marked lesions in the upper part of the dermis. Lesions starting and less marked in the deeper part of the dermis.

Figure 9: Histological section of human skin

On the histological section (Fig.10), in order to illustrate the situation, the details of the lesions on cells can be identified through: the pyknotic aspect of the nuclei (retraction and dark color) and the acidophilic character (homogenous pink and orange-like color) of the cytoplasm (Fig. 24).

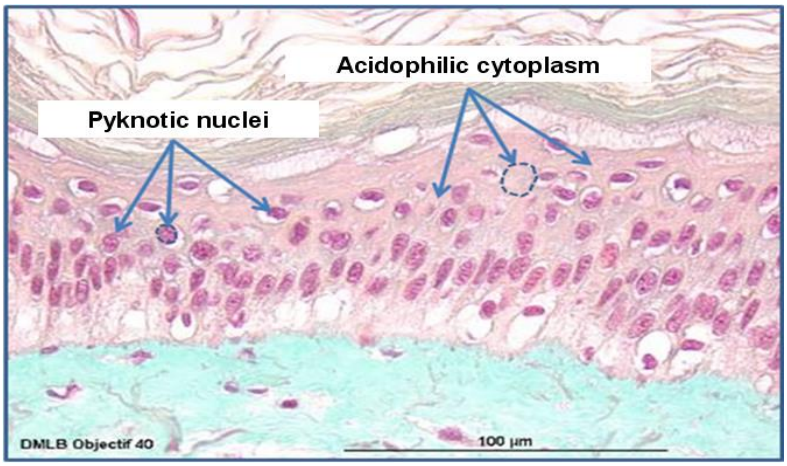


Figure 10: Histological section of human skin, 4 minutes exposure to 30 µl 70 % HF

In conclusion, hydrofluoric acid penetrates very rapidly with lesions appearing within the first minute. Therefore it is essential to perform decontamination as soon as possible. Every minute counts. The precocity and efficacy of decontamination prevent the appearance or can restrain the development of cutaneous lesions (Fig.11). Scars are often keloidal (thick fibrous tissues), coupled with pain and hypersensitivity to cold. Those physical sequelae are often associated with major psychological suffering[22].

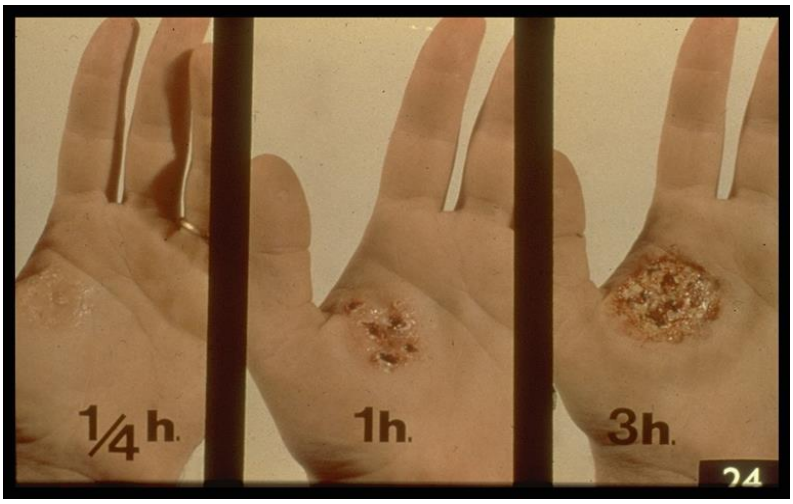


Figure 11: Simulation of the spontaneous evolution of a cutaneous HF burn

These experimental observations match clinical observations of industrial accidents, as in the case of the spectacular aspect of a 70 % HF injury in a 45 years old worker[79] (Fig. 12).

Applied treatment was immediate rinsing with water (for 15 minutes) and saline solution during transport.

Medical management in hospital included Ca and Mg I.V. infusion + local application of calcium gluconate gel.

Final result: one year of sick leave.

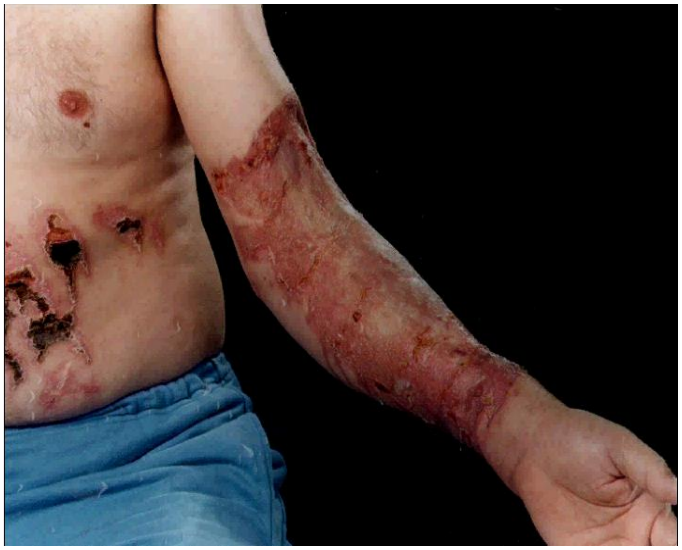


Figure 12: 70 % HF injury

1.1.2 Ocular splashes

Ocular splashes often happen at the same time as cutaneous splashes, particularly in cases of facial contamination. The diagram below represents the eye's anatomy (Fig.13).

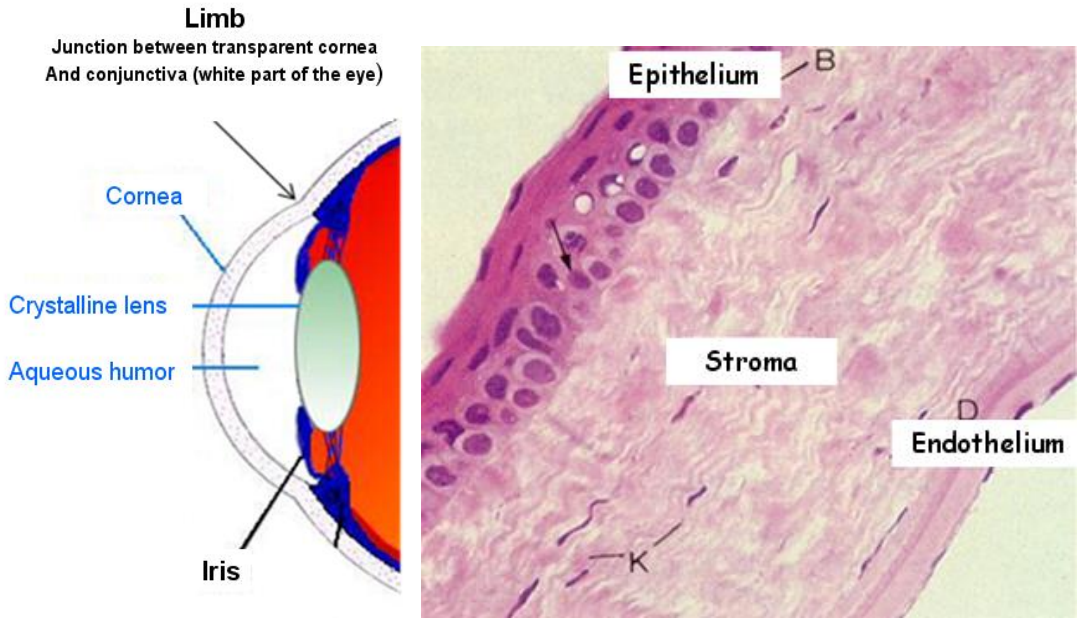


Figure 13 a) and b): a) Diagram of the anatomy of the anterior chamber of the eye, b) Histological image of a section of the cornea

The eye is very sensitive to acid splashes. Inorganic acids (such as hydrochloric or sulfuric acids) do not penetrate beyond the corneal stroma (medium layer which is rich in collagen and the spatial structure of which maintains the corneal transparency). They induce necrosis by protein coagulation and therefore restrain the extent of penetration[23,24]. The properties of hydrofluoric acid are similar to those of the other acids on the corneal surface. However, after destruction of the corneal epithelium, HF penetrates deeper and fluoride ions cause severe lesions.

As a partially dissociated acid (pK_a = 3.2), hydrofluoric acid can:

- penetrate into ocular tissues much deeper than the other acids,
- react with calcium and magnesium ions to form insoluble precipitates,
- quickly produce an opacification of the cornea and more severe lesions in the anterior chamber of the eye (Fig. 13a & 13b) and near contact lenses crystalline lens.

Ocular splashes of hydrofluoric acid destroy the corneal epithelium (Fig. 14) then generate edema of the stroma and ischaemia in the zone of the pericorneal limbus and of the adjacent conjonctiva. The deep penetration of fluoride ions causes an important inflammatory reaction and can be characterized by:

- stromal edema formation, which is often associated with bad prognosis for tissue regeneration transparency in cases of chemical ocular burns[25],
- opacification of the cornea (Fig.14),
- and even necrosis of the structures of the anterior chamber[26].

Figure 14: Opacification of the crystalline lens

1.2 Serious consequences of penetration of fluoride ions

Chelation properties of fluoride ions are the cause of toxic potential specific to HF damage. Local chelation by calcium and magnesium ions triggers ionic dysequilibria which change the physiological and biochemical cellular cycles. Initially limited to the tissues of the contact zone, those dysequilibria spread with fluoride ions diffusion and quickly generalize as indicated by concentration of electrolytes in the peripheral blood[27].

Thus, in addition to dehydration (for anhydrous HF) and corrosive action at the surface, there are systemic (in the whole body) hypocalcemia and hypomagnesia, in the case of concentrated solutions or for extended contact surface. The hypocalcemia triggered by the chelation of fluoride ions is difficult to reverse and can be lethal for splashes of very concentrated HF, even when they are not extensive (from about 2 % of the body surface) [28]. Coupled with hyperkalemia (release of intracellular K^+ ions during the phenomenon of cells necrosis), hypocalcemia can lead to lethal cardiac rythm disturbances (ectopic arrhythmia, tachycardia and ventricular fibrillation[29]).

Rapidity of the phenomenon, from few minutes to few hours, prevents the body from mobilizing its calcium resources, even though they are extensive.

In conclusion, whereas injuries induced by strong acids do not produce specific lethal risks, injuries induced by hydrofluoric acid can have severe or even lethal consequences[27, 30, 31, 53, 54, 55].

1.3 First aid rinsing after a hydrofluoric acid splash

After a chemical splash, the first actions are rinsing to decontaminate and undressing the victim[31]. If the victim wears contact lenses, they must be removed without causing any additional ocular trauma. Given the double danger of hydrofluoric acid, it is vital to decontaminate as soon as possible with an effective rinsing method.

Camarasa[22] reports the case of a worker who had unscrewed with bare hands, for better dexterity, some screws soiled by HF which sealed the window of a HF gas cylinder. Feeling extensive stinging, he washed with water after 3 hours and was treated with calcium gluconate after several hours. This accident had severe consequences: large physical and psychological sequelae: the ends of the stumps remain painful and sensitive to the cold; he now wears fingerless gloves permanently. The accident led to one year of sick leave, a 40 % permanent partial disability, and a professional re-qualification with change of position.

1.4 Power and limits of the mechanical effect of rinsing

Water rinses off the chemical agent by mechanical sweeping and dilution effects. Mechanical rinsing or external decontamination with water permits the removal of about 90% of the chemical at the surface of the skin or the eye. Water cannot control the double aggressive potential of hydrofluoric acid, which is both corrosive and toxic.

With a 280 mosmoles/kg osmotic pressure, 0.9 % saline solution is isotonic to blood but remains hypotonic to the eye (the osmotic pressure of a normal, not damaged cornea is about 420 mosmoles/kg). Therefore, saline solution, like water, can only achieve a mechanical and diluting rinsing.

1.5 Principle and advantages of hypertonicity of washing

In 1993, Roberts and Walker[32] studied the percutaneous absorption-enhancing properties of water. When skin is exposed to a chemical agent and is washed with water, there is a temporary increase in skin blood flow and an enhanced absorption of this chemical agent. This is what is called the Wash-In effect of water. This term was first used by Moody and Maibach[33,34]. They again demonstrate the same percutaneous absorption-enhancing properties of water on the skin. On the eye, the same phenomenon does exist. It was well demonstrated by a german team[35,36] on cell culture and *ex vivo* studies where respectively swallowing/explosion of cells and edema can be observed. A French team has also shown this phenomenon *in vivo* with the appearance of an edema when washing is performed with saline solution[37]. The common German and French expertise enables to publish recommendations for washing chemical exposures[38].

The effect of the hypertonicity of water can easily be highlighted on a fibroblast cell culture. This experiment allows the comparison of the effect of two rinsing liquids: water (20 mosmol/Kg) and a hypertonic solution (800 mosmol/kg). The pictures below show the results (Fig. 15): culture a) before rinsing, b) when rinsing begins, c) after rinsing[39].

With water, the cell volume increases progressively until cells « explode ». With the hypertonic solution, there is a small retraction with no deleterious effect.

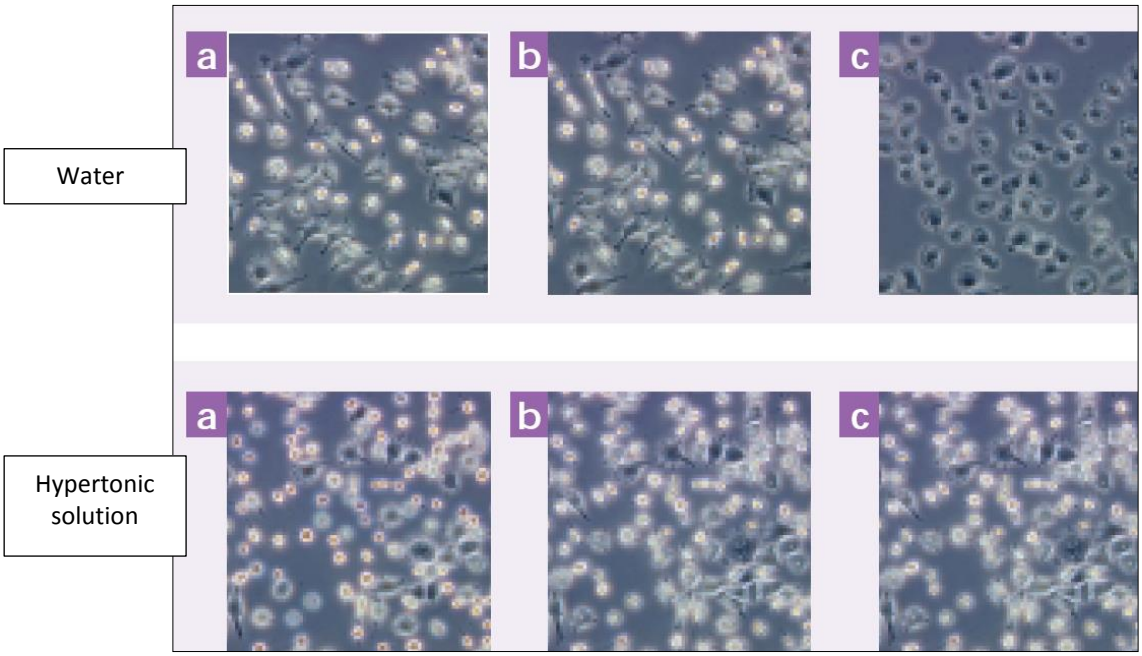


Figure 15: Effects of osmolarity onto a cell culture of fibroblasts

When the osmotic force is not enough, it cannot reverse the diffusion of the aggressive chemical through the skin or the eye and pull it outside the tissues. Rinsing with a hypertonic solution can physically stop or limit the diffusion into the eye or the skin and can generate a flow from the inside of tissues towards the outside. Drained by this flow, the aggressive chemical can thus come out of the tissues. The influence of the rinsing hypertonicity is shown by the following diagrams (Fig. 16):

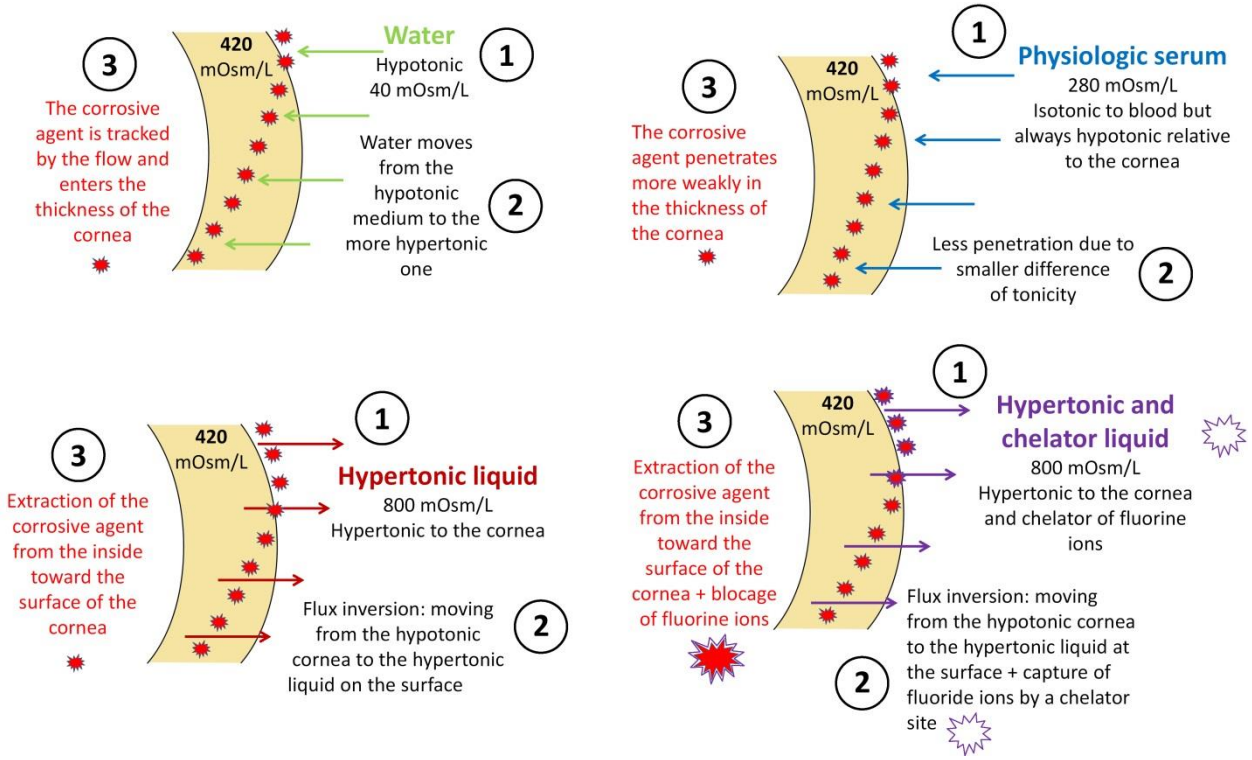


Figure 16: Role of the hyperosmolarity of an ocular rinsing solution

This phenomenon of osmosis allows the decrease of the lesion severity. In case of a hydrofluoric acid splash, the rinsing solution must act on the acidity, which is the cause of the superficial attack of tissues, and it must chelate the fluoride ions, the penetration of which into the deep layers generates a toxic hypocalcemia. The hypertonicity of the rinsing solution makes the chemical aggressor that has already penetrated come out and thus permits the chemical and chelating properties of this solution to act on the double aggressive potential of the chemical. The principle of hypertonicity of a rinsing solution applies to ocular and cutaneous splashes.

1.6 Results and analysis of the conventional rinsing protocols

Experimental works[40, 41, 42, 43, 44, 45] and treatment protocols [13, 46, 47, 48, 49] of HF accidents have identified and evaluated solutions that claim to decrease the severity of HF induced lesions. “Rinsing with water followed by local application or injection of calcium gluconate” is by far the most used protocol. As stated above, water helps the removal of HF from the surface by mechanical sweeping. Then calcium gluconate chelates the fluoride ions that have spread over.
Calcium gluconate can be applied through various protocols:

- locally applied as a gel,
- in hypodermic or subcutaneous injections,
- in local or regional intra-arterial (I.A.) or in intravenous (I.V.) injections.

Depending on the re-appearance of the feeling of pain for the patient, calcium gluconate can be applied several times, until pain no longer resolves.

Examples of decontamination with “water plus calcium gluconate” protocol, have proved its efficacy for low or medium concentrations[50, 51, 52, 53, 54] but its use on high concentrations does not always prevent the development of severe lesions, or even the patient’s death. A recent review explains such treatment[55] strategies.

Lethal cases of cutaneous burns by concentrated hydrofluoric acid have been published. They may even be due to splashes on about 10 % of the body surface that had been immediately washed with water.

- Mayer[56] *et al.* reported a case of 70 % HF splash, over 9-10 % of the body surface (posterior side of thighs), which lead to the patient's death, even though he had been immediately washed with water. He had severe hypocalcemia and cardiac arrest.
- Mullett[57] *et al.* reported a case of 70 % HF splash over 8 % of the body surface (right leg), immediately washed with tap water for 15 minutes. A late I.V. injection of 10 % calcium gluconate did not prevent the patient from dying from cardiac arrest.
- Tepperman[58] *et al.* described a pure HF splash over 2.5 % of the body surface, on the face, complicated by a small intoxication by inhalation. The victim had been washed with water after 10 minutes. 10 % calcium gluconate was injected under hospital supervision two hours after the splash. Cardiac arrest followed. It is clear that, when cutaneous exposure of HF is associated to inhalation, the lethal risk is increased. Timely and accurate wound treatment and respiratory tract care can play vital roles in the management of patients[59].

Applied topically or injected after water rinsing, calcium gluconate mainly acts on the chelation of fluoride ions. We have seen above that the origin of the penetration of the fluoride ions is the acid attack. If the acid is not removed thoroughly, then it continues destruction of the corneal epithelium or the epidermis, and thus it facilitates deeper tissular destruction by the fluoride ions. Calcium gluconate has only a limited action on the acid (see 2.1.1 in *vitro* experiments); therefore, it cannot stop both the corrosive action of the acid ions and the toxicity of the fluoride ions. Moreover, it is recommended to apply calcium gluconate several times, thoroughly massaging the area in order to facilitate its penetration. While binding fluoride ions, it helps reducing patient's pain[60]. Recently, a clinical study showed that arterial infusion of calcium gluconate for treating hydrofluoric acid burns of distal human limbs effectively relieved pain and caused no adverse effects[61, 62]. However, such applications cannot neutralize highly concentrated fluoride ions (concentrated HF solution and/or large body surface splashes). In serious cases, calcium gluconate can slow down the development of the injury, but progressive complications can occur.

The advantages and disadvantages of water plus calcium gluconate application methods are presented in the following table (Fig.17):

Protocol	Avantages	Limits
Water rinsing	▪ External rinsing by sweeping, physical effect, main effect of the washing ▪ Effect of dilution, physical effect, minor effect,	▪ Risk of hypothermia for extended lesions ▪ Hypotonic rinsing favouring the penetrating flow of fluoride ions from the outside to the inside of tissues (wash-in effect) ▪ No action on the acidity and the corrosivity of the hydrofluoric acid ▪ Non sterile
Calcium gluconate application	▪ Chelation of the fluoride ions when migrating towards deep layers	▪ Limited action on acidity (H^+ ions) ▪ Multiple applications required ▪ Factor depending on the victim's pain

Figure 17: The advantages and disadvantages of water plus calcium gluconate application

- **Ocular application of salt solutions:** other protocols recommend, after a primary emergency rinsing with water, the application of salts such as: magnesium chloride ($MgCl_2$), magnesium sulfate ($MgSO_4$), magnesium oxide (MgO)… Sodium chloride (NaCl)[63], calcium chloride ($CaCl_2$)[64], 0.2 % Hyamine and 0.03 or 0.05 % Zephiran which are quaternary ammonium salts, or even lanthane chloride ($LaCl_3$)[65,66] may be used for rinsing. These protocols have been studied in rabbits' eyes by McCulley[67] and coll. This study showed that these treatments may cause secondary effects when applied on the eye. Experiments on primary rinsing using sodium chloride followed or not by ocular irrigation or by sub-conjunctival injection of 1 % calcium gluconate diluted solution have been realized by Beiran et al.[68]. Local applications of MgO or $MgSO_4$, irrigations with 0.2 % Hyamine or 0.05 % Zephiran as well as sub-conjunctival injection of 10 % calcium gluconate have proved responsible for the appearance of ocular lesions in normal eyes.

- **Various protocols:** comparative studies[69] have experimentally estimated treatments containing Zephiran, Hyamine, calcium acetate and calcium gluconate on cutaneous burns by 38 % hydrofluoric acid.

- **Saline Solution:** at the same time, replacing water rinsing by saline solution rinsing (0.9 % sodium chloride) has been suggested. This is in accordance with the idea of increasing osmotic pressures in order to try to make the aggressive chemical go out. However, as shown in Fig. 16, the osmotic pressure of saline solution is too weak. Therefore this kind of rinsing cannot stop the diffusion of the hydrofluoric acid into the eye and skin.

Conclusion

Classical rinsings (external rinsing with water or saline solution, followed by treatment with calcium gluconate or with other salts meant to chelate fluoride ions), are essentially based on the principle of mechanical rinsing. These protocols can remove the main amount of the splash at the surface of the eye or the skin. They do not prevent hydrofluoric acid diffusion as they are hypotonic and they weakly act on acidity.

2 Results of rinsing with Hexafluorine® solution

2.1 How to improve rinsing protocols?

In addition to the main rinsing effect by mechanical sweeping, rinsing must also enable quickly and simultaneously:

- to limit or stop the diffusion of hydrofluoric acid into the eye or the skin. The aggressive product quantity that penetrates in the eye or the skin is the origin of the chemical lesion,

- to simultaneously inhibit all the aggressive potentials of the chemical.

2.2 Comparative studies of various rinsing methods

Developed by PREVOR Laboratory, Hexafluorine® solution was created to improve water rinsing properties by limiting hydrofluoric acid diffusion into the skin and the eye and to stop the corrosiveness and the toxicity of this chemical agent. Hexafluorine® solution's mechanism action is multiple:

- **Sweeping effect**: like water, Hexafluorine® solution rinses the exposed surface quickly. 90 % of the rinsing effect is due to the mechanical effect. This is the main effect of the washing.

  Therefore, only a small quantity of chemical remains on the surface and can penetrate into the skin layers. This small quantity is enough to induce a chemical lesion, which will develop until the complete inactivation of all corrosive molecules.

- **Hypertonicity**: unlike water, Hexafluorine® solution is a hypertonic liquid: rinsing with Hexafluorine® solution physically prevents the penetration of protons and fluoride ions into tissues and, doing so, contributes to complete decontamination of the tissues in contact.

- **Absorption of H^+ ions**: due to its chemical properties, Hexafluorine® solution can inactivate the acidity still available quickly and thus prevent the destruction of the epithelial layers and restrain the penetration of fluoride ions.
  Every molecule of Hexafluorine® solution can bind 3 H^+ ions simultaneously[70]. The absorption power of H^+ ions was highlighted by *in vitro* experiments (Fig.19).

Thanks to this almost immediate inactivation of the acid (20 seconds), the pH is quickly brought back to acceptable physiological zone limits (between 5.5 and 9) thus stopping the corrosive attack.

- **Chelation of F^- ions:** Hexafluorine® solution traps the F^- ions on the surface, and does not give them time to penetrate towards deeper tissues.
  Every molecule of Hexafluorine® solution can chelate 6 F^- ions at once. This result in a residual concentration of fluoride ions of less than 10^{-6} mol/l (pF= 6), which is not dangerous as it is below the limit concentration of toxicity (10^{-5} mol/l, pF = 5) (Fig. 20).

Conclusion

Properties of Hexafluorine® solution enable it to perform:

- a rinsing at the surface of the skin or the eye by sweeping mechanism and dilution,
- a physical pressure gradient stopping the penetration of hydrofluoric acid. Hypertonicity attracts HF out of the tissues,
- a complete rinsing by controlling both the corrosive and the toxic dangers of HF, due to its chemical properties.

2.2.1 *In vitro* experimentation

The following experience does not deliberately include the mechanical effect of the washing at the surface of the eye or the skin. The experiment emphasizes the dilution combined to the action on the acidic and toxic dangers of the hydrofluoric acid. Then, hereafter, the estimation of the efficacy of Hexafluorine® solution, in comparison with other rinsing methods such as water by itself or 10 % gluconate calcium has been based simultaneously on the corrosive potential (pH measurement) and on the toxic potential of hydrofluoric acid (pF measurement).

Material and method

PREVOR laboratory has developed a method for the *in vitro* testing of the efficacy of rinsing solutions for chemical splashes (Fig. 18).

Figure 18 : PREVOR in vitro dosage protocol to test the efficacy of rinsing solutions

Dosage of 1 mL of a normal (1N) solution or 10 mL of a 0.1N solution by an increasing volume of a decontaminating solution has been performed.

10 mL of 0,1 N (0.2 %) hydrofluoric acid are poured into a beaker. An increasing volume of rinsing solution: water, 10 % calcium gluconate or Hexafluorine® solution is added milliliter by milliliter while stirring. Then the evolution of concentration in acid (pH measurement) and in fluoride ions (pF measurement) is observed.

The pH and pF measurements are made with a *HEITO* pH meter-fluorimeter. The two following graphs show the experimental results (Fig.19 and 20):

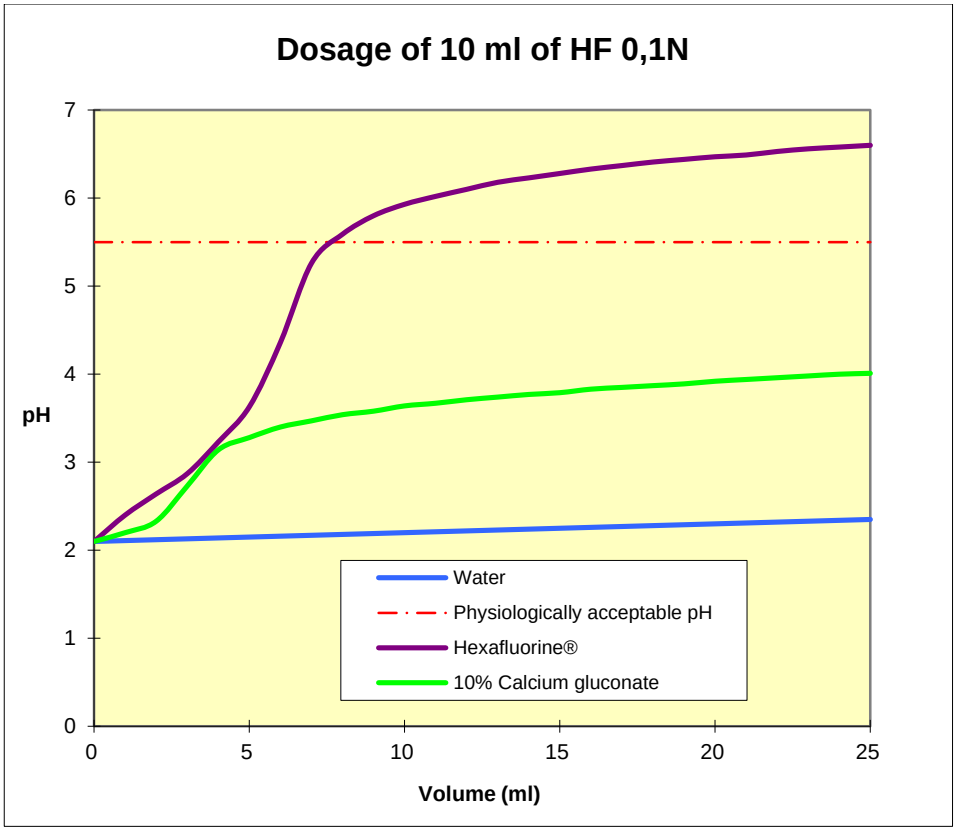


Figure 19: Evolution of the corrosive potential (pH) of a HF solution
in presence of an increasing volume of various rinsing solutions

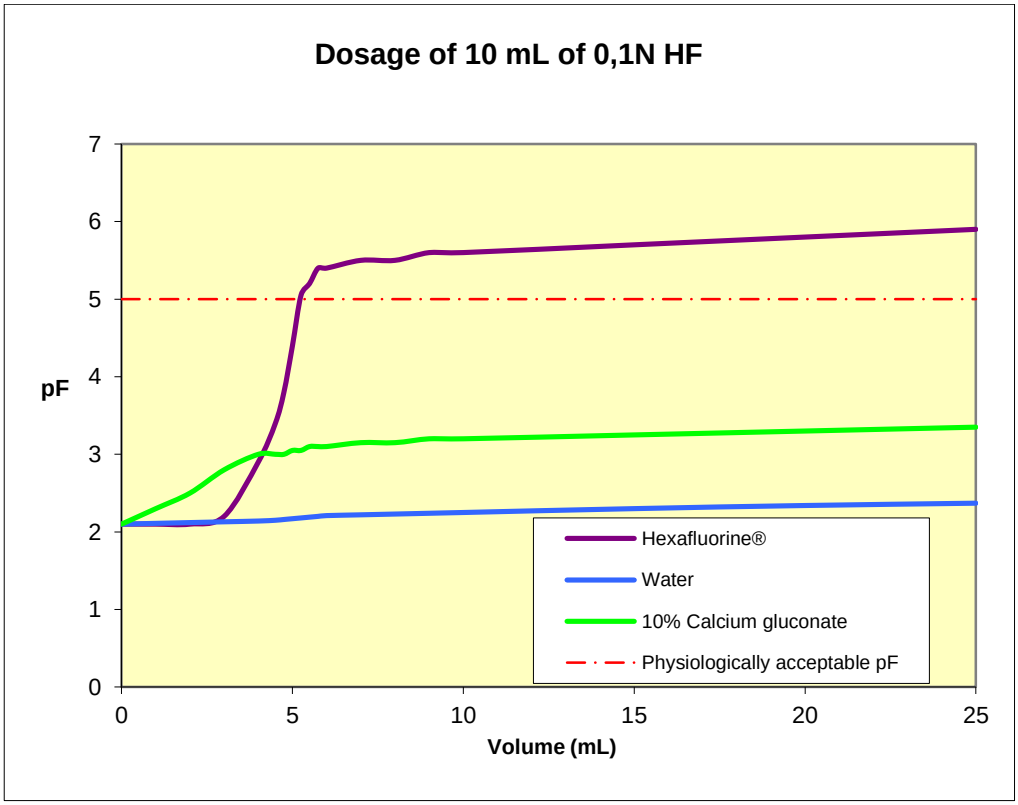


Figure 20: Evolution of the toxic potential of a HF solution
in presence of an increasing volume of various rinsing solutions

Discussion

In the first graph, the pH scale allows the observation of the zones in which acids are aggressive. In the pH zone between 5.5 and 9, the product is harmless (pH in the zone of physiologically acceptable level). In the case of acids, the lower the pH value is, the more corrosive the acid is; it is then called a strong acid.

After addition of a small volume of Hexafluorine® solution (8 mL), the 10 mL solution of 0.1 N hydrofluoric acid returns to the physiologically acceptable area. The resulting mixture is no longer aggressive.

25 mL of water added to the 10 mL 0.1 N HF only has a weak effect of dilution. The pH remains under 2.5: the solution is still corrosive.

The addition of 8 mL of 10 % calcium gluconate decreases the concentration in protons (H^+) by 100 times; the pH reaches 3.5 (the pH being a logarithmic unit, a 10^2 decrease is equivalent to 2 units on the scale: 1.5 + 2 = 3.5). It shows that calcium gluconate has some effect on the acid ions. However, the pH value remains in the area of chemical aggressiveness. The mixture is still corrosive.

In the second graph, the pF notation expresses the concentration in released fluoride ions, which thus reveals its toxic potential. The lower the pF value, the higher the concentration in fluoride ions and the stronger its toxic potential gets.

The mathematical relation between pH and concentration in protons $[H^+]$ is:

$$\mathbf{pH = - \log [H^+]}$$

By analogy, the mathematical relation between pF and concentration in fluoride ions $[F^-]$ is:

$$\mathbf{pF = - \log [F^-]}$$

For a pF value above 5, the product is said to be harmless (pF in the physiologically acceptable area). On the graph of the hydrofluoric acid evolution pF in presence of an increasing volume of various rinsing solutions, we can observe that a small volume of Hexafluorine® solution (5 mL) enables the 10 mL of 0.1N HF to be brought back to the zone of no danger.

Without mechanical washing, the progressive addition of water dilutes the hydrofluoric acid solution. The residual mixture HF/ water remains aggressive with a pF value near 2 after a 25 mL additional volume of water.

The addition of an increasing volume of a 10 % calcium gluconate solution reduces (by a factor of 10) the concentration of released fluoride ions (final pF = 3 for 5 mL added). Calcium gluconate lowers the toxic potential. In the specific and comparative conditions of our experiment, the addition of 25 mL of 10 % calcium gluconate does not enable the pF to return to the area of non-aggressiveness. That is why several applications are usely required in the classic protocol.

2.2.2 *Ex vivo experimentation*

2.2.2.1 *Ocular injuries*

Experimental methods for studying ocular injuries

New models have been developed for the evaluation of the chemical contamination / decontamination of the eye. A study on the EVEIT® model (*Ex vivo Eye Irritation Test*) has been performed by a german team in order to visualize the diffusion of HF into the cornea and compare various rinsing methods[71]. The study compares the following situations:

- no rinsing,
- water rinsing,
- rinsing with a 1 % calcium gluconate solution, which is the reference suggested by the literature, although potentially toxic, for the specific decontamination of ocular HF splashes,
- rinsing with Hexafluorine® solution.

The EVEIT® model has proved its capacity to act similarly to living ocular tissues when in contact with corrosive chemicals[72]. It consists of enucleated rabbit eyes maintained in a 4°C humid atmosphere in order to conserve all the properties of the corneal epithelium. They are used for experiment within 12 hours after collection from dead animals intented for human consumption.

Changes in the structure of the tissue following the diffusion of chemical inside the cornea was observed by OCT-HR (*Optical Coherence Tomography – High Resolution*), in spatial and temporal high resolution[73]. This method visualizes the kinetics of corrosive molecules penetration during the initial stage of an ocular chemical lesion. The OCT-HR technique enables the observation and measurement in real time of the diffusion velocity and penetration depth. This method also measures the thickness of the cornea, with a resolution of one micrometer (Fig. 21).

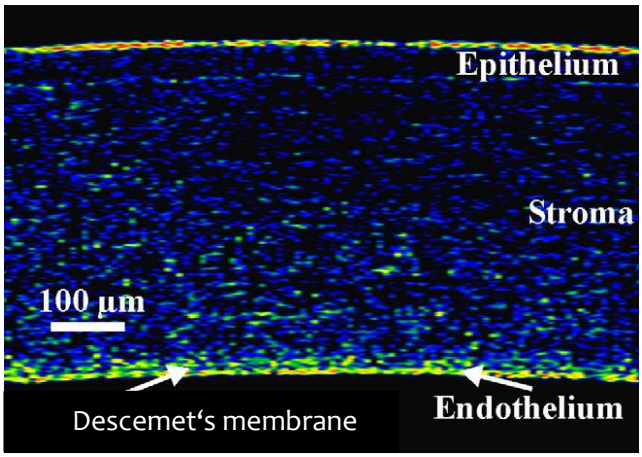


Figure 21: High resolution OCT picture of an ex vivo rabbit cornea

The damage observed is due to micro-structural changes in the cornea in direct relation with molecular chemical interactions.

All these changes are the origin of the loss of transparency that has been macroscopically observed. Because of its high accuracy, this method is naturally adapted to the comparison of various ocular decontaminating solutions' efficacy.

To obtain an ocular lesion by HF, 25µl of 2.5 % (1.25 mol/L) solution soaked on a 10 mm diameter filter paper is kept in contact with a cornea for 20 seconds. Then, the rinsing started 25 seconds after the removal of the filter paper. One group of corneas was kept unwashed, one was rinsed with tap water, a third one with 1% calcium gluconate and a last one rinsed with Hexafluorine® solution. The washing lasted for 15 min at a 66.7 mL/min flow rate, using 1000 mL of each solution.

Results

HF penetrates into the whole of the cornea within 240 seconds (Fig. 22).

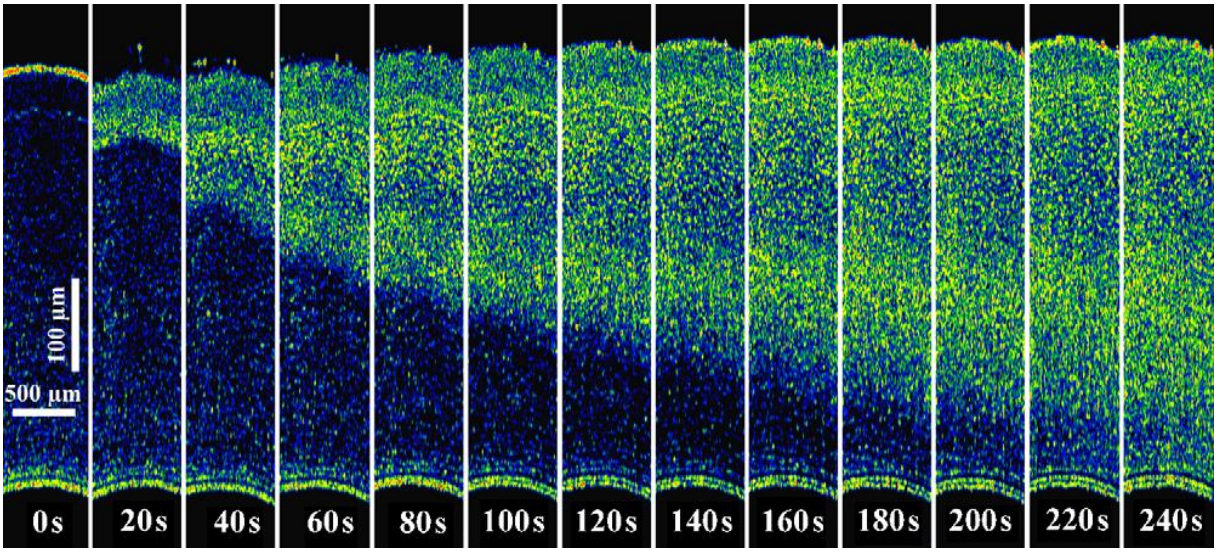


Figure 22: Sequence of OCT-HR pictures showing the 2.5 % HF penetration into the cornea

Initially transparent, the cornea becomes opaque when damage occurs.

Opacification of cornea, which significates that a lesion is developing, has appeared in all the following groups:

- exposed to HF and not treated,
- exposed to HF and then rinsed with water,
- exposed to HF and then washed with 1 % calcium gluconate.

When ocular HF decontamination is done with Hexafluorine® solution, the cornea remains transparent. Thus, the experiment clearly shows the action of Hexafluorine® solution on ocular decontamination of HF, in comparison with the other rinsing solutions.

This conclusion (Fig. 23) is corroborated by data about the corneal thickness reduction after Hexafluorine® solution washing. Not observed with the other tested solutions, this result shows the action of the hypertonicity of Hexafluorine® solution as it stops and limits the diffusion of the hydrofluoric acid in the eye and being able to react on its corrosive and toxic dangers.

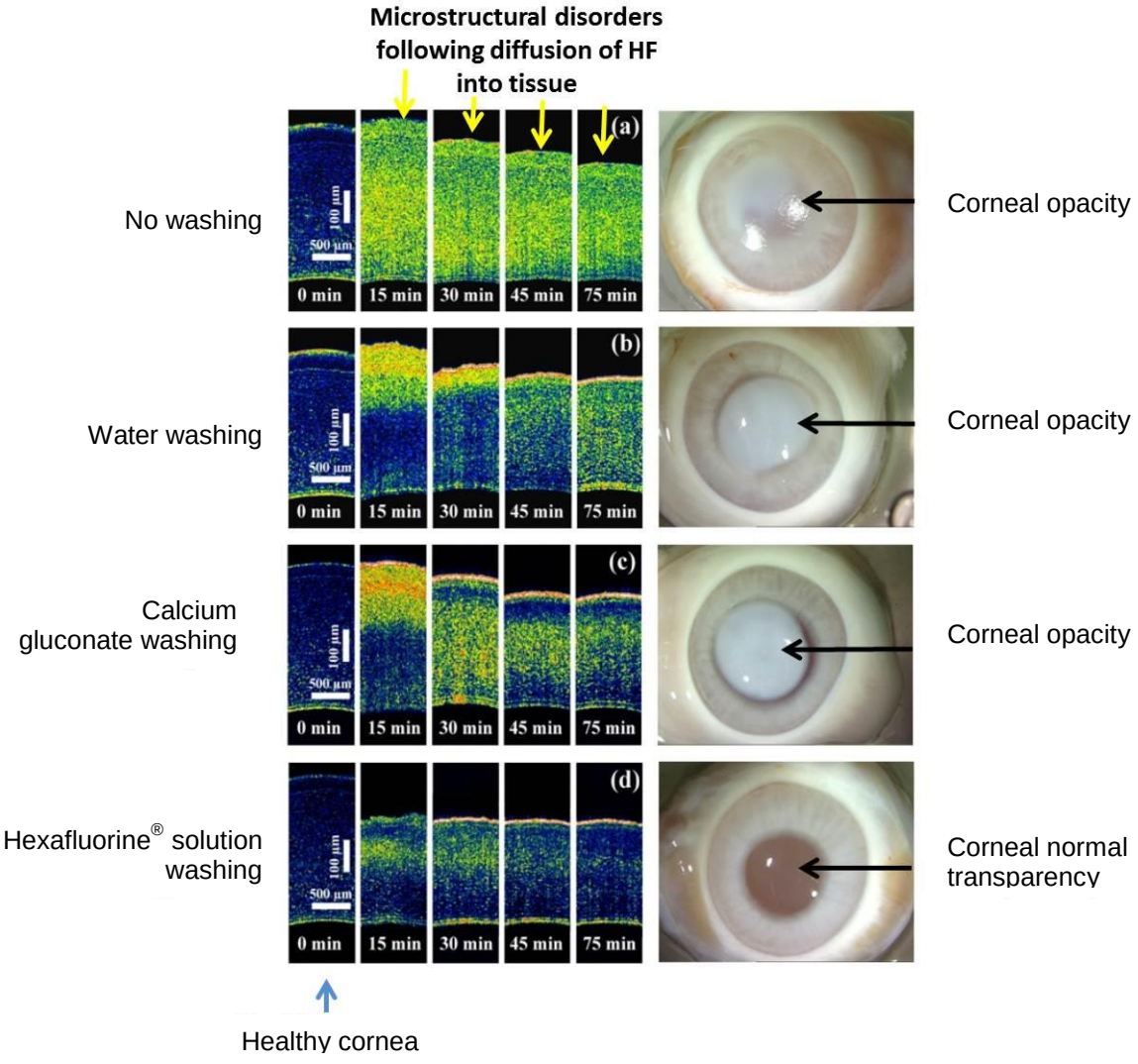


Figure 23: Influence of various rinsing solutions onto the diffusion of hydrofluoric acid into cornea on an ex vivo model of rabbit eye, 20 second contact with 25 µl 2.5 % HF, 15 minute washing.

In the experiment, the healthy cornea is in blue. When the HF diffuses and induces a lesion to the cornea, microstructural disorders appear as yellow color. It is clear in this experiment that washing with Hexafluorine® solution limits the diffusion of hydrofluoric acid into the cornea.

2.2.2.2 *Experimental method for studying cutaneous injuries*

Considering how difficult it is to extrapolate animal studies onto human standards, working on human skin explants maintained alive is a first step ahead. Experimental conditions are:

- concentrated 70 % hydrofluoric acid, in order to simulate a situation representing the most serious industrial exposures,
- a 20 seconds contact time with soaked filter paper,
- a 30 µL quantity of HF on a surface of 1 cm diameter in order to get a severe enough injury, though maintaining the whole structure of tissues in order to realize a valuable comparison of various washing solutions,
- histological analysis in order to observe the progression of tissular lesions from the most superficial layer of epidermis to the deep layer of dermis,
- experimentation in parallel on three samples in order to guarantee the reproductibility of results.

These quantitative data were chosen to reproduce the concentrations observed for a splash on the skin. It was indeed measured experimentally after an immersion in water of a whole human body (2 m², without clothes), it remains only on the surface of the skin, the maximum quantity of 250 mL of liquid which viscosity is similar to water.

Results

Positive controls exposed to HF a non decontaminated exposed explants show an attack of the epidermis and dermis within five minutes, as mentioned in paragraph 1.1.1. The lesions increase until complete necrosis during the 24th hour. The examination of the progression of cellular damages during the 5 first minutes:

- no lesion after a 20 seconds contact,
- alterations of the superficial layers of epidermis start within the 1st minute,
- basal layer of epidermis is attacked within the 3rd minute,
- most superficial layer of dermis (papillary dermis) is attacked within the 4th minute,
- a lesion at underlying reticular dermis within the 5th minute.

The following table sums up the chronology of the lesions (Fig. 24):

Time of exposure	Microscopical lesions
1 min	Start of penetration within the superficial layer of epidermis.
2 min	Attack of the basal layer (the deepest layer) of epidermis.
3 min	Epidermis completely damaged. Apparition of the first lesions in papillary dermis (the most superficial layer of dermis).
4 min	Epidermis completely damaged. The papillary dermis is severely attacked.
5 min	Epidermis completely damaged. Attack of the reticular dermis begins (the deepest layer of dermis).

Figure 24: Chronology of lesions on human skin during a 70 % HF burn

With this model of human skin explants, after validation of the experimental burn, the challenge was to compare various methods for washing HF burns. We selected two of them: water washing followed by the application of a 2.5 % calcium gluconate (CaG) cutaneous gel *versus* Hexafluorine® solution.

The explants exposed to 30 µl 70 % HF for only 20 seconds, and then immediately rinsed with water for 15 minutes followed by a unique superficial application of 2.5 % Calcium gluconate gel show:

- at 5 and 10 minutes, no deterioration of the structures of either the epidermis or dermis was observed.
- at 15 minutes after a 20-seconds exposure, very clear cellular deteriorations appeared in the epidermis and in the papillary and reticular dermis, in comparison with non-washed explants.
- these were decreased at 30 min, and were no longer observed after 1 and 2 hour(s).
- at 4 hours, slight edematous changes were visible in the epidermal basal layers.
- these alterations were clearly increased at 24 hours showing an appearance of coagulation necrosis including pyknotic nuclei and acidophilic cytoplasm in the papillary dermis. These changes were less apparent in the reticular dermis.

Finally, with a unique and superficial CaGlu topic application, the injury formation is initially delayed, starting after 15 minutes and declining completely afterwards, until it reappears secondarily first under the shape of edematous lesions. A unique superficial CaG application stops the corrosive and toxic potential of HF temporarily. However, its action does not last. In these specific experimental conditions, the process of lesions starts again after 4 hours under an edematous form and then a necrotic aspect in the whole epidermis and upper part of the dermis after 24 hours.

The above observations and comments highlight the benefit of the usual recommendations about protocols using water and local CaG applications:

- intervene as early as possible after the splash,
- make the calcium gluconate penetrate as deep as possible by massaging the area in order to improve its efficacy,
- repeat local applications of calcium gluconate as many times as required (usually when pain reappears).

Exposed in the same conditions, the explants washed with Hexafluorine® solution showed no lesion at all, whatever the time of observation, from 1 minute to 24 hours.

In a schematic way, the following table sums up the comparative results of decontamination methods in the experimental conditions described above (Fig. 25).

<table>
<tr><th colspan="2">Time of observations of skin layers</th><th>T
(Non treated control sample)
20 explants</th><th>F
(HF with no washing)
18 explants</th><th>FWCaG
(HF 20s + water washing + calcium gluconate)
16 explants</th><th>FHexa
(HF 20s + 400 mL Hexafluorine® solution)
16 explants</th></tr>
<tr><td rowspan="3">T0</td><td>Epidermis</td><td rowspan="21">Good

morphology</td><td rowspan="3">Good

morphology</td><td rowspan="8">Good

morphology</td><td rowspan="21">Good

morphology</td></tr>
<tr><td>Papillary dermis</td></tr>
<tr><td>Reticular dermis</td></tr>
<tr><td rowspan="3">20 s</td><td>Epidermis</td></tr>
<tr><td>Papillary dermis</td></tr>
<tr><td>Reticular dermis</td></tr>
<tr><td rowspan="3">5 min</td><td>Epidermis</td><td rowspan="2">PN + AC*</td></tr>
<tr><td>Papillary dermis</td></tr>
<tr><td>Reticular dermis</td><td>PN + AC*
relatively</td></tr>
<tr><td rowspan="3">10 min</td><td>Epidermis</td><td rowspan="12">PN
=
Pyknotic nuclei

AC
=
Acidophilic Cytoplasms</td></tr>
<tr><td>Papillary dermis</td></tr>
<tr><td>Reticular dermis</td></tr>
<tr><td rowspan="3">15 min</td><td>Epidermis</td><td>PN + AC*
Relatively</td></tr>
<tr><td>Papillary dermis</td><td>PN + AC*</td></tr>
<tr><td>Reticular dermis</td><td>Some necrotic cells</td></tr>
<tr><td rowspan="3">30 min</td><td>Epidermis</td><td rowspan="5">Good

morphology</td></tr>
<tr><td>Papillary dermis</td></tr>
<tr><td>Reticular dermis</td></tr>
<tr><td rowspan="3">1 h</td><td>Epidermis</td></tr>
<tr><td>Papillary dermis</td></tr>
<tr><td>Reticular dermis</td></tr>
<tr><td rowspan="3">2 h</td><td>Epidermis</td><td rowspan="3">Slightly edematous cells with relative acantholysis</td></tr>
<tr><td>Papillary dermis</td></tr>
<tr><td>Reticular dermis</td></tr>
<tr><td rowspan="3">4 h</td><td>Epidermis</td><td rowspan="3">Good morphology</td></tr>
<tr><td>Papillary dermis</td></tr>
<tr><td>Reticular dermis</td></tr>
<tr><td rowspan="3">24 h</td><td>Epidermis</td><td>Complete necrosis</td><td>Very edematous cells with very clear cytoplasm</td></tr>
<tr><td>Papillary dermis</td><td rowspan="2">PN + AC*</td><td>PN + AC*</td></tr>
<tr><td>Reticular dermis</td><td>Lesser damages</td></tr>
</table>

*PN=Pyknotic nuclei; AC=Acidophilic Cytoplasms

Figure 25 : Schematic summing up of the results of comparative decontamination of experimental burns by 70 % HF on human skin explants

This experiment also shows that Hexafluorine® solution can simplify the decontamination procedure when used within the first minute. Water followed by calcium gluconate is better than no decontamination and should be improved by several calcium gluconate applications. When the time of contact is higher than one minute, washing with Hexafluorine® solution can be followed by calcium gluconate application to improve the protocol and limit the lesions.

2.2.3 *In vivo* experimentation

2.2.3.1 *Skin lesion with 70% HF*

An initial experiment[70] was performed on rabbits in order to observe lesions in histological sections, comparing water washing, water washing followed by a local application of 2.5 % calcium gluconate gel and washing with Hexafluorine® solution.

120 rabbits, type New Zealander hybrid Albinos «Blanc du Bouscat», were divided into 6 groups. For the three washing methods, we have studied two groups, each one constituted of 20 rabbits. With three deaths not due to the experiment, 117 observations were carried out.

The cutaneous lesion was caused by the application of a 1 cm diameter filter paper soaked into 70 % HF.

This corresponds to an exposed area of less than 1 % of the complete body surface of the animal. In order to keep its properties, the HF reserve was renewed every 10 minutes.

Animals were shaved in order to maintain the properties of skin. The HF soaked filter paper was applied for 20 seconds then the various washing methods were applied:

- water washing only with a 10 liters/minute flow for 5 minutes,
- water washing only with a 10 liters/minute flow for 3 minutes followed by a 5 minute massage with 2.5 % calcium gluconate gel,
- washing with Hexafluorine® solution for 3 minutes (500 mL).

Complete observation lasted 6 days. The consequences of exposure were manifested as irritations or edema. The selected classification for the valuation of the intensity of reactions was set up according to Draize scale (no lesion, visible, extended or severe lesion).

The following table (Fig. 26) shows the results:

Draize scale (score)	Lesions	Injury intensity
0-1	Erythema or edema	No mark
2-3		Visible lesion
4		Extended lesion
> 4	Out of Draize scale	Severe lesion

Figure 26: Draize scale

Given the specificity of evolution of HF lesions (color, depth) and because it can reach stages of severity beyond those usually observed with other chemicals, we have decided to provide a description beyond Draize's scale.

The main observations about the stage of lesion after washing are summed up as follows (Fig. 27):

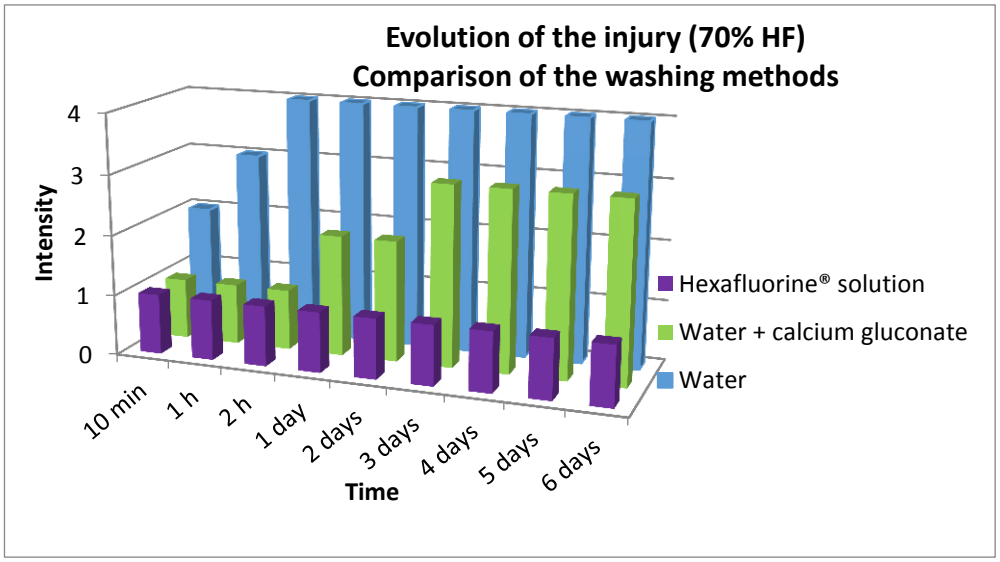


Figure 27: Comparison of the effects of the washing methods onto the evolution of a HF lesion in rabbit

Conclusion

- Washing with water removes the HF to the surface and dilutes it but it does not limit its diffusion through the skin and does not react with it and, therefore not efficient enough for stopping the evolution of a lesion which becomes severe.
- After washing with water, the secondary care with calcium gluconate prevents the appearance of lesion, at least during the first 24 hours, but a unique application is not sufficient for the complete elimination of all fluoride ions. When treatment is stopped, an injury reappears because the acidic effect is not controlled and the residual rate of released fluoride ions is still above the non-toxicity limit.
- The immediate use of a solution specific to HF, such as Hexafluorine® solution, attracts the HF to the surface of the skin and dilutes it, limits its diffusion through the skin thanks to its hypertonicity and suppresses the action of hydrofluoric acid: it does not allow the H^+ ions to create the superficial lesion and in consequence, the F^- ions do not have the opportunity to bond with calcium in tissues. The 6 days observation of the animals showed no sequelae after a unique wash with Hexafluorine® solution whereas, after washing with water, a secondary therapeutic management is required and so as to be efficient, calcium gluconate requires repeated applications and / or sub-cutaneous or intra-vascular injections.

2.2.3.2 *Evolution of serum calcium levels during a 70 % hydrofluoric acid injury*

A study has focused on the evolution of calcium serum level[70] in the blood, in 62 Wistar male rats, 50g each,that have been contaminated with 70 % hydrofluoric acid. Rats were classified into 4 study groups and 2 control groups.
Observations were scheduled after 10 minutes, 1 hour, 4 hours, 24 hours and 5 days. Rats were divided into 4 groups depending on the washing method used:

- water washing: 10 liters/minute for 5 minutes,
- washing with water and calcium gluconate: 10 liters/minute for 3 minutes then massage with 2.5 % calcium gluconate for 5 minutes,
- washing with water and calcium chloride ($CaCl_2$): 10 liters/minute water flow for 3 minutes then 10 % $CaCl_2$ 0.2 liter/minute flow for 3 minutes,
- washing with Hexafluorine® solution for 3 minutes (500 mL).

The lesion is due to the 20 seconds application of a 1 cm side square filter paper soaked in 70 % HF (supplied by Atochem). It represents 0.6 % of the body surface of an animal. The rat is thoroughly shaved in order not to change the superficial properties of skin.

The supervision of calcium serum (calcium concentration into the circulating blood) was made on 60 rats, divided in 4 series. Every series was made of 5 groups of 3 rats each. With 7 deaths not due to the experiment, 53 observations were performed. The research was made on blood samples (Fig. 28) then, after slaughtering, on the anatomopathological exam of liver and kidneys. Observations were scheduled after 10 minutes, 1 hour, 4 hours, 24 hours and on 5th day.

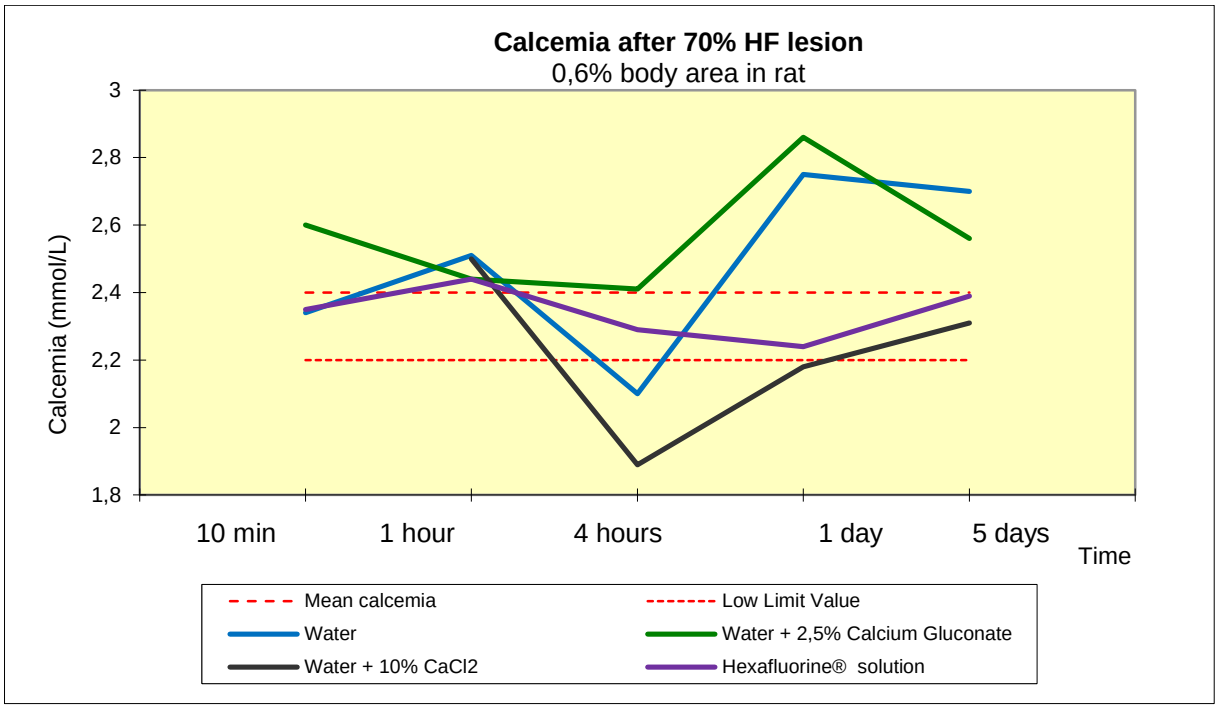


Figure 28: Evolution of calcemia, during a 70 % HF burn, in rats

Analysis shows that all the washing methods produce similar results after 1 hour. After 4 hours, a clear hypocalcemia can be observed for water and water + $CaCl_2$ washing methods. Then, an improvement is observed after 24 hours.

Results also clearly show that serum calcium remains constant after washing with Hexafluorine® solution.

By optical microscopy, the histological study of liver and kidneys showed no significant lesions.

2.2.3.3 *Experimental study with a 50 % HF skin injury during 3 min + 30s delay*

The study was performed as a blind controlled experimental study on Sprague Dawley rats which were anesthetised and shaved on their back. The injury was performed by applying 50 % HF during 3 minutes followed by a 30 second delay before decontamination.

4 groups were created depending on the washing method used:

- no washing as a control group,
- water washing, 500 mL during 3 minutes (group W),
- water washing, 500 mL during 3 minutes followed by a single application of 2.5 % calcium gluconate (CaGlu) (group Ca),
- Hexafluorine® solution, 500 mL during 3 minutes (group H).

Evaluation of the lesion's severity following a modified Draize scale

Four filter papers (10 mm in diameter) were soaked in 50 % hydrofluoric acid and applied on the shaved back of each rat for 3 minutes. A modified Draize scale (Fig. 30) was used to analyse the results[74].

Score	Observations
0	No visible injury
1	Diffuse erythema
2	Distinct erythema
3	Distinct erythema plus wounds or discolored spots
4	Distinct erythema plus wounds or discolored areas covering > 50% of the burn
5	A necrotic wound covering the whole burn

Figure 30: Modified Draize Scale

Results:

The severity of the injury was significantly different between Hexafluorine® solution and water + CaGlu groups at day 2 and 3 (in favour of the latter group), but this was not observed at day 4 and 5 (Figure 31).

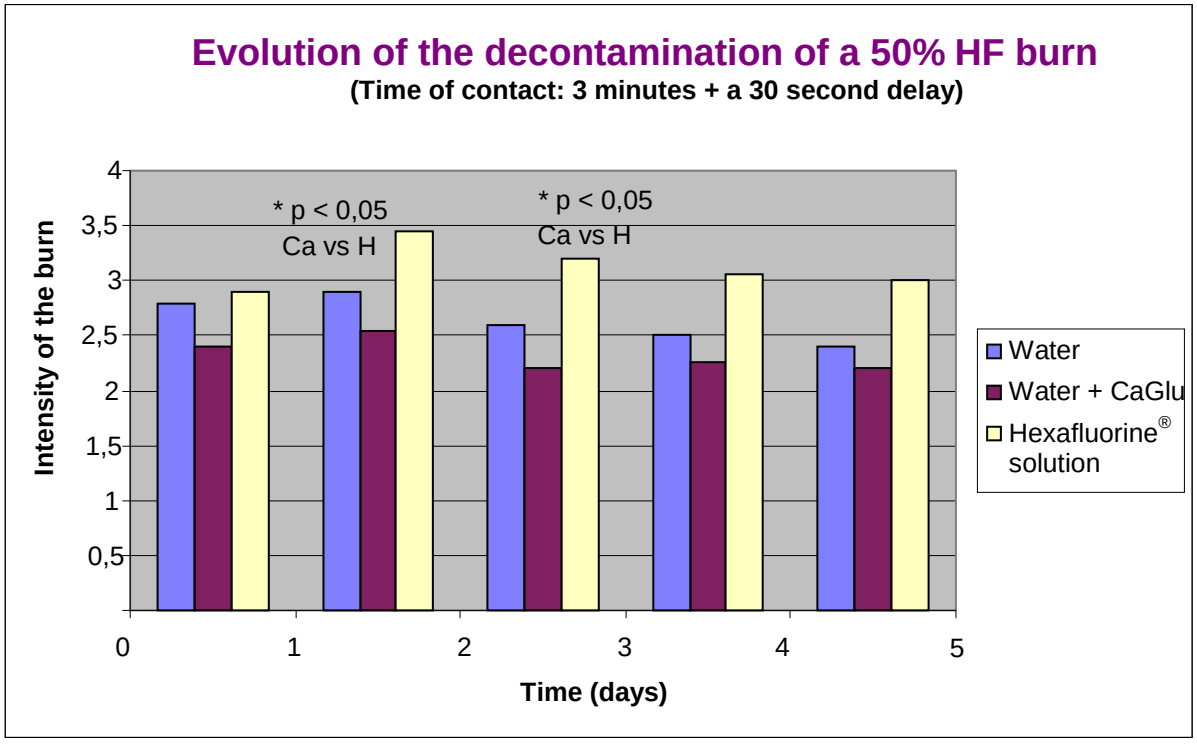


Figure 31: Evolution of the decontamination of a 50% HF burn

Conclusion:

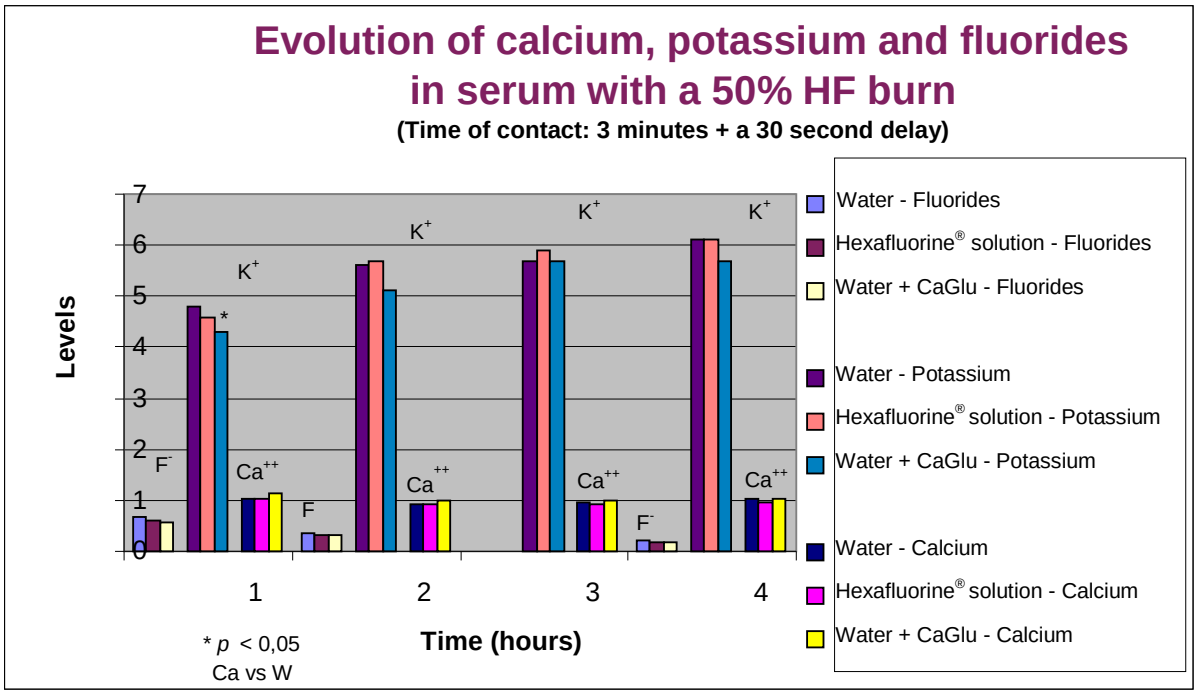
The authors concluded that water rinsing followed by topical calcium should remain the standard first aid treatment for skin exposure to hydrofluoric acid even at day 4 and 5, all three decontamination protocols gave the same results without any significant difference[75, 76].

Systemic toxicity

A filter paper (3.5 x 6 cm) was soaked in 50 % HF and applied on the back of each rat for 3 minutes. Blood samples[77] were taken and analysed for ionized calcium and potassium (before injury and after injury at 1, 2, 3, 4 hours after) and also fluoride (1, 2, 3, 4 hours after injury).

Results:

- The untreated animals exposed to HF developed hypocalcemia, hyperkalemia, and hyperfluoridemia.
- The only significant difference was observed in serum potassium at 1 hour between the group water + calcium gluconate and the group water alone.



*No data about fluoride in serum were given at 3 hours.

Figure 32: Evolution of calcium, potassium and fluoride in serum

Conclusion:

The authors conclude that there is no difference between washing with water alone and Hexafluorine® solution. However, considering that there is no significant difference excepting the value between water and water + CaGlu at one hour for potassium level (4.8 vs 4.3 mmol/l), it can be concluded that there is no significative difference in the three groups.

Conclusion of these two studies:

There is no significant difference of efficacy between the three groups of decontamination at the end of each study. This can be explained because the exposure model was too strong; it did not allow observing decontamination in good conditions.

The lesion with 50% HF is quickly severe and painful, the 3 minutes of contact with 50% HF + 30 seconds delay, used in the experiment, is then not representative of the accidental situation.

If the lesion has already appeared, decontamination with Hexafluorine® solution must be followed by a specific treatment against toxic fluoride ions such as calcium gluconate.

May be adding a fourth group in this study, such as Hexafluorine® solution followed by calcium gluconate, could have made the difference.

2.3 References in industry

2.3.1 Isolated cases with early management (Woeste, Krupp, Alcan, Arques International)

These cases are gathered in a recapitulative edition[78].
Described below, the cases from Woeste, Krupp and Alcan have recently been published[79].

2.3.1.1 *A case in WOESTE, Verbert, Germany, 1997*

A worker fell into a bath made of 1505 liters of water, 30 liters of 31/33 % hydrochloric acid and 233 liters of 59 % hydrofluoric acid. He was completely immersed. Due to the immediate action of his colleagues, his body was quickly washed with Hexafluorine® solution, his eyes were rinsed with an ocular water shower. On the body, the worker only had slight lesions on his abdomen and back. However, he developed a severe lesion of the left eye.

Finally, the victim only suffered of a severe lesion of the left eye, probably due to an insufficient decontamination, whereas, given the extreme aggressiveness of the mixture involved and the attack of 100 % body surface, this case might have been lethal (as shown in Fig. 4, paragraph 1.1).

2.3.1.2 *A case in Krupp, Werdohl, Germany, 1996*

While he was filling a bath with hydrofluoric acid and nitric acid, a worker was the victim of an ocular 38 % hydrofluoric acid splash. He immediately washed his eye with Hexafluorine® solution and suffered no damage. He was back to work on the next day.

2.3.1.3 *A case in Alcan, Göttingen, Germany, 1993*

Two workers were splashed by 5 % hydrofluoric acid. Both were rapidly decontaminated with Hexafluorine® solution. The workers went back to hospital for evaluation the day after. They did not have any work time loss.

2.3.1.4 *A case of facial splash of 70 % HF vapors, Cristalleries, Arques, France, 1996*

Since 1993, in order to improve the management of victims of hydrofluoric acid splash, instead of using water, the company's medical and safety services have chosen to use Hexafluorine® solution for the emergency washing of any hydrofluoric acid splash. The use of calcium gluconate is maintained as a secondary treatment if required.

A 35 year old technician, with 12 years of seniority in the company, was splashed onto the right cheek by 70 % HF vapours when opening a gate in the hydrofluoric acid circuit[80]. He immediately felt pain in the splashed area. Because he was wearing impermeable protective glasses, his eyes were not splashed. He immediately headed for a DAP (Autonomous Portable Shower). He pulled out the pin and started decontamination with the Hexafluorine® solution DAP directing it towards the painful area. He felt a cooling sensation and mentioned the immediate and complete disappearance of pain. In accordance with the protocol for use to which he had been trained on site, he used the whole 5 liter contents which accounts for the 5 minutes of washing. He then went to the infirmary.

After medical examination, no particular sign was observed, except a slight painless erythema. The technician did not require any sick days, so there was no work time loss.

The next day, the erythema has almost disappeared, the patient did not feel any pain, but, as a precaution, calcium gluconate gel was applied. The following week, the patient underwent a medical examination, during which no squelae were observed. One month after the accident, another medical examination lead to the same conclusion. Then, it was decided to stop any further medical management.

2.3.2 Isolated case with delayed management

In Sao Paulo, Brazil[81], a worker was the victim of a 70 % HF splash onto about 10 % body surface (left cheek, external side of the left arm and thigh, external and anterior sides of the same leg).
The victim was immediately showered for « some minutes », then his clothes were removed and the victim was showered for the second time. Some blisters appeared under the surface of face and leg. The initial treatment of the lesions combined compresses soaked in a magnesium oxide solution (Fig. 33) and the IV injection of analgesics.

At this stage, clinically, after decontamination with water, the burn had already occurred and the pain was persistent.

Transferred to hospital, the victim was **secondarily decontaminated with Hexafluorine® solution 3 hours after the accident** (Fig. 34). The spraying of a 5 liter DAP (Autonomous Portable Shower) (Fig. 34) for 5 to 6 minutes **gave a feeling of coolness of the lesions and decreased the pain**. The lesions are clinically estimated between first and third grade. **The redness of the affected areas which, initially, were simply erythemic, quickly disappeared.**

In addition to cutaneous decontamination, the treatment included:

- IV injection of 40 mL 10 % calcium gluconate in 500 mL sterile isotonic glucose solution,
- inhalation of 5 mL isotonic solution enriched with 3.5 mL of 3.5 % calcium gluconate,
- sub-cutaneous injection into the area around the lesions with 40 mL of 10 % calcium gluconate (Fig. 35),
- application of 2.5 % calcium gluconate gel by massaging the affected area (Fig. 36).

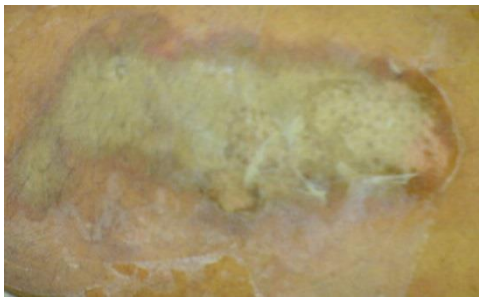


Figure 33: After washing with water and application of magnesium oxide

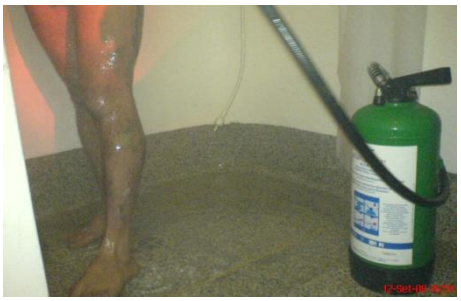


Figure 34: Secondary and late washing with Hexafluorine® solution

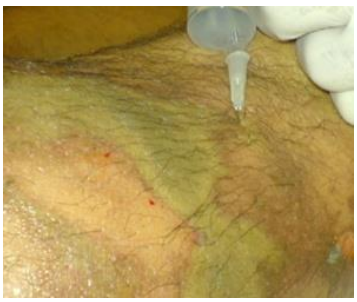


Figure 35: Sub-cutaneous injections of calcium gluconate

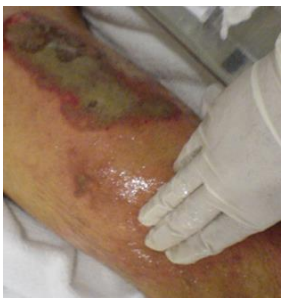


Figure 36: Application of CaG gel

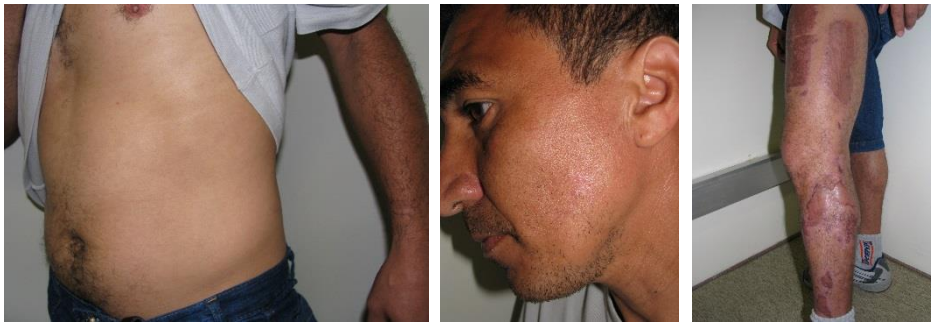


Figure 37: Final condition of victim, after skin grafts, 90 days later

The whole initial therapeutic management took 5 hours. There was only slight respiratory discomfort, but no systemic symptoms appeared, and specifically no sign of cardiac complication shows on monitoring. On the biological level, there was a slight decrease to 1.4 (normal: 1.9-2.5) of circulating magnesium on same day. The day after, there was a small decrease of serum calcium 7.9 (normal: 8.5-10.5).

The patient left the intensive care section at the 48th hour. By the 4th day, the patient felt no more pain. Grafts proved secondarily necessary.

The pictures (Fig.37) showing complete healing were taken 90 days after the splash.

After three hours of contact, decontamination with Hexafluorine® solution seemed to bring an improvement in stopping the progression of HF burn. If this accident is compared to a similar one (paragraph 1.1.1), the use of water followed by delayed use of Hexafluorine® solution versus water allows to decrease sequelae. This shows that it remains some active hydrofluoric acid in the skin that can be removed and stopped by Hexafluorine® solution. However, Hexafluorine® solution is not intended to treat an established lesion. It is a device that must be firstly used, as soon as possible, to decontaminate HF splahes, ideally within the minute following the splash.

2.3.3 Testimonials

2.3.3.1 *Panasonic, Matsuhita Electronics, Germany*

Testimonial from Panasonic, Matsuhita Electronics GmbH, Esslingen, Germany (1996-1998). This company uses hydrofluoric acid for glass cleaning. HF comes in 40 % hydrofluoric acid barrels and is diluted to 12 % HF. Matsuhita Electronics has been using Hexafluorine® solution for more than two years to wash HF splashes. Staff training made the protocol of first aid washing with Hexafluorine® solution operational and effective. Since implementing Hexafluorine®solution this company has reported no situation requiring secondary treatment due to hazardous splashes (testimonial letter).

2.3.3.2 *Sobodec, France*

Summary of the oral presentation, extract from « Chemical splashes: prevention, first aid actions and management », presented in the convention « Quality on work premises » organized by CRAM Aquitaine in November 2000 in Bordeaux (complete French version on www.preventica.com).

SOBODEC is a glass decorating company, whose activities include grinding glass (chemical attack of glass in a bath comprising hydrofluoric acid). A chemical splash can happen:

- during handling of the products,
- during preparation and renewing of bath with transfer pumps,
- during maintenance on machines or transfer pumps.

The exposed staff members are employees who prepare the bath and the maintenance team. To prevent chemical splashes, the following is required:

- wearing of individual protections such as gloves, masks, boots, aprons, overalls, glasses or eyeshades
- good ventilation before baths,
- presence safety shower DAP) and an Eyewash (eye washing device) of Hexafluorine® solution,
- training of staff on chemical risks and washing protocols.

Two kinds of accidents may happen:

- either splashes of concentrated corrosive product,
- or the penetration of a much diluted product during a long exposure time.

In the first case, the victim immediately feels a burn and must wash as soon as possible with Hexafluorine® solution. M. Sajous, safety manager at SOBODEC, reports an accident in which the victim could not wash early enough because of the first-aid post being too far away. Taken to hospital and with secondary treatment, the victim was given sick leave but with no sequelae. From then on M. Sajous' advises –with good reason - to install washing devices close to the work places. Conversely, water washing has proved much less effective.

When HF is diluted and washing is delayed, pain appears lately, up until 24 hours for an extended contact (as explained in paragraph 1.1.1). In such cases of delayed management, the protocol must be different because the product has already penetrated into the tissues. Then, the cutaneous application of calcium gluconate or injections under medical control may be necessary.
Finally, when treatment is performed by external rescue services (firefighters, medical rescue teams, hospital staff) a file containing the medical safety data sheets (MSDS) of the chemicals used at the work post and the details of the Hexafluorine® solution washing protocol must be given to the victim to enable better analysis and coordination of the secondary management.

2.3.4 Series of splashes in the industrial environment

2.3.4.1 *Eleven cases in Mannesmann, Remscheid, Germany*

From 1994 to 1998, eleven cases using Hexafluorine® solution have been referenced in Mannesmann, Remscheid, Germany. This study has been published in the international journal, *Veterinary and Human Toxicology*[82].

Over a period of four years, 11 splashes of hydrofluoric acid occurred (Fig.38 and Fig.39):

- 6 splashes by a mixture 6 % HF / 15 % HNO_3
- 5 splashes by 40 % HF

- HF splashes have hit men, aged 35 $\pm$ 11 years,
- one 40 % HF splash has hit both eye and skin
- one splash by the mixture 6 % HF / 15 % HNO_3 was only ocular (Fig. 38),
- cutaneous splashes have hit 0.2 % (1 finger) to 16.5 % body surface (Fig. 39), among which 6 splashes have hit 4 % or more,
- one splash by the mixture 6 % HF / 15 % HNO_3 and one splash by 40 % HF have affected more than 10 % body surface, respectively 10.5 % and 16.5 %.

Splashes have mostly attacked hands, limbs (superior or inferior), face and eyes, as well as thorax. All hydrofluoric acid splashes, whether pure or mixed, have been washed within the first two minutes (between 30 and 120 seconds) after the splash, on the accident scene, while victim's clothes were removed in the case of a cutaneous splash. Washing with Hexafluorine® solution was performed by the victim or by a witness. For every HF splash, a secondary wash with Hexafluorine® solution was performed in the infirmary. The patient was given clean clothes.

No sequelae were observed for all splashes washed with Hexafluorine® solution as first aid. No secondary treatment required and no work time loss.

Ocular Splashes	40 % HF	40 % HF + 15 % HNO_3
Number	1	1
Area	1 eye	1 eye
Primary washing	Hexafluorine® solution	Hexafluorine® solution
Secondary washing	Hexafluorine® solution	Hexafluorine® solution
Secondary treatment	0	0
Sequelae	0	0
Lost work time	0	0

Figure 38: First aid washing of ocular HF splashes using Hexafluorine® solution

Cutaneous Splashes	40 % HF	40 % HF + 15 % HNO_3
Number	5	5
% body surface	0.2 % 1 % 4.5 % 4.5 % 16.5 %	0.2 % 2.25 % 4 % 4.5 % 10.5 %
Primary washing	Hexafluorine® solution	Hexafluorine® solution
Secondary washing	Hexafluorine® solution	Hexafluorine® solution
Secondary treatment	0	0
Sequelae	0	0
Lost work time	0	0

Figure 39: First aid washing of cutaneous HF splashes using Hexafluorine® solution

2.3.4.2 *Sixteen cases in Outokumpu (Avesta) Sweden*

16 cases have been referenced in the series from Avesta Welding, Sweden. This study is published in the journal *Veterinary and Human Toxicology*[83].

Between 1998 and 1999, 16 cases of ocular or cutaneous splashes by hydrofluoric acid occured in the AVESTA plant in Sweden. 80 % of exposed workers are men and the average age of victims was 39 ± 11 years; one third of the victims were external workers.

There were two cases of splash by 70 % hydrofluoric acid. The others were due to a mixture of hydrofluoric acid and nitric acid (HNO_3) with pH = 1. Another splash was containing, in addition to the HF/HNO_3 mixture, some sulfuric acid, still with pH = 1. This splash hit both face and eyes. Two cutaneous splashes happened at hot temperatures (about 45 °C) with stripping acid (HF/HNO_3). All splashes were washed with Hexafluorine® solution as a primary action within the first minute in 75 % cases. Three splashes with the diluted HF/HNO_3 mixture were washed after one hour.

All victims reported an immediate cessation of pain during or just after washing with Hexafluorine® solution. More than 60 % workers were taken to hospital for a control medical examination. No sequelae were observed. The victim of the ocular splash of hydrofluoric acid, with an unknown concentration, developed signs of secondary irritation several hours after accident. This irritation may be due to the use of calcium gluconate to do an "aggressive wash" in hospital. The victim of a facial and buccal hot splash presented a few phlyctenae on the eyelid the day after accident.

The next table (Fig. 40) shows various cases of splashes in Avesta in Sweden:

Number of cases	Corrosive product	Hit area	Contact time	Sick leave (days)
2	70 % HF	Left forearm + mouth	< 1 min	0-1
1	HF (unknown concentration)	One eye	< 1 min	0
2	HF + HNO_3 pH=1	One eye	< 1 min	0-0
1	HF + HNO_3 + H_2SO_4 pH=1*	One eye	3-5 min	3
1	HF + HNO_3 pH=1	Two eyes	< 1 min	0
1	HF + HNO_3 pH=1	One thigh	< 1 min	0
2	HF + HNO_3 pH=1	Two thighs	1h - 1h30	2 –2
1	HF + HNO_3 + H_2SO_4 pH=1**	Face	3-5 min	3
2	HF + HNO_3 pH=1	Face + mouth + forehead	< 1 min	1-1
3	HF + HNO_3 pH=1	Forearms + arms + hand + elbows	< 1 min	0-0-1
1	HF + HNO_3 pH=1	Wrist	2 h	0

Figure 40: Series of cases of HF exposures in Avesta Sweden

*Sixteen total patients but one with both eye/skin splash.
**HF + HNO_3 + H_2SO_4 pH = 1 was involved in one cutaneous and one ocular splash.

Results

Globally, 32 detailed cases have been reported.
In all cases, no severe lesion has developed after washing with Hexafluorine® solution. No secondary treatment has been necessary in more than 75 % treated cases, including the two cases of splashes by very concentrated 70 % HF. There were no death, while in 5 out of 32 cases, the combination of the route of exposure, the HF concentration and the percentage of affected body surface might have put the vital prognosis at stake, according to the criteria developed above in figure 4, paragraph 1.1.

On average, victims had only one day of lost work time (σ = 1.1).

There was a complete and extremely fast relief of pain, whereas, in the development of chemical lesions, it is well known that:

- pain may be remarkably intense,
- pain is relative to the chemical reactivity of fluoride ions as mentioned in paragraph 1.1,
- pain is a characteristic element which shows the evolution of lesions and the efficacy of decontamination.

Furthermore, even in cases of secondary decontamination and delayed management, there is an interest to first decontaminate with Hexafluorine® solution and then apply secondary treatment such as calcium gluconate.

2.3.5 The Institutional point of view about Hexafluorine® solution use

- **INRS**[84] (Institut National de la Recherche Scientifique, French National Institue for Scientific Research), in its brochure Aide Mémoire Technique ED953, « Manipulations in chemistry laboratories: Hazards and prevention », advises the following protocol in case of chemical burns: *« As soon as possible, wash with clean water for 15 minutes, removing clothes and accessories soaked by the chemical; follow instructions given by the company doctor or the medical officer and contact a medical service. If another method is advised, follow the userguide and instructions given by the company doctor or the medical officer»*.

- **CNAM**[85] (Caisse Nationale d'Assurance Maladie, French National Health Insurance) in its R442 Recommendation (signed by the national technical committee of metalworking industry on November 13th, 2008) from the series "Prevention of chemical risks : activities of surface treatment " gives exactly the same advice as the ones recommended in the INRS ED953 brochure and adds : in the part of the paragraph dealing with collective prevention in surface treatment using HF : *Hexafluorine® solution showers and ocular fountains in the chapter about hydrofluoric acid* (Fig.41a and 41b).

Décapage, dérochage	Acide fluorhydrique	Très toxique et corrosif par contact, inhalation et ingestion : irritations, brûlures, lésions, ulcérations (peau, voies respiratoires, yeux, tube digestif). Sensation de brûlure retardée. Provoque des hypocalcémies, des nécroses des tissus et des os. Tableau MP 32.	***Collective*** Couvrir les bains. Captage des vapeurs et des aérosols par aspiration au niveau de la cuve. Douche de sécurité et fontaine oculaire à l'hexafluorine. ***Individuelle*** Gants (butyle, néoprène), écrans de protection, masque équipé de filtre BEP_3, vêtements anti-acides et bottes anti-acides Prévoir la trousse de secours[3] notamment les produits spécifiques (gluconate de calcium en solutions injectable et buvable, comprimés de calcium, crème au gluconate de calcium) en cas d'accident.

Figure 41a: Institutional recommendation by CNAM, French original version

Etching, metal cleaning	Hydrofluoric acid	Very toxic and corrosive by contact, inhalation and ingestion: irritation, burns, lesions, ulcerations (skin, respiratory tract, eyes, gastrointestinal tract). Delayed burning sensation. Causes hypocalcemia and necrosis of the tissues and the bones. Table MP 32	**Group Protection.** Cover vats. Capture vapors and aerosols by exhaust ventilation near tanks. Hexafluorine safety shower and eyewash. **Individual Protection.** Gloves (butyl, neoprene) , protective screens, mask equipped with BEP_3 filters, acid-resistant clothing, acid-resistant boots. Prepare a first-aid kit, notably with specific products (calcium gluconate in injectable and orally-administered forms, calcium tablets, calcium gluconate cream) in case of accident.

Figure 41b: Institutional recommendation by CNAM, translated from the above original French version

- **INRS**[86] again, in its brochure concerning laboratories involved in the teaching of chemistry (reference ED 1506) advises:

« *The installation of eye washing devices in every laboratory is also recommended*». *Specific products designed for first aid treatment of ocular or other chemical burns can complete the display and improve the efficacy of washing with water, which must immediately follow. Such products can be delivered by autonomous portable showers and should only be used under the agreement of medical service and should be renewed regularly* ».

- **Swedish Arbetsmiljö Verket (Swedish Work Environment Authority)**[87]

Kunskapsöversikt: Spolvätskor för behandling av akut exponering för fluorvätesyra och andra starka syror och baser
"*Overview of current knowledge" Report 2010:6: Irrigation fluids for treatment of acute exposure to hydrofluoric acid and other strong acids and bases.*

"Chemicals are commonly used in Swedish workplaces and many common substances are highly corrosive acids and bases. The Swedish Work Environment Authority is responsible for developing regulations and guidelines on what first aid equipment should be provided in areas where these types of chemicals are present."…/...
"The Swedish Work Environment Authority has therefore commissioned this independent review of the literature and a compilation of experiences from industrial users."

Evaluation covers documentation of two products, Hexafluorine® and Diphoterine® solutions, including practical experience using these decontaminating agents. These products are classified as medical devices (Class IIa). They have undergone a variety of toxicity tests. Taken together, classification, reported toxicity tests and case reports show that the products can be considered safe for use.

"Our conclusion is therefore that Hexafluorine works more effectively than water when irrigation begins immediately, but it is doubtful if the product can prevent systemic effects after skin exposure if chemical burn has already developed. It can therefore be questioned if Hexafluorine® solution should be used for secondary treatment e.g. at the hospital." .../...

In Conclusion:

"Based on visits in the Swedish industry, we note that users of Hexafluorine® and Diphoterine® solutions give predominantly positive opinions. The products are perceived as practical and easy to use, the users also emphasize the advantage that the same product can be used on multiple types of chemicals and experience that it works better than water. The time factor is very important for the effective treatment and availability is thus critical. For example, most people exposed in the eyes immediately suffer from blepharospasm with disorientation as a result. This may make it difficult to get to an emergency station quick enough in comparison to constantly carry around the irrigation fluid. With regard to international use, it has been difficult to get a clear picture of the extent of use. In several cases, use of the products occurs within major international corporations with several factory sites. The products are also classified for use within the EU and are sold in most European countries and also to other parts of the world..."

- **In the book**[88] **"Les intoxications, prise en charge initiale, 3ème edition" (Intoxications, initial management, 3rd edition)**, there are sheets presenting the key antidotes. A new sheet is dedicated to Hexafluorine® solution, describing it as an aqueous amphoteric hypertonic solution for washing hydrofluoric acid splashes. The sheet indicates that washing with Hexafluorine® solution cannot replace the calcium gluconate prescription. Hexafluorine® solution is presented as an alternative for washing hydrofluoric acid off of the mucous membranes and skin.

- **Lille Poison Control Center - France (2012)**[89]

  The Lille Poison Control Center recommends making Hexafluorine® solution eye baths available in order to implement 'washing with water or Hexafluorine® solution ' as first-line treatment in the event of HF exposure.

Extrait de la page du site internet du CAP de Lille http://cap.chru-lille.fr/GP/magazines/96685.html	Translation of the web site page http://cap.chru-lille.fr/GP/magazines/96685.html
***PREMIERS SOINS* en cas d'exposition** Le **PRONOSTIC** est fonction de la précocité des soins Si vous portez secours à une victime, utilisez une protection personnelle adéquate afin de ne pas devenir aussi une victime. • En cas de contact cutané : • Déshabiller le sujet • Lavage à l'eau ou à l'hexafluorine : il doit être • IMMEDIAT • LARGE , il faut laver plus que la zone supposée atteinte • ABONDANT • PROLONGE , pendant 10 à 15 min • Iraitement neutralisant spécifique : Gel de gluconate de calcium à 2.5% • massage de la zone brûlée , application large et immédiate après le lavage .Le pansement se renouvelle toutes les 3-4 h pendant 24 h. • En absence de ce gel , on peut utiliser des compresses imbibées de solution de gluconate de calcium , faire des bains (surtout en cas d'atteinte des doigts) de GC . • En cas d'atteinte oculaire : • Lavage identique • Collyre à base de gluconate de calcium à 1% et consulter un ophtalmologue en urgence • Remarques , dans les 2 cas : • penser à vérifier l'état des vaccinations antitétaniques • surveillance étroite pendant 48 h • Nécessité d'une prise en charge hospitalière en cas de contamination étendue ou de contamination avec de l'acide concentré car il y a un risque d'intoxication générale grave .Il faut une surveillance et un traitement spécifique. • En cas d'inhalation : • Eviction de la zone d'exposition • Prise en charge symptomatique et surveillance hospitalière 24 H • En cas d'ingestion : • Si le sujet est conscient : administrer per os des ampoules de gluconate de calcium • Sinon : mesures de réanimation • Transfert médicalisé à l'hôpital	***FIRST AID in cases of exposure*** The Prognosis depends on early care If you rescue a victim, use adequate personal protection to avoid becoming a victim too. • In case of skin contact: • Undress • Water washing or Hexafluorine: it must be • IMMEDIATE • LARGE, wash more than the supposedly affected area • ABONDANT • EXTENDED for 10 to 15 minutes • Specific neutralizing traitement: 2.5% calcium gluconate gel • Massage the burned area, wide and immediate application after washing .The dressing is renewed every 3-4 h for 24 h. • In the absence of this gel can be used compresses soaked calcium gluconate solution, making bath with CG (especially for infringement fingers). • In cases of ocular exposure: • Wash identical • Eye drops containing 1% calcium gluconate and seek emergency ophthalmologist • Notes, in the 2 cases: • Remember to check the status of tetanus vaccinations • Close monitoring for 48 hours • Need for hospital treatment in the event of widespread contamination or contamination with concentrated acid as there is a risk of serious systemic poisoning. It needs specific monitoring and treatment. • In case of inhalation: • Eviction of the exposed area • Symptomatic Care and hospital surveillance 24 hours • If swallowed: • If the subject is conscious: give oral calcium gluconate bulbs • Otherwise: resuscitation • Medical transfer to hospital

- **Weizman Institute (Israeli institute for occupational health and safety) – Israel (2009)**

  The Weizman Institute recommends use of Hexafluorine® solution to 'treat the victims of hydrofluoric acid and other hazardous products containing fluorine'.

2.4 Physical-chemical data about Hexafluorine® solution

- Clear and colorless liquid
- pH between 7.2 and 7.7
- Density : 1.047
- Osmotic pressure: 1030 mosmoles.

2.5 Evidence of Hexafluorine® solution innocuousness

The tests of innocuousness performed on Hexafluorine® solution are summed up in the following table (Fig. 42):

Type of test	Animal	Realized by	Test number	Result
Ocular irritation	Rabbit	Safepharm Laboratories UK	133/8	**Non irritant** (indice 1.3)
Cutaneous irritation	Rabbit	Safepharm Laboratories UK	133/7	**Non irritant** (indice 0.0)
Inocuity by oral route of a 2000 mg/Kg dose	Rat	CERB France	990553 ST	**Non toxic** > 2000 mg/kg
Sensitization using Magnusson Kligman method	Guinea pig	CERB France	20030418 ST	**Non sensibilizing**
Cytotoxicity	Fibroblast culture	Integra Italy	REL/622A/07 /IRRC/ELB,	**Non cytotoxic**
Genotoxicity	5 strains of Salmonella typhimurium 1 strain of Escherichia coli	Citoxlab France	42214 MMT	**No mutagenic activity**

Figure 42: Evidence of Hexafluorine® solution innocuousness

2.6 Hexafluorine® solution classified as a medical device

Hexafluorine® solution has been classified as a medical device (MD) by the competent authorities according to the European Directive 93/42 because it is used for initial washing of skin/eye HF splashes without pharmacological effect.

Hexafluorine® solution may be used on damaged skin and eye.

It is classified as IIa (CE 0459).

It is sterile.

3 General conclusion

Technical prevention and first aid care on work premises allow control frequency and severity of accidents by chemical splash and, particularly, those due to hydrofluoric acid. The severity of injuries by hydrofluoric acid depends on (Fig. 43):

- the time of contact of HF with skin or eye surface,
- the concentration of HF,
- its temperature,
- extend of the affected surface[90].

Route of exposure with HF	Affected surface	HF Concentration
Cutaneous	1 %	Anhydrous
	5 %	> 70 %
	7 %	50 à 70 %
	10 %	20 à 50 %
	20 %	< 20 %
Ingestion or inhalation		> 5 %

Figure 43: Lethal risk of burns by HF

When applying the Dünser table mentioned above to the situation, among 32 cases of accidental exposures to HF reported in chapter 3.2 (references of cases occurred in industry with early washing with Hexafluorine® solution), 5 victims incurred a lethal risk. However, there has been no death and even no systemic effect have been observed after decontamination with Hexafluorine® solution used immediately, whether followed or not by a complementary application of calcium gluconate, when necessary. In the case report decontaminated with Hexafluorine® solution at a 3 hour delay after water washing, no systemic effet was observed, even if the affected area was 10 % of the total body surface area with 70 % HF exposure.

Therefore, it is crucial to wash hydrofluoric acid splashes as soon as possible, and display first aid washing devices close to exposed staff[91]. It is also important to offer exposed workers as well as safety and medical personnel in charge of chemical decontamination, a quick simple and secured decontamination protocol, whatever the concentrations and the affected body surface area.

Washing with water only and washing with water followed by application or injection of calcium gluconate, have not always given any evidence of their optimal efficacy in the most serious situations. The international literature indeed reports some tragic cases for which heavy secondary therapeutic managements are crucial with no guarantee of avoiding a lethal outcome[92, 93, 94, 95,]. Some disabling sequelae have been described. All of such accidents are particularly accidents involving high concentrations of HF.

Hexafluorine® solution is a washing solution for ocular and cutaneous splashes by hydrofluoric acid, and has been developed by Prevor Laboratory in order to realize an efficient decontamination. Hexafluorine® solution improves the main important physical effect of the washing which is the removing of hydrofluoric acid at the surface of the skin and eye.
The present dossier gives answers to the questions concerning its efficacy:

- The use of *ex vivo* models, such as human skin explants or rabbit eyes shows that Hexafluorine® solution can physically limit the diffusion of hydrofluoric acid because of its osmotic pressure.

- The *in vitro* experiments show the double effectiveness of Hexafluorine® solution on corrosivity (pH measurement) and toxicity (pF measurement). Water dilutes hydrofluoric acid and does not act on either of those two hazards. Calcium gluconate acts mainly on toxicity but has limited effectiveness on acidity.

- Hexafluorine® solution has helped to avoid the appearance of lesion in an *in vivo* burn model due to 70 % HF and to maintain a constant calcemia concentration. In the experiment, other tested solutions do not have such effects.

The success of clinical cases regarding use of Hexafluorine® solution, presented in this dossier, comes both from:

- its properties of an aqueous solution by physically removing and diluting the most important amount of the hydrofluoric acid at the surface of the skin or the eye,

- its hypertonic properties limiting the diffusion of the acid through the skin and eye and creating a flux from the inside to the outside of the tissues,

- its ability to absorb the acid ions and chelating the fluoride ions.

In cases of delayed washing with Hexafluorine® solution, the burn may have already appeared. Decontamination is then necessary but not sufficient and a secondary treatment with the gluconate of calcium is required. In cases of delayed use of Hexafluorine® solution, after 1 minute, prolong the washing with Hexafluorine® solution following the recommended protocol and apply calcium gluconate if needed.

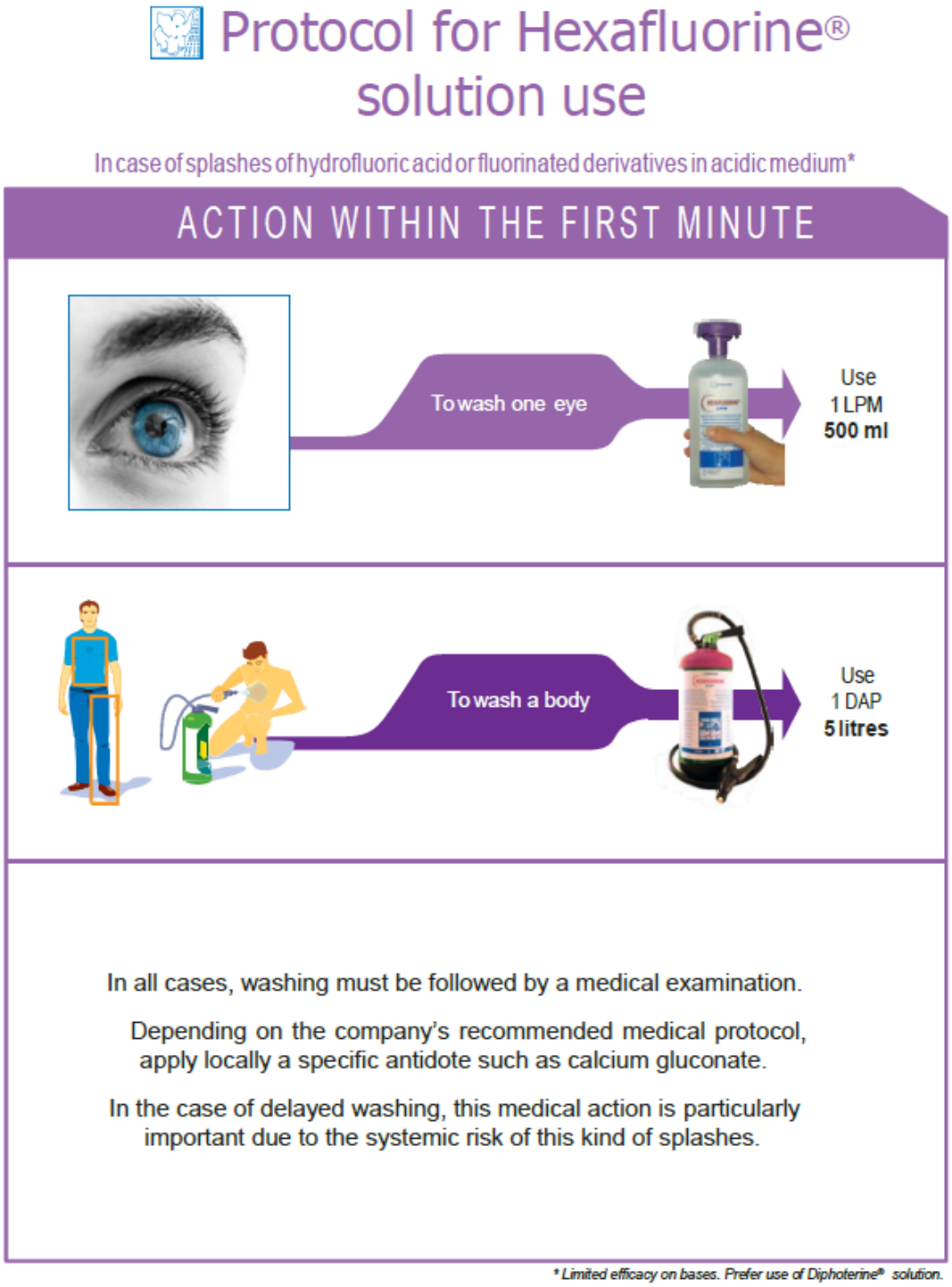
It is thus necessary to decrease the contact time and wash as soon as possible to optimize the effectiveness of Hexafluorine® solution.

Within companies, chemical risk awareness and training of employees exposed to chemicals, as well as health and safety staff, will make it possible to minimize the risk of chemical splashes and, if need be, to effectively decontaminate oneself in emergency situations.

The next chapter suggests technical tools to improve management of HF splashes' victims.

4 Improvement of management of victims of chemical splashes due to Hexafluorine® solution

4.1 Protocol for use of Hexafluorine® solution



WASHING PROTOCOL WITH HEXAFLUORINE® SOLUTION*

Start washing within the first minute following the splash, beginning **with uncovered areas**.

Remove clothing and/or contact lenses.

Continue washing the **unclothed areas** as quickly as possible.

Do not put back on clothes stained with washing residue or the chemical.

Consult a specialist.

GENERAL WASHING INSTRUCTIONS

Never delay washing.

For optimal effectiveness use Hexafluorine® solution **as first aid**. Use the entire contents of the container.

If there is no available Hexafluorine® solution, use water and then wash with Hexafluorine® solution as soon as possible.

For a contact time **greater than one minute**, prolong the washing of the exposed area for **3 to 5 times the duration of contact time**. In case of an ocular splash, it is not necessary to continue washing for more than 15 minutes.

Then, depending on the company's recommended medical protocol, apply locally a specific antidote such as **calcium gluconate.**

Then immediately seek medical advice.

After a first aid ocular washing with Hexafluorine® solution, the use of **Afterwash II® solution** is recommended to facilitate a quicker return to a physiological state.

If **oral mucosa** is affected by the splash, rinse the mouth with Hexafluorine® solution and then spit it out.

If the **ear canal** is affected, wash fast with Hexafluorine® solution by instilling 500ml inside the canal, leaning the head to one side, in order to allow the liquid to flow out of the ear.

As in any case of unilateral rinsing of one ear with a liquid at room temperature, a dizzy feeling, with no serious consequences, can occur. It will spontaneously decline within a few minutes.

Container	Container Average diffusion time
LPM (500 ml)	3 minutes
DAP (5 l)	5 minutes

** Limited efficacy on bases. Prefer use of Diphoterine® solution.*

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Toxicology Laboratory & Chemical Risk Management

4.2 Activity spectrum

Hexafluorine® solution can be used on:

- hydrofluoric acid, whatever its concentration,
- HF mixed with other acids,
- fluorides in an acidic medium,
- simple acids (H^+ ion),
- Lewis acids such as BF_3,
- organofluorides compounds with fluoride ions that can be released into tissues.

On fluorides in a basic middle, Hexafluorine® solution has a limited efficacy. On alkali, its efficacy is limited to a mechanical and hypertonic washing. In such cases, the use of Diphoterine® solution is advised.

Below is the list of products tested with Hexafluorine® solution (Fig. 44) on user's requirements. This list is updated and available in the PREVOR website following address:

http://www.prevor.com/FR/sante/RisqueChimique/produits_testes/produitsTestesV2.php

PRODUCTS	CAS N°	TOXICITY
(HEXA)FLUOROSILICIC ACID	16961-83-4	SEE HYDROFLUOSILISIC ACID
ACID SOLUBLE OIL		TOXIC / CORROSIVE
ALODINE 1200		TOXIC / CORROSIVE
ALODINE 1200 SB		TOXIC / IRRITANT
ALODINE 4595 R4-F		HARMFUL / IRRITANT
ALODINE 4780		TOXIC / CORROSIVE
AMMONIUM BIFLUORIDE	1341-49-7	TOXIC / CORROSIVE
AMMONIUM FLUORIDE ETCHANT AF 87,5-12,5 VLSI SELECTIPUR		
AMMONIUM HYDROGEN FLUORIDE	1341-49-7	TOXIC / CORROSIVE
ANTOX 71 E		CORROSIVE / TOXIC
AUROCA RENOVATEUR INOX		
BHF 39/1		
BORON TRIFLUORIDE ANHYDROUS	2095-58-1	TOXIC / CORROSIVE / REACTS WITH WATER
BORON TRIFLUORIDE DIHYDRATE	13319-75-0	TOXIC / CORROSIVE
BORON TRIFLUORIDE DIMETHYL ETHERATE	353-42-4	CORROSIVE / FLAMMABLE / REACTS WITH WATER
BORON TRIFLUORIDE ETHERATE	109-63-7	CORROSIVE / FLAMMABLE / REACTS WITH WATER
BORON TRIFLUORIDE IN ACETIC ACID	373-61-5	CORROSIVE / HARMFUL
BULCOAT 33	17439-11-1	TOXIC / CORROSIVE
CDR 1045		CORROSIVE / TOXIC
CERAMEX		
CHEMOLUX TI-II		CORROSIVE / TOXIC
CUPOSIT ACCELERATOR 19H		IRRITANT
DEOXIDINE SC 56 CF		TOXIC / CORROSIVE
DISODIUM HEXAFLUOROSILICATE	16893-85-9	TOXIC
ELECTROLYTE RS 01		HARMFUL / CORROSIVE / SENSITIZER
FLUORINE	7782-41-4	TOXIC / CORROSIVE
FLUOROBORIC ACID	16872-11-0	CORROSIVE / TOXIC
FORAPERLE		IRRITANT / HARMFUL / TOXIC

GARDACID P449		CORROSIVE / TOXIC
GRANODINE 1993-E3		HARMFUL / IRRITANT
GREENFLUX ACTIVATE 1000 - ACTIVATEC 1000 - ECO GREENFLUX FP 38976 (FLUOROBORATES)		IRRITANT / HARMFUL WHEN INGESTED
HCR 840LIQUID (500)		VERY TOXIC / CMR /CORROSIVE
HEXAFLUOROPHOSPHORIC ACID	16940-81-1	CORROSIVE / TOXIC
HEXAFLUORURE DE TUNGSTENE	7783-82-6	CORROSIVE / TOXIC
HYDROFLUORIC ACID	7664-39-3	CORROSIVE / TOXIC
HYDROFLUORIC ACID / AMMONIUM FLUORIDE		CORROSIVE / TOXIC
HYDROFLUORIC ACID / NITRIC ACID		CORROSIVE / TOXIC
HYDROFLUOSILISIC ACID	16961-83-4	CORROSIVE
LIPASTE-NLE4		HARMFUL / CORROSIVE
M GLASS ETCH	**1333-83-1**	SEE SODIUM BIFLUORIDE
M GLASS ETCH 3%/SULFURIC ACID 16%		
MAGNESIUM FLUOROSILICATE	16949-65-8	TOXIC
NETTOR AL 12 (HF/H2SO4)		CORROSIVE / TOXIC
NITRIC ACID 15 % AND HYDROFLUORIC ACID		CORROSIVE / TOXIC
NITRIC ACID ETCHANT SF 68-01 VLSI SELECTIPUR		
OCTAFLUOROCYCLOPENTENE	559-40-0	IRRITANT / TOXIC
PHOSPHORIC ACID / AMMONIUM FLUORIDE		CORROSIVE / TOXIC
PHOSPHORUS TRIFLUORIDE	7783-55-3	TOXIC / CORROSIVE
POTASSIUM BIFLUORIDE	7789-29-9	TOXIC / CORROSIVE
PROCAP AV		TOXIC / CORROSIVE
PRÜFLÖSUNG 10	7789-23-3	TOXIC
SILICON TETRAFLUORIDE	07783-61-1	CORROSIVE / TOXIC
SODIUM BIFLUORIDE	1333-83-1	TOXIC / CORROSIVE
SOUDINOX		TOXIC / CORROSIVE
STRIP ISO-VERRE NORMAL		TOXIC / CORROSIVE
STRIP ISOVERRE®		CORROSIVE / TOXIC / CARCINOGENIC
SULPHUR HEXAFLUORIDE	2551-62-4	TOXIC / IRRITANT
SYSTOCHROMAT 1653/1		TOXIC / CORROSIVE
TIN (II) FLUORIDE	7783-47-3	HARMFUL / IRRITANT
TONER 100		TOXIC /CORROSIVE
TRIETHYLAMINE TRISHYDROFLUORID	73602-61-6	TOXIC / CORROSIVE
CHLORINE TRIFLUORIDE	7790-91-2	CORROSIVE / TOXIC WHEN INHALED / FLAMMABLE
TURCO 4104		CORROSIVE / TOXIC
TURCO ALUMIGOLD FLUSSIG		CORROSIVE / TOXIC
TURCO LIQUID SMUT-GO NC		CORROSIVE / TOXIC
TURCO SMUT-GO#4		CORROSIVE / TOXIC
UNICHROME CR 842		VERY TOXIC / CMR / CORROSIVE
WELD-GUARD STAINLESS STEEL PICKLING GEL		TOXIC / CORROSIVE

Figure 44: List of products tested with Hexafluorine® solution washing

4.3 Washing time

Washing must be performed as a primary action, as early as possible, in the first minute after the splash whether it is ocular or cutaneous. The later the washing, the longer the time of contact between hydrofluoric acid and skin cells, the more the lesion risk increases and the more the time of washing must be extended.

In case of first aid washing (within 1 minute), the contents must be completely used. Given our current knowledge, for washing in different conditions as those recommended by the protocol, we consider that the washing time must correspond to 3 to 5 times the time between splash and start of washing. The longer the time of contact, the more significant the lesions are. Once more, **staff must be sensibilized to the hazards of handling HF and decontamination devices must be installed closed to accident sources in order to shorten the time of decontamination after contact. This can be vital in numerous cases.**

The efficacy of washing with Hexafluorine® solution is limited when washing with water as a primary action. Because of its hypotonicity, water creates an osmotic flow from the outside towards the inside of tissues and, doing so, progressively trains a part of substances from the contact surface towards the deep layers of skin or eye. Therefore it is easy to understand why Hexafluorine® solution must be directly available on sites with HF splash hazards, in order to start washing as early as possible after a splash. Obviously, washing initially with water is better than doing nothing.

Decontamination with Hexafluorine® solution may be followed by secondary applications of calcium gluconate, depending on the protocol set up under the responsibility of the medical authority. PREVOR distributes 2.5 % calcium gluconate tubes, content 40 g, manufactured by KAYS. Calcium gluconate gel is classified as a medical device (MD) type IIa, CE0120.

In any case, a splash due to hydrofluoric acid remains a serious accident. It is always recommended to have a medical evaluation performed in order to decide on a potential secondary management.

Remember!

Never delay the washing

The victim's clothes must be removed, eyes opened and contact lenses removed.

The victim must be washed with Hexafluorine® solution, as a primary action, within the first minute after a hydrofluoric acid splash. Then ask advice from a specialist.

4.4 Packaging

The following table (Fig. 45) displays all the available packaging:

	Wall Mounted Eyewash (500 mL)	Portable Eyewash (500 mL)	Autonomous PortableShower (5L)
Use	Ocular use	Ocular use	Use on body
Intervention time for optimal efficacy	**< 1 min**		
Shelf-Life	**2 years**		
Content	2 bottles of 500 mL Hexafluorine® solution + 1 bottle of 200 mL of Afterwash II® solution	500 mL Hexafluorine® solution	5 liters
Rinsing time	**500 mL Hexafluorine® solution: 3 minutes of washing**		**5 minutes**

Figure 45: Types of Hexafluorine® solution packaging

500 mL Hexafluorine® solution packagings (eyewashes bottles or soft plastic pouches) are sterilized by autoclave. Their shelf-life is 2 years when sealed and 6 months when ready to use. The 500 mL eyewash of the wall mounted station is directly ready to use and has a shelf-life of 2 years.

To promote the smoothest possible return to a physiological state, it may be useful and comfortable to use secondarily, following Hexafluorine® solution washing, Afterwash II® solution which is isotonic to the cornea. Osmotic pressure of Afterwash II® solution is almost the same as cornea osmotic pressure.

Afterwash II® solution is therefore more appropriate to this situation than simple saline solution which is hypotonic (280 milliosmoles/l), or of course water, whose osmolarity is almost inexistent. Indeed, tap water creates a second osmolar trauma in reverse direction on already potentially damaged eye tissue.

When started, the autonomous portable shower (DAP) must be immediately and completely used. Every packaging is for a unique utilization. After each use, make sure that the washing solution is set back into working order, meaning either replaced the solution or the device changed, so that the first aid material is always ready to use.

Presentation of the different types of packaging of Hexafluorine® solution (Fig. 46, 47, 49) and calcium gluconate gel (Fig. 48).

Figure 46:
500 mL portable Eyewash
(for complete washing of one eye)

Figure 47: Wall mounted Eyewash station
(2 bottles of 500 mL for complete washing of two eyes of Hexafluorine® solution and 1 bottle of Afterwash II® solution)

KAYS 40 g calcium gluconate gel tubes are supplied with a wall mounted display or as 10 tube refills.

Figure 48: KAYS Medical 2.5 % calcium gluconate gel tubes

Figure 49: Autonomous portable shower (DAP) 5 L of Hexafluorine® solution to wash complete body

Figure 50: Protection box for DAP with antifreeze system

5 Material safety data sheet of Hexafluorine® solution

The Material Safety Data Sheet of Hexafluorine® solution is available on the PREVOR web site (www.prevor.com).

6 Technical data from the SDS of hydrofluoric acid

6.1 Physical-chemical data

Formula : HF, may partly dissociate into H^+ and F^- in water (pK_a = 3,2)

Chemical name : hydrofluoric acid, hydrogen fluoride

Class: Weak Mineral Acid

CAS number: 7664-39-3

EINECS Number: 231-634-8

EC index: anhydrous HF 009-002-00-6, aqueous solutions of HF 009-003-00-1

Physical, chemical properties and specificities [96] :

- Molar mass: 20.006 g/mol
- Colorless liquid for temperatures below 20 ° C, very volatile
- Boiling point 19.5°C (in atmospheric pressure)
- Density at 0°C: 1.002
- Vapour density (air = 1) : 0.7
- Vapour pressure: 13.3 kPa at –28.2°C, 53.3 kPa at 2.5°C et 150 kPa at 30°C
- HF Produces irritant and corrosive white vapours when in contact with water,
- HF Miscible with water in any proportion and thus great faculty to be concentrated
- When very concentrated, HF remarkably volatile
- Unlike other acids, HF attacks glass. Aqueous solutions of HF attack most metals. HF does not attack platine, gold, silver and mercury
- HF reacts violently with anhydrous alkali or bases in concentrated solutions
- HF corrosive action and penetrating potential cause deep tissular destruction

Hydrofluoric acid is the smallest mineral acid. It can be indefinitely concentrated, first as a HF monomer then as a dimer or polymer $(HF)_n$. In water, it only dissociates a little (its dissociation constant pk_a= 3,2, meaning about one molecule out of 1000 = $1/10^{-3.2}$). Thus, hydrofluoric acid can appear under three forms in water: H^+, F^-, HF.

Therefore, one must be careful with pH measurement because, for HF, it does not represent all the acid potential. This is very different from strong acids which completely dissociate in water.

For instance, hydrochloric acid, HCl, is to be found in water completely in the form of H^+ and Cl^-. pH measurement which only takes the H^+ ions concentration in account is not a real parameter indicating the danger of HF.

With equal pH, for instance when pH=0, the HF concentration is 1000 times higher than the concentration in HCl.

6.2 Storage

Solutions with a HF concentration above 70 % or anhydrous HF must be stored in stainless steel barrels. More diluted HF solutions may be stored in containers made of aluminium bronze, lead or synthetic resin materials.

6.3 Labeling

According to the Global Harmonized System and the EC regulation CLP 1272/2008, the labeling of HF is (Fig. 52):

Product	Danger	Caution	Danger class	Pictogram	H comments
Hydrogen fluoride	Acute toxicity	Danger	2*		**H330**: causes severe skin burns and ocular lesions.
	Acute toxicity	Danger	1		**H310**: causes severe skin burns and ocular lesions.
	Acute toxicity	Danger	2*	Danger	**H300**: causes severe skin burns and ocular lesions.
	Cutaneous corrosivity	Danger	1A		**H314**: causes severe skin burns and ocular lesions.
Hydrofluoric acid** ... %***	Acute toxicity	Danger	2*		**H330**: causes severe skin burns and ocular lesions.
	Acute toxicity	Danger	1	Danger	**H310**: causes severe skin burns and ocular lesions.
	Acute toxicity	Danger	2*		**H300**: causes severe skin burns and ocular lesions.
	Cutaneous corrosivity	Danger	1A ou 1B**		**H314**: causes severe skin burns and ocular lesions.
	Ocular irritation	Attention	2**		**H319**: causes a severe irritation of eyes.

* The reference (*) is also present in the column of specific concentrations limits and M factors, where it shows that the involved entry is restrained by specific concentrations limits for acute toxicity according to the EC directive 67/548/CEE. When there is the reference (*), the claasification of this entry as acute toxicity must be the object of a specific attention.

** Corrosive for skin class 1A for concentrations ≥ 7 %
Corrosive for skin class 1B for concentrations between 1 and 7 %
Irritant for eyes class 2 for concentrations between 0.1 and 1 %, with in this case H319 comment: « Causes a severe irritation of eyes ».

*** Some substances (acids, bases…) are sold and circulate in aqueous solutions with diverse concentrations. Then these solutions require a different labeling, because their potential dangers depend on the concentration.

Figure 52: European labeling according to the CLP

In addition to the above table, are the C comments of caution. For class 1 and 2 of acute toxicity, the C comments are (Fig. 53):

Type of CA (Caution Advice)	Number	Comment
Prevention CA (Toxicity by oral way)	P264 P270	Wash… thoroughly after handling. Do not drink, eat or smoke when handling this product.
Intervention CA (Toxicity by oral way)	P301 + P310 P321 P330	IN CASE OF INGESTION: call an ANTIPOISON CENTER or a doctor immediately. Specific treatment (ckeck label). Rinse mouth.
Storage CA (Toxicity by oral way)	P405	Keep locked.
Elimination CA (Toxicity by oral way)	P501	Empty content/container into
Prevention CA (Toxicity by cutaneous way)	P262 P264 P270 P280	Avoid contact with eyes, skin or clothes. Wash… thoroughly after handling. Do not drink, eat or smoke when handling this product. Wear protective clothes and gloves, protective gear for eyes and face.
Intervention CA (Toxicity by cutaneous way)	P302 + P350 P310 P322 P361 P363	IN CASE OF CONTACT WITH SKIN: wash thoroughly with water and soap. Call an ANTIPOISON CENTER or a doctor immediately. Specific measures (ckeck label). Immediatley remove contaminated clothes. Wash contaminated clothes before use.
Storage CA (Toxicity by cutaneous way)	P405	Keep locked.
Elimination CA (Toxicity by cutaneous way)	P501	Empty content/container into
Prevention CA (Toxicity by inhalation)	P260 P271 P284	Do not breathe dust/fumes/gaz/fog/vapours/sprays. Only use in wide or space or well ventilated place. Wear breathing protective gear.
Intervention CA (Toxicity by inhalation)	P304 + P340 P310 P320	IN CASE OF INHALATION: take victim outside and keep resting in a position of easy breathing. Call an ANTIPOISON CENTER or a doctor immediately. Specific treatment is urgent (check label).
Storage CA (Toxicity by inhalation)	P403 + P233 P405	Store in a well ventilated place. Keep container sealed and airtight. Keep locked.
Elimination CA (Toxicity by inhalation)	P501	Empty content/container into

Figure 53: Risk comments for class 1 and 2 of “Acute toxicity” danger

For class 1A or 1B, skin corrosive/irritant agents, the P phrases are (Fig.54):

Caution Advice Prevention	**P260:** Do not breathe dust/fumes/gaz/fog/vapours/sprays. **P264:** Wash thoroughly after handling. **P280:** Wear protective clothes and gloves, protective gear for eyes and face.
Caution Advice Intervention	**P301 + P330 +P331:** IN CASE OF INGESTION: rinse mouth. DO NOT purge. **P303 +P361 +P353: I**N CASE OF CONTACT WITH SKIN (or hair): remove contaminated clothes immediately. Rinse skin with water/ shower. **P363:** wash contaminated clothes before use. **P304 + P340: I**N CASE OF INHALATION: take victim outside and keep resting in a position where breathing is easy. **P310:** Call an ANTIPOISON CENTER or a doctor immediately. **P321:** Specific treatment (check label). **P305 + P351 + P338: I**N CASE OF CONTACT WITH EYES: rinse thoroughly with water for several minutes. If victim wear contact lenses, remove them when easy to remove. Keep on rinsing.
Caution Advice Storage	**P405:** Keep locked.
Caution Advice Elimination	**P501:** Empty content/container into

Figure 54: Risk comments for class 1A and 1B of cutaneous corrosion/irritation » danger

7 Glossary

Acantholysis

Dislocation of the epidermis' medium layer cells, due to the diminution of their reciprocal adherence, causing the formation of cavities into the epidermis.

Calcemia

Medical name for the concentration of calcium in blood. Normal rate for an adult between 2.2 and 2.6 mmol/L (with normal levels of blood proteins).

Cation

Name of the positive ions (such as: Ca^{2+}, Mg^{2+}, K^{+}, Na^{+}).

Caustic

Every chemical substance that destroys tissues. Regulations more often use « corrosive » which is the modern word for caustic.

Chelation

IUPAC[1] definition: The formation or presence of bonds (or other attractive interactions) between two or more separate binding sites within the same ligand and a single central atom. A molecular entity in which there is chelation (and the corresponding chemical species) is called a 'chelate'.

Coagulation

Transformation of a liquid organic substance into a solid or semi-solid mass, of more or less gelatinous consistency.

Collagen

Fibrous glycoprotein with a function comparable to a framework. It is the most common protein of the body, representing ¼ of all proteins. Collagen is secreted by the cells of the conjuctival tissues. Its molecular weight is 300 kDa. Collagen is a protein made of three associated polypeptidic chains (illustration Fig. 55).

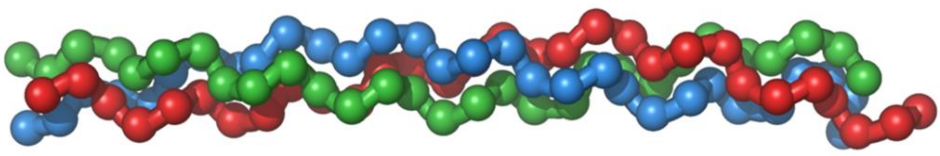

Figure 55: The three chains constituting collagen

As these three chains can combine in different ways, we should deal with collagens and not only collagen. Every type of collagen has got its own structure and is to be found in specific organs.
For instance, collagen of type I acts in the formation of skin, and particularly during the process of wound healing. Unlike elastine which is also present in conjunctival tissues, collagen is unextensible and has a good resistance to traction. The degradation of collagen is difficult and requires specific enzymes, the collagenases (family of matricial metalloproteinases).

[1] International Union of Pure and Applied Chemistry web site: http://goldbook.iupac.org/C01012.html

Conjunctiva

Conjunctiva is a thin smooth, bright and moist mucous membrane. It covers the inner surfaces of the eyelids (palpebral conjunctiva) and reflects, thus forming an irregular cul-de-sac (fornix), to cover the anterior or outer face of the eyeglobe (ocular or bulbar conjunctiva). Inflammation of the conjunctiva is called conjunctivitis (pinkeye).

Corrosive

A substance attacking violently a material and causing its corrosion.

Dermis

Dermis is the medium layer of skin, between the epidermis above and the hypodermis below. Made of conjunctival tissue, the dermis is subdivided in two (Fig. 56):

- the papillary dermis, which is the most superficial, is constituted of columns rich in blood vessels and cells. It "fits" into the deep layers of the epidermis at the level of the dermis-epidermis junction,
- the reticular dermis is more fibrous and thicker. It is sub-jacent to the papillary dermis.

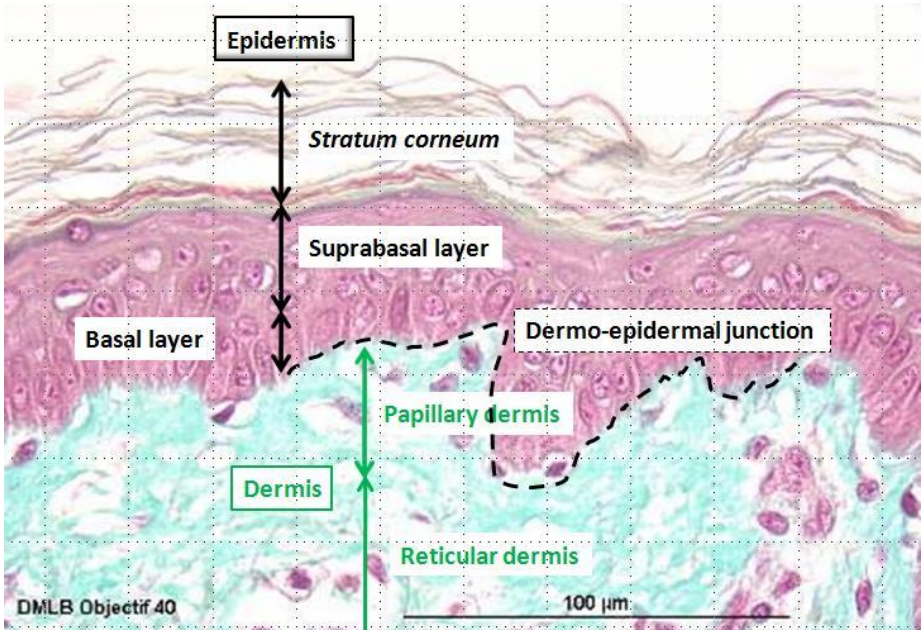

Figure 56: Different skin layers

Electrolyte

Substance that can dissociate when in a solution. An electrolyte may be made of ions (for instance, sodium chloride) or molecules. An electrolyte is called strong when all its constituents ionize in a solution. This applies to salts, strong acids and alkali. An electrolyte is called weak if only a part of its constituents dissociate in a solution.

Epidermis

Epidermis is the most superficial skin layer. It is made of 5 sub-layers of cells (Fig.57). The epidermis is only about one millimeter or even less thick. Its thickness depends on the groups under consideration and on the parts of the body. For instance, in humans, the epidermis is thicker on the palm of the hand and on the sole of the foot (because of the thickening of the corneal layer).

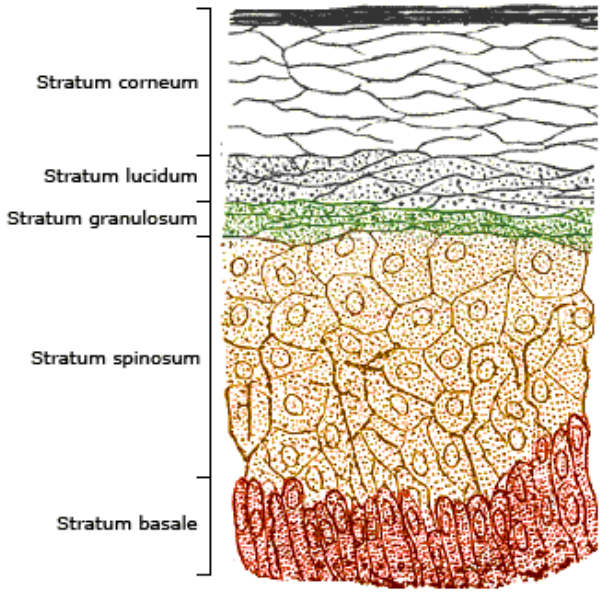

Figure 57: the sub-layers constituting the epidermis

Epithelial

Adjective relating to the epithelium

Epithelium

Tissue with the function of coating external parts and internal cavities of the body, made of tightly juxtaposed cells, with no interposition of fiber or fundamental substance (which makes them different from conjunctival tissues).There are several types of epithelium depending on the shape, the function and the number of layers of constituting cells. The epithelium of skin (Fig. 58) is multilayer like the epithelium of cornea. The epithelium of skin is keratinized, whereas the epithelium of eye is not (Fig. 59).

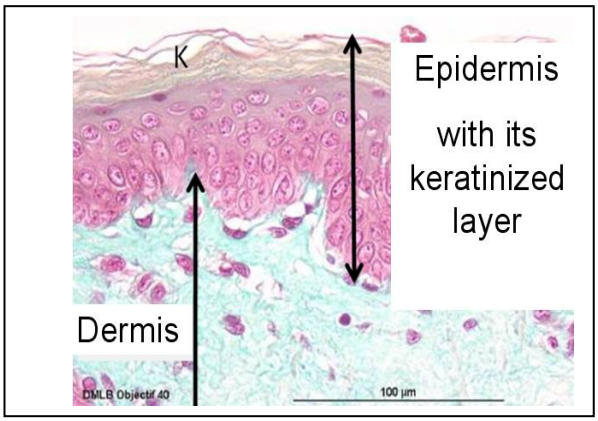

Figure 58:
Epidermis = epithelium covering the surface of skin

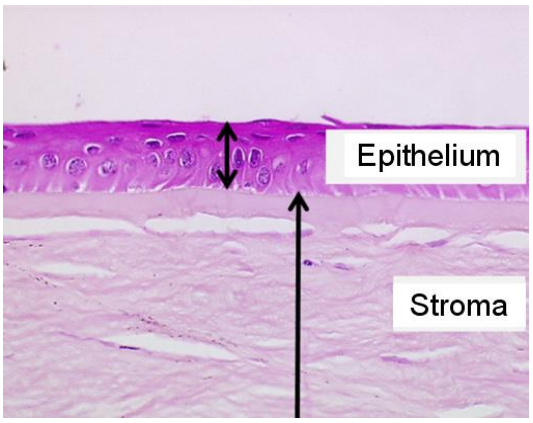

Figure 59: epithelium of cornea

Erythema

Generic name of cutaneous alterations having a more or less intense redness of the integuments (covering tissue, skin) as a common clinic character. It disappears with pressure (Fig. 60). Sunburns are good illustrations of eythematous reactions.

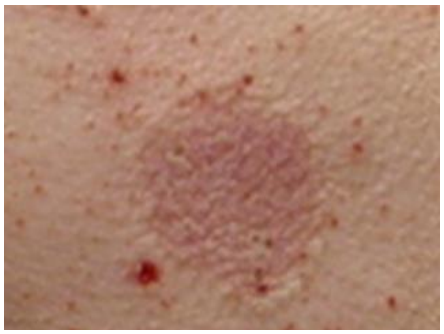

Figure 60: Local cutaneous erythema (irritation by contact)

Histology

Science and techniques studying microscopically the structure of organic tissues.

Histological

Adjective relating to histology.

Hypercalcemia

Calcium concentration in the blood higher than normal rate.

Hypertonicity

State of a liquid or a solution with an osmotic pressure (or tension) higher than that of another liquid, in the presence of which it is put and which is used as a reference.

Hypocalcemia

Calcium concentration in the blood lower than normal.

Hypothermia

Decrease of body temperature below 35 °C.

Hypotonicity

State of a liquid or solution with an osmotic pressure lower than that of the reference milieu.

Innocuousness

Quality of anything without danger.

Ischemia

Ischemia is a slow down or a stop of the vascularization of a zone of the body. Myocardial infarction is an illustration of ischemia.

Keloids

Object in the shape of a scar, resulting from a growth of the dermis at the level of a cured wound. It is made of lesions of firm consistency, which are unsteadily raised and slowly extensive in a more or less radicular way, and harden all along their evolution. They can also be nodular. It is of fibrous nature. It is mostly constituted of collagen, excessively synthetized by fibroblasts during the cicatricial stage of reconstruction. Its extension spreads beyond the initial zone of trauma, which makes the difference between a keloid scar and an "only" hypertrophic scar. Its color varies from pink to dark brown (for black skins). A keloid scar may look really bad, and sometimes be painful and/or itching.

Normality

The normality of an acid solution corresponds to the number of moles of H^+ ions that may be released per liter of this solution. For a monoacid such as HF, a solution containing one mole per liter is called one time molar 1M or one time normal 1N. For a diacid such as H_2SO_4 which delivers two H^+ ions for one mole of acid, a molar solution will be two times normal or 2 N.

Necrosis

This word is used for a wide range of morphological changes, which follow the definitive pathological stoppage of the vital process of the cells constituting the living tissues. The nuclei of necrotic cells may become *pyknotic* (definition below).
Histologically (check *histological*), there are two types of necrosis:

Coagulative necrosis

It implies the preservation of the contours of coagulated cells (check coagulation). Appearance of ghost cells (Fig. 61). It is thought that the increase of intracellular acidity does not only damage structure proteins but also enzymatic proteins, and thus stops proteolysis. The cytoplasm looks uniformly pink with an acidophilic tinctorial character. Finally, the process of coagulative necrosis protects the general architecture of tissues. This aspect is typical of a death of cells due to oxygen deprivation (hypoxia).
The myocardial infarction is an excellent illustration, in which acidophilic and coagulated anucleate cells (the nucleus of which is no longer visible) can be observable *in situ* for several weeks.

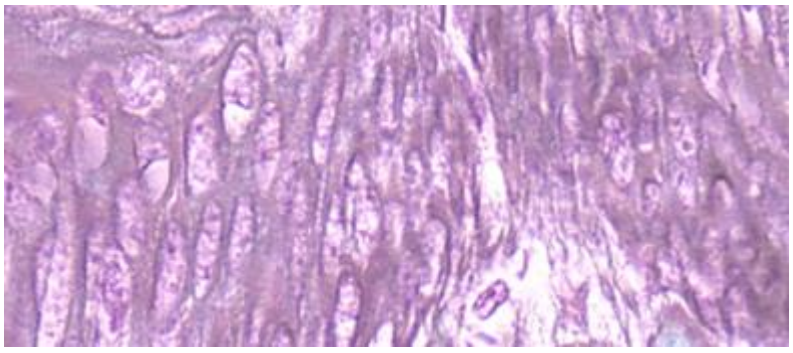

Figure 61: Ghostly aspect of epidermal cells during a liquefactive necrosis

Liquefactive necrosis

Conversely, liquefactive necrosis results from the progressive action of degradation enzymes inside cells lethally attacked by an external cause (thermal burn, chemical corrosion or toxicity, microbial agents…). The morphological appearance of liquefactive necrosis results from the denaturation of intracellular proteins by enzymatic digestion. The cytoplasmic content (internal milieu of cells) turns into a viscous liquid mass. Necrotic cells cannot maintain the integrity of their cytoplasmic membrane and they release their contents and thus an inflammatory reaction of the surrounding tissue is started. The necrotic tissue loses its architecture (Fig. 62). The process of necrosis takes several hours to become visible. A common example: the formation of yellowish pus mostly made of leukocytes suffering from liquefactive necrosis due to an acute inflammatory response which settles in response to a bacterial infection.

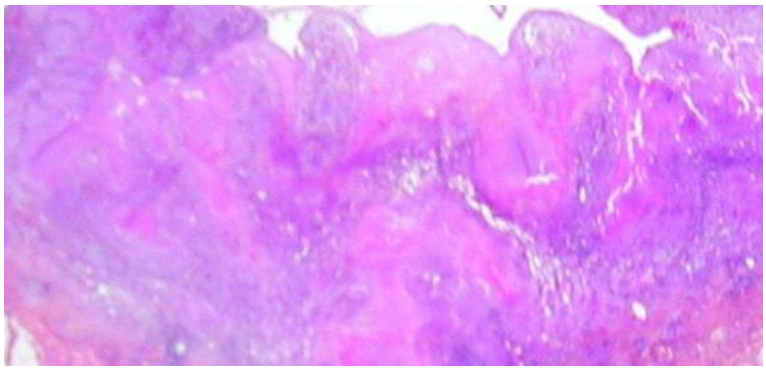

Figure 62: Liquefactive necrosis

Edematous

Suffering from edema

Edema

Serious infiltration of different tissues and specifically of the conjunctival tissue covering skin or mucosa. Concerning the skin, the edema appears as a painless swelling without redness, on which a fingerprint may be visible for a little time.

Osmolarity

Osmolarity is equivalent to the number of osmotically active particles per liter of solution and permits the measurement of osmotic pressure.

Osmotic

Osmotic pressure or tension = force applied by two liquids, of different concentrations in dissolved molecules or electrolytes, onto both sides of the semipermeable membrane that separates them. The word « osmosis » was created by the Scottish chemist Thomas Graham from the Greek word ὠσμός, meaning “thrust”, to name the force that tends to balance molecular concentrations. Osmosis is therefore defined, through its experimental highlighting, as the phenomenon of diffusion of solvent molecules (in general, water) through a semipermeable membrane that separates two liquids with different solute concentrations. The migration of solvent from one side to the other creates a difference of hydrostatic pressure which compensates exactly for the difference of osmotic pressure (Fig. 63).

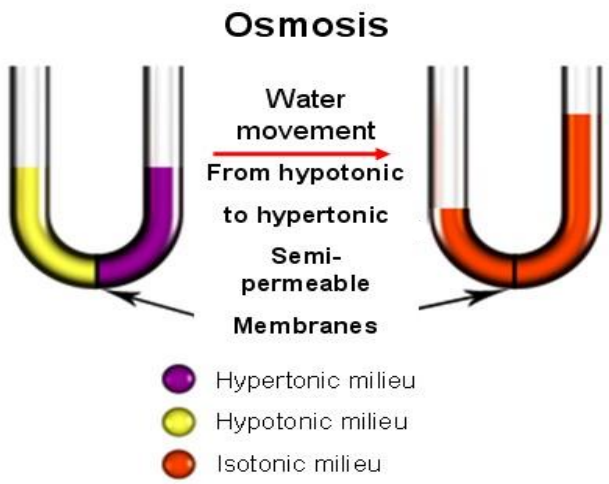

Figure 63: Principle of osmosis

pF

Opposite of the logarithm of the concentration in free fluoride ions. The more the pF rises, the lower the concentration in free fluoride ions is. And the smaller the pF is, the higher the concentration of free fluoride ions is.

« Physiological » pF

Zone of non-danger for a given range of concentration in free fluoride ions.

pH

Opposite of the logarithm of the concentration in proton (H^+). The more the pH increases, the lower the concentration in acid is. And the smaller the pH is, the higher the concentration in H^+.
« Physiologically acceptable pH range »: Zone of non-danger for a given range of concentration of H^+ and OH^- ions, between acidic and basic milieu.

The physiologically acceptable area

The physiologically acceptable area is an area where the pH or the pF is non harmful. For pH, the area is for pH values between 5.5 and 9, and for pF, values above 5.

pK_a

Dissociation constant relating to an acid.

Phlyctena

A cutaneous phlyctena (blister, vesicle) is a circumscribed rise of the cutaneous epidermis, due to a collection of clear liquid into a newly formed cavity resulting from the detachment of the epidermal lamina from the dermis. This word applies to both vesicle and blister.

Pyknotic

Typical aspect of the nuclei of necrotizing cells. It is a condensation of DNA, the main constituent of nuclei, which is responsible for their morphological modification. The nuclei appear as a compact and basophilic (affinity of basic stains) solid mass (Fig. 64).

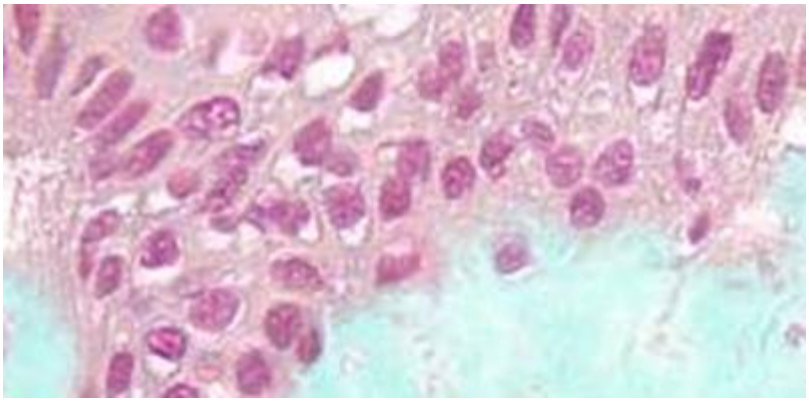

Figure 64: Pyknotic aspect of the nuclei of epidermal cells necrotized by penetration of 70 % HF

Proton

Positive ion which is the entity H^+.

Stroma

Layer formed by an extracellular matrix constituted of collagen lamellae and few cells (mostly keratocytes). All these elements sit in some fundamental substance, constituted of glycorpoteins and proteoglycans. The stroma accounts for 90 % of the complete thickness of human cornea.

Stromal

Relating to the stroma (layer of the cornea at the level of eyes).

8 Hexafluorine® solution bibliography

The bibliography about Hexafluorine® solution is available on PREVOR's web site (www.prevor.com).

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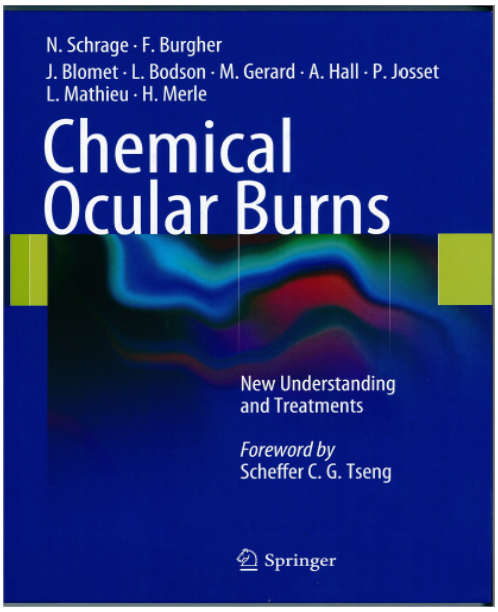

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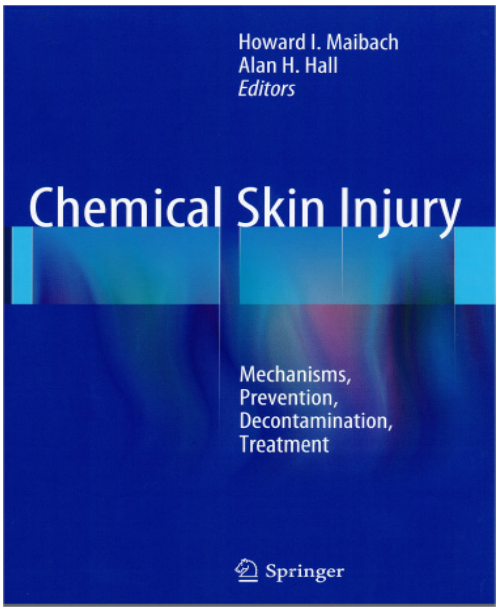

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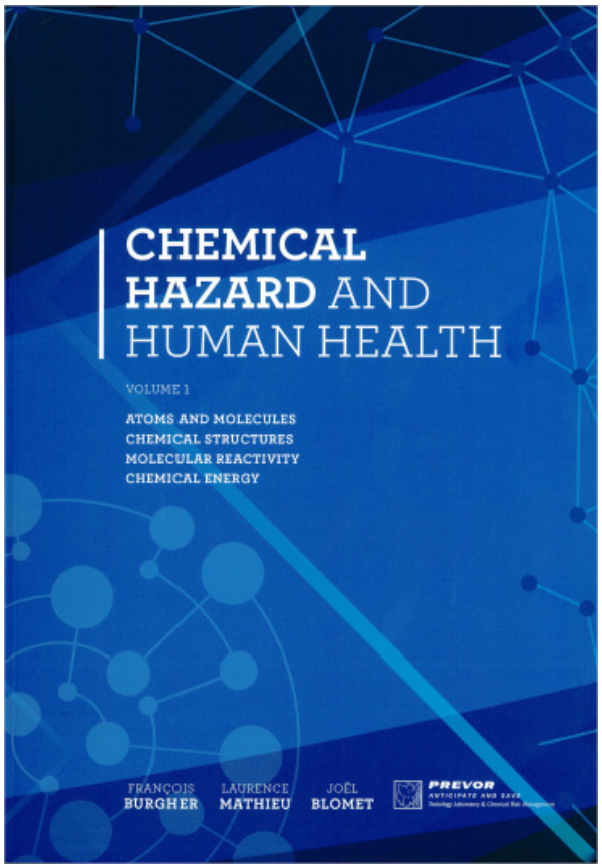

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