CHEMICAL SPLASHES

→ DIPHOTERINE® → HEXAFLUORINE®

PRINCIPLES AND INDICATIONS FOR USE

Why use Diphoterine® or Hexafluorine®?

AN EMPLOYEE HAS BEEN SPLASHED WITH A CHEMICAL AND HAS BEEN DECONTAMINATED WITH DIPHOTERINE® OR HEXAFLUORINE®

- To stop the chemical’s action on the eye or skin and to easily remove it
- To increase effectiveness in comparison with washing with water or saline solution:
  * Improved intervention time for optimal efficacy use within one minute as opposed to 10 seconds for water washing
  * Effective for binding a wide variety of different chemical substances
  * Decreases requirements for care beyond initial decontamination, sequelae and lost work time
  * For hydrofluoric acid: simultaneous action on both its corrosiveness and toxicity
  * In the event of delayed washing:
    - Diphoterine® stops the chemical’s harmful effects,
    - has a positive effect on the healing time, facilitating patient management

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# TABLE OF CONTENTS

1 - INTRODUCTION
   - Mechanism and management of chemical burn injuries
     1.1 – Factors determining the severity of chemical burns ........................................ p. 3
     1.2 – Speed and effectiveness of washing chemical splashes .................................... p. 3

2 – DIPHOTERINE®
   2.1 – Diphoterine®'s mechanism of action .................................................................... p. 5
   2.2 – Washing with Diphoterine®: advantages compared to water ................................ p. 5
   2.3 – When and how should Diphoterine® be used? ...................................................... p. 11
   2.4 – Management of a chemical splash washed with Diphoterine®............................ p. 12
      2.4.1 – Medical findings ................................................................................................. p. 12
      2.4.2 – Patient management in the company medical department .............................. p. 14
      2.4.3 – Treatment by a specialist or at the hospital ...................................................... p. 15
   2.5 – Formulation, innocuousness and classification of Diphoterine® ......................... p. 15

3 – HEXAFLUORINE®
   3.1 – Hexafluorine®'s mechanism of action ................................................................. p. 18
   3.2 – Washing with Hexafluorine®: advantages compared to water ............................ p. 19
   3.3 – When and how should Hexafluorine® be used? .................................................... p. 23
   3.4 – Management of a chemical splash washed with Hexafluorine® ......................... p. 24
      3.4.1 – Patient management in the company medical department .............................. p. 24
      3.4.2 – Treatment by a specialist or at the hospital ...................................................... p. 26
   3.5 – Formulation, innocuousness and classification of Hexafluorine® ....................... p. 27

4 – CONCLUSION

5 – BIBLIOGRAPHY

6 – SUMMARY SHEETS
   - Diphoterine® ........................................................................................................... p. 31
   - Hexafluorine® ........................................................................................................ p. 32
   - Vigilance system feedback ...................................................................................... p. 36

Improvement of the management of chemical splashes
THE MECHANISM AND MANAGEMENT
OF CHEMICAL BURN INJURIES

1.1 – FACTORS DETERMINING THE SEVERITY OF CHEMICAL BURNS

- Chemical burns are the result of a chemical reaction between a corrosive or irritating molecule and one or more biochemical components of the skin or eye.

The severity of a chemical burn depends mainly on:
- nature and concentration of the chemical,
- energy of the reaction,
- duration of contact.

It also depends on physical factors such as the involved pressure or the temperature, the area and the extent of the affected tissues and whether the tissues are healthy or not. The effectiveness of emergency decontamination and first aid care influence the appearance and the development of the chemical burn and consequently, the significance of the sequelae (1).

1.2 – SPEED AND EFFECTIVENESS OF WASHING CHEMICAL SPLASHES

- It is well-known, by all professionals in the field of prevention and safety, that the early washing of a chemical splash makes it possible to decrease the severity of the burn. Historically, water was the obvious universal means of decontamination. This was a great advance in limiting the severity of chemical burn lesions (2). However, this progress was limited by two factors:
  - time it takes to intervene and thus the duration of chemical contact,
  - concentration of the major corrosive agents (3).

This very short recommended intervention delay of about 10 seconds, is, in practice, difficult to achieve at the time of the accident which can lead to worsening of the lesions caused by a corrosive agent.

Study and the elucidation of the mechanism of the chemical burn (Figure 1) has led the PREVOR® Laboratory to conceive solutions for “active washing”, which can be considered as improvements on washing with water. An amphoteric molecule with multiple binding sites, capable of reacting with corrosive and irritating agents and preventing or decreasing their action on the tissues was added to the effects of mechanical washing and passive dilution provided by water decontamination. The types of chemicals which result in chemical burns are acids, bases, oxidising agents, reducing agents, chelating agents, alkylating agents and certain solvents. The active washing solution is also hypertonic, which interrupts the penetration of a corrosive or irritating agent into the tissue. The purpose of active washing, with solutions such as Diphoterine® and Hexafluorine®, is to prevent or decrease the after-effects of chemical burns.
# CHEMICAL BURNS

**SEVERITY FACTORS**

<table>
<thead>
<tr>
<th>&gt; Type of elementary chemical reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>- acid-base</td>
</tr>
<tr>
<td>- redox reaction</td>
</tr>
<tr>
<td>- dilution</td>
</tr>
<tr>
<td>- alkylation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>&gt; Energy level of the reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased harmful potential of the product</td>
</tr>
<tr>
<td>- pH and pKa</td>
</tr>
<tr>
<td>- oxidation-reduction potential</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>&gt; Molar concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 0.2 N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>&gt; Area of affected tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expresse in percentage of the body surface or in cell</td>
</tr>
<tr>
<td>- in the eye</td>
</tr>
<tr>
<td>- on healthy skin</td>
</tr>
<tr>
<td>- on already damaged skin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>&gt; Period of chemical contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>- time elapsed before the start of effective washing</td>
</tr>
<tr>
<td>- delay due to first washing with water</td>
</tr>
<tr>
<td>- not effective washing solution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>&gt; Aggravating factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>- temperature</td>
</tr>
<tr>
<td>- solid particles</td>
</tr>
<tr>
<td>- evaporation of solid substances</td>
</tr>
<tr>
<td>- splash under pressure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>&gt; Symptoms and Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to normal</td>
</tr>
<tr>
<td>&gt; Inflammation Pain</td>
</tr>
<tr>
<td>then Cleaning</td>
</tr>
<tr>
<td>Healing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>&gt; Sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>- corneal opacity</td>
</tr>
<tr>
<td>- joint stiffness</td>
</tr>
<tr>
<td>- stenosis</td>
</tr>
</tbody>
</table>

---

**Figure 1**: chemical burn injuries and aggravating factors
DIPHOTERINE®

2.1 – DIPHOTERINE®’S MECHANISM OF ACTION

> Diphotherine® is a general-purpose washing solution for ocular and cutaneous chemical splashes. Diphotherine® is a hypertonic, amphoteric and multi-site washing solution. It therefore has a double effect:

- mechanical properties of washing with water
- additional neutralising and chelating properties which accelerate and optimise the process of decontamination.

The hypertonicity of Diphotherine® prevents the chemical from penetrating the tissue and makes it possible to create a reverse flux capable of pulling the chemical out of the tissue.

Its amphoteric character and its various reactive sites enable it to act on the irritating and corrosive agents which cause chemical burns. These include acids, bases, oxidising agents and reducing agents...

2.2 – WASHING WITH DIPHOTERINE®:
ADVANTAGES COMPARED TO WATER

> As with water, the purpose of using Diphotherine® rapidly is to attempt to prevent chemical burns. The more rapidly Diphotherine® is used, the shorter the contact with the chemical will be. The risk of a chemical burn occurring will thus be minimised.

Concerning the action performed on the corrosive substance, Diphotherine®, compared to water, neutralises the aggressive nature of the chemical (acid, base, oxidant, reducer or chelator) much more rapidly and effectively with less washing.

![Figure 2: Influence of osmotic pressure and amphoteric properties on washing effectiveness](image)

Water (2 min)
Diphotherine® (3 min)
Physiological pH
0.9% NaCl (3 min)
2.34% NaCl (3 min)
DIPHOTERINE®

► Diphoterine®'s effectiveness has been proven on an experimental and a clinical level. The analysis of these data concerning chemical decontamination with Diphoterine® is based on three levels of scientific evidence.

• Convergent clinical data:

In spite of the difficulties of performing studies on first aid in the workplace and the inevitable limitations related to the interpretation of the results, much of the data collected on human subjects provide convergent elements.

Many accounts of Diphoterine® use have been provided by companies (1). Generally transmitted by occupational health doctors, the reports can be criticised one by one, either for a problem of methodology or interpretation, but when all of these several hundred cases of Diphoterine® use are combined, the coherence of the whole reveals some certainties about its effectiveness:

- no harmful effects,
- decrease in pain,
- no after-effects,
- absence of or only a small amount of secondary care,
- absence of or only a few days of work loss.

The French National Institute of Research and Safety decided to independently verify the effectiveness of various chemicals splash decontamination methods, including Diphoterine®. For that purpose, an investigation (2) was carried out with the help of company medical doctors in France. 73 companies and more than 60 accidents were taken into consideration. This study shows Diphoterine®'s action on a varied sample of chemicals, and indicates that Diphoterine®, when used according to the recommended protocol, is always at least as effective as water. The continuation of this investigation (3) showed that the results, for a total of 145 chemical splash cases studied, were superior for concentrated bases. In the study performed by Martinswerk (1), the superiority of Diphoterine® washing on bases, both in terms of effectiveness and washing safety, was also confirmed despite the small size of the statistical series:

<table>
<thead>
<tr>
<th>Washing Solution</th>
<th>Diphoterine®</th>
<th>Acetic Acid</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>No secondary care</td>
<td>100 % +/- 15</td>
<td>0 % +/- 15</td>
<td>0 % +/- 15</td>
</tr>
<tr>
<td>Simple secondary care</td>
<td>0 % +/- 15</td>
<td>80 % +/- 15</td>
<td>25 % +/- 15</td>
</tr>
<tr>
<td>Medicalised secondary care</td>
<td>0 % +/- 15</td>
<td>20 % +/- 15</td>
<td>75 % +/- 15</td>
</tr>
<tr>
<td>Number of days of work loss</td>
<td>0.18 % +/- 0.4</td>
<td>2.91 % +/- 4.3</td>
<td>8 % +/- 8.12</td>
</tr>
</tbody>
</table>

For isolated reported cases, the examples are also very significant. Take the case of 2 large cutaneous splashes of concentrated sulphuric acid with equal concentrations (95%): the one washed with water led to serious after-effects, and six months of work loss, and the other washed with Diphoterine® resulted in neither after-effects nor work loss (4).
Experimental in vivo data which confirm the clinical results:

When the chemical burn does occur, its development is determined by two phenomena:

- the cleaning phase (inflammation, destruction), which is increased in cases of chemical burns,
- the repairing phase (healing), which is decreased.

In vivo experimental studies have confirmed that when the development of the chemical burn is stopped, the healing of the injured tissues is carried out in better conditions. The effectiveness of washing with Diphoterine® was compared (8,9) to washing with saline solution on a concentrated cutaneous hydrochloric acid burn in rats. Diphoterine® stopped the development of the chemical burn, which led to the following consequences:

- a significant reduction of pain (reduction of concentrations of substance-P in the first 48 hours, p < 0.05; increase of the concentration of ß-endorphin after 7 days, p < 0.05),
- a reduction of inflammation (reduction of the interleukin-6 after 48h, p < 0.01; after 7 days, p < 0.05),
- better healing of the skin (size of the lesion after 7 days: Diphoterine® 4 mm² versus saline solution 6 mm², no washing 12 mm²).

A study of a 15.3% ammonia ocular burn in rabbits (10) has allowed an understanding of the chemical burn mechanism and has showed the relevance of even delayed treatment of such a burn. This experimental burn model was then tested in order to compare the effectiveness of Diphoterine® versus saline solution (11). After washing with Diphoterine® there is:

- an absence of a stromal oedema, while it has been observed after washing with saline solution or even when there is no washing,
- an inflexion of the pH, which has not been observed after washing with saline solution or when there is no washing.

The presence of a stromal oedema, resulting from inflammation due to the burn and the hypotonic effect of washing, is known to be an aggravating factor in the development of chemical burns (12).
• Experimental data *ex vivo / in vitro* which explain the clinical results:

These studies have allowed us to understand and confirm the clinical results obtained. One of these (13) compares the effectiveness of different washing solutions in exposure to 5ml of 0.5 M caustic soda or hydrochloric acid and shows the limitations of water washing on corrosive agents. Despite adding an amount of water which represented 50 times the amount of caustic soda or of hydrochloric acid contamination, water did not bring the pH level back to physiological values.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Added Water (250 ml)</th>
<th>Added Diphoterine® (Previn®) (100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5M Caustic Soda</td>
<td>pH = 11.8</td>
<td>pH &lt; 9</td>
</tr>
<tr>
<td>0.5M Hydrochloric Acid</td>
<td>pH = 2</td>
<td>pH = 6.3</td>
</tr>
</tbody>
</table>

Physiological zone (no burn): 5.5 < pH < 9

An experiment on enucleated pig eyes measured the effect of both early and delayed washing on the development of the intra-ocular pH: only washing with Diphoterine® showed an improvement of the intra-ocular pH, even if the washing was delayed.

In this same publication (13), the physical limits of water washing on fibroblast cultures is shown. Water is hypotonic. When there is a chemical burn, the osmotic pressure of the cornea increases up to 1280 mosmoles/kg. Washing with a hypotonic solution (such as water) can cause osmotic shock and a cytolyis (destruction of cells after swelling). See also the Kompa et al’s publication (14) on the direct effect of a washing solution’s osmolarity on the cornea’s osmolarity.

The following table clearly shows the advantages of using Diphoterine®.
| WATER | | DIPHOTERINE® |
|---|---|---|---|---|
| Advantages | Limitations | Advantages | Limitations |
| Chemical agent(s) at the surface of the affected tissues are carried away | | Chemical agent(s) at the surface of the affected tissues are carried away | |
| Dilution | | Dilution | |
| Polyvalent | | Polyvalent | Theoretical and experimental effectiveness proven on major chemical groups. Should be verified case by case for specific chemical agents |
| Hypotonic | Favours a part of the chemical agent's penetration of the tissue, especially in the eyes | Hypertonic | Stops the chemical agent's penetration of the tissue and carries the chemical away from the interior to the exterior of the tissue |
| No action on corrosive or irritating agents | Development of the chemical burn | “Neutralising” action on the potentially irritating or corrosive nature of the chemical agent | Stops the development of the burn |
| Optimal intervention time: the first 10 seconds | | Optimal intervention time: within the first minute 6 times superior | Increased security of first aid |
| Possibility of serious physical after-effects, even death(3) | | Decrease or absence of after-effects (compared to water) Better prevention of chemical burns | |
| In certain cases, complex secondary treatment with reconstructive surgery (3) | | Decrease or absence of secondary treatments Prevents after-effects Decrease in work loss | A medical consultation is necessary in every case |
| Non-toxic | Expiry date to be observed and weekly maintenance to be carried out | Non-toxic, sterile | Expiry date must be observed |
A recent published study (15) shows the usefulness of Diphtherine® even in cases of delayed washing, within the first hours following an accident. The study compares, for equivalent grades of burns, the differences which occur after washing with Diphtherine® versus washing with saline solution before treatment of a burn due to an alkaline chemical. This study shows a significant reduction in the amount of time needed for the reepithelization of the cornea:

<table>
<thead>
<tr>
<th>Reepithelisation time in days</th>
<th>Diphtherine®</th>
<th>Saline Solution</th>
<th>Value of p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>1.9 +/- 1</td>
<td>11.1 +/- 1.4</td>
<td>p &lt; 10^-7</td>
</tr>
<tr>
<td>Grade II</td>
<td>5.6 +/- 4.9</td>
<td>10 +/- 9.2</td>
<td>p &lt; 0.02</td>
</tr>
<tr>
<td>Grade III</td>
<td>20 +/- 14.1</td>
<td>45.2 +/- 23</td>
<td>p = 0.21 NS</td>
</tr>
</tbody>
</table>

_Absence of ocular Grade IV with Diphtherine®_

A published case (16) of a severe ocular chemical burn (Grade IV) shows the benefit of delayed washing with Diphtherine® and describes the associated secondary treatment, principally aimed at reducing inflammation and pain, as well as preventing infection. The case evolved towards progressive reepithelization in less than 21 days, and complete stable healing in 180 days. No surgical treatment was necessary in this case.

**Summary of the advantages of using Diphtherine® over water or saline solution**

<table>
<thead>
<tr>
<th>Results with Diphtherine®</th>
<th>Ocular (ammonia in rabbits (10,11))</th>
<th>Cutaneous (hydrochloric acid in rats (9,12))</th>
</tr>
</thead>
</table>
| in vivo versus saline solution | - Decrease in corneal oedema  
- Reduction of the intraocular pH  
- Reduction in the time needed for tissue healing | - Reduction of pain  
- Reduction of inflammation  
- Reduction in the time needed for tissue healing |
| Clinical tests in industry (3) versus water | - Decrease in requirement for care beyond initial decontamination  
- Decrease in lost work time  
- Decrease in after-effects | |
| Clinical tests in hospitals (15,16) versus saline solution | - Decrease in the time needed for healing | |

The advantage of Diphtherine® is that it acts directly on the corrosive or the irritating agents. This results in the prevention or minimisation of the inflammatory phenomena which occur very early in response to a cutaneous or ocular chemical splash. Hence the necessity, in order to achieve optimal effectiveness, of an immediate intervention at the site of the accident and of the presence of Diphtherine® as a first aid treatment at work stations.
2.3 – WHEN AND HOW SHOULD DIPHOTERINE® BE USED?

> Diphotereine® is indicated in first aid washing of all types of ocular and cutaneous chemical
spashes.
   It has a limited effect on hydrofluoric acid splashes because of both the corrosive and toxic
mechanisms of this acid. It is preferable in these cases to wash with Hexafluorine®, which spe-
cifically addresses both of these problems.
Carried out within the first minute and using the entire amount in the appropriate product
container, the purpose of external washing with Diphotèreine® is to prevent or minimise the
appearance of lesions and thus the risks.

WASHING PROTOCOL WITH DIPHOTERINE®

Wash with Diphotereine® as the primary action and as rapidly as possible
within the first minute for optimal efficacy
and
remove clothing and/or contact lenses.
Continue washing, being sure to use the entire contents of the
Diphotereine® container Consult a specialist

GENERAL INSTRUCTIONS

Never delay washing
For optimal effectiveness, use Diphotereine®
available at the site of the accident
If Diphotereine® is not available, use water and take the
injured person to the hospital

OCULAR WASHING:

> Less than one minute of chemical contact requires 3 minutes of washing, that is to say
all the contents of a 500 ml bottle or a portable eyewash.
There is a minimal time period of about 10 seconds before the beginning of the chemical's
penetration. For that reason, water can sometimes be effective, in particular with weak
corrosive agents. However, water, because of its hypotonicity, creates a flow into the tissue
from the surface to the deep structures of the cornea. That makes it possible, in practice,
for the corrosive agent to penetrate the anterior chamber more easily and more deeply. (13)
> Particular case of the SIEW (Sterilised Individual Eyewash): Decontamination with a SIEW, containing 50 ml of Diphoterine®, requires washing within the first 10 seconds. In cases where washing has not begun within the first 10 seconds, it must be supplemented with a 500 ml bottle or a portable eyewash.

> Contact lenses: wearing contact lenses at work stations without protection and with exposure to chemical risk is generally discouraged. It is preferable to wear special protective prescription glasses. Safety goggles or a facial mask, to be placed over corrective lenses may also be used. Prescription glasses worn alone are not sufficient. In the case where contact lenses are worn, it is necessary to remove them as rapidly as possible in order to avoid any overconcentration of the chemical or deterioration of the contact lens, which will hinder the effectiveness of washing within the first seconds.

**IN THE EVENT OF A CUTANEOUS SPLASH** within the first minute:

> Use a Micro DAP, a portable self-contained hand spray (100 ml) or Mini DAP (200 ml), for a cutaneous projection on a respective area equivalent to a hand or an arm.

> For a more extended chemical splash on the body use a 5 litre DAP.

**IN THE EVENT OF CHEMICAL CONTACT with oral mucous membranes** within the first minute:

> Possibility of washing with Diphoterine® and then spitting it out.

### 2.4 - MANAGEMENT OF A CHEMICAL SPLASH WASHED WITH DIPHOTERINE®

#### 2.4.1 - Medical findings

Three types of cases are possible during the examination:

1° case: absence of lesions

This happens frequently, because the Diphoterine® protocol has been applied correctly. Usually, no damage is observed and no secondary treatment is necessary. Consequently, there is generally no lost work time.

2° case: observation of a benign lesion

(for eyes: grade I and II of the Roper-Hall classification).

Benign occurrences observed in different situations concern most often the eyes than the skin. They are possibly delayed 24 or 48 h. It is a matter of ordinary signs of inflammation (simple ocular redness and slight sensation of pain). They require the application of a therapeutic protocol, generally anti-inflammatory and/or anti-infection, by a specialist. It has been proven, notably concerning the eyes (12), that effective management of inflammatory symptoms is indispensable to the favourable development of the healing process.

There are different possible causes of these benign lesions. They can be due to:

- the nature of the chemical agent
  - product in solid form, responsible for mechanical erosion of the cornea with inflammation,
  - sensitising character (for example, chromium solution),
  - chemical splash under pressure

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**500 ML FOR 1 EYE TO BE USED WITHIN THE FIRST MINUTE**
**2 DIPHOTERINE®**

**2.4.1 – Medical findings**

- not respecting the initial washing protocol
  - delayed washing,
  - insufficient washing,
  - initial washing with water (almost non-existent osmotic pressure. In these cases, the penetration of the corrosive agent towards the interior of the tissue is facilitated leading to deeper, more serious lesions),
  - Use of Diphoterine® as an eyebath, without the mechanical effect.

- possible side-effects concerning an eventual prescribed medical treatment (for example reaction to certain components of topical ocular pharmaceutical solutions).

Both acquired fundamental knowledge and a very strict vigilance system established a number of years ago, have eliminated all possibilities of negative interference of Diphoterine® used before medical treatment.

**3rd case: Serious lesions (Ocular: grade III or IV of the Roper-Hall classification)**

They are generally due to delayed washing observed after accidents in the home or, more rarely, at the time of criminal attacks where chemicals are used. According to the severity of the burn and its development, a complementary treatment (more or less complex and long) is essential. These cases require a very specialised and complex approach in a hospital setting.

**Clinical examination : Signs of the severity of an ocular burn (17)**

Conjunctival hyperemia : diffused ocular redness by simple vasodilation of the conjunctival veins is not serious, sign of a simple conjunctival irritation.

Conjunctival limbal ischaemia (whitish zone): is due to the interruption of blood circulation at the level of the conjunctivo-limbic vessels. The extent of this ischaemia is the principal sign of the severity of the burn. Ischaemia greater than one-half of the limbic circumference is a factor in a poor prognosis.

This ischaemia is often associated with chemosis (conjunctival oedema which is an elevated ring, often hemorhagic (red spots). The corneal oedema will be at the origin of a decrease in transparency, and the iris can just be made out or not seen at all (porcelain cornea). The result is then a decrease in visual acuity.

An ulcer of the cornea which is complete (affecting all of the corneal surface) and deep (affecting the epithelium and the corneal stroma) is a sign of severity. Paradoxically, in these cases, visual acuity can be preserved.
Clinical Exam: Signs of seriousness of an ocular chemical burn (17) continued...

In minor corneal injuries, such as superficial punctual keratitis, visual acuity is often decreased.

Associated lesions
- Burns on the eyelids: 1°, 2° or 3° degree
- Burns on the face or other parts of the body, which can have implications for patient survival

2.4.2 - Patient management in the company medical department

Washing with Diphtherine®, immediately carried out according to PREVOR's recommendations and using the entire contents of the container, prevents the burn from occurring or considerably decreases its severity.

> IN THE EVENT OF AN OCULAR SPLASH

Make sure that Diphtherine® washing has begun:
- with a SIEW (50 ml) within the first 10 seconds following the splash
- or with an Eyewash (500 ml) within the first minute

If not, for a contact time with the chemical substance greater than 1 minute, the chemical burn can already develop. Resume the initial washing performed with 500 ml of Diphtherine® and follow it by a second washing, ideally for 5 minutes. A chemical burn is a biological invasion followed by an inflammatory reaction of the ocular tissues. Diphtherine® acts to stop this aggression. Then use a container of Afterwash®, which is isotonic with human tears, to facilitate a more rapid return to a physiological state.

> IN THE EVENT OF A CUTANEOUS SPLASH

Make sure that Diphtherine® washing has begun within the first minute.
If not, for a contact time greater than 1 minute, resume washing with Diphtherine® for 3 to 5 times the duration of contact.

Then, in all cases, the patient should be referred to a specialist who will decide more precisely the action to be taken based on the lesions observed.
2.4.3 – Treatment by a specialist or at the hospital

OCULAR CHEMICAL BURN CLASSIFICATION (ROPER-HALL),
prognosis and therapeutic protocol
according to a comparative clinical study (15) Diphoterine® versus normal saline solution

<table>
<thead>
<tr>
<th>Grade</th>
<th>Initial clinical exam</th>
<th>Prognosis</th>
<th>Therapeutic protocol after washing with 500 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Epithelial ulcer, no limbal ischaemia</td>
<td>Favourable</td>
<td>Verification of the anti-tetanus vaccination, rifamycin 6 times/day, 2% ascorbic acid 6 times/day, tropicamide 6 times/day</td>
</tr>
</tbody>
</table>
| 2     | Corneal oedema
       | Ischaemia < 1/3 of the limbal circumference | Poor | Verification of the anti-tetanus vaccination, rifamycin 6 times/day, 2% ascorbic acid 6 times/day, dexamethasone combined with neomycin 6 times/day for 7 days, 1% atropine 3 times/day, 1 g ascorbic acid orally 3 times/day and installation of symblepharon rings. The treatment is maintained until complete reepithelialization of the cornea. |
| 3     | Complete corneal ulcer > 1/3 and
       | Ischaemia > 1/2 of the limbal circumference | Poor | Verification of the anti-tetanus vaccination, rifamycin 6 times/day, 2% ascorbic acid 6 times/day, dexamethasone combined with neomycin 6 times/day for 7 days, 1% atropine 3 times/day, 1 g ascorbic acid orally 3 times/day and installation of symblepharon rings. The treatment is maintained until complete reepithelialization of the cornea. |
| 4     | Opaque cornea with non visible iris
       | Ischaemia > 1/2 of the limbal circumference | Poor | Verification of the anti-tetanus vaccination, rifamycin 6 times/day, 2% ascorbic acid 6 times/day, dexamethasone combined with neomycin 6 times/day for 7 days, 1% atropine 3 times/day, 1 g ascorbic acid orally 3 times/day and installation of symblepharon rings. The treatment is maintained until complete reepithelialization of the cornea. |

A recently published case of an ocular grade IV burn, showed the advantages of using Diphoterine® under these conditions (15). The patient was treated approximately one hour after the chemical assault and an ocular washing with one litre of Diphoterine® was carried out. The treatment described in the above table was used for this patient. The emergency number of PREVOR (+33 1 30 34 76 76) is placed at your disposal during business hours (time zone, France, GMT +1) for further information.

2.5 – Composition, innocuousness and classification of Diphoterine®

- Composition and properties of Diphoterine®
  - Aqueous saline solution containing Diphoterine®, does not contain phosphates
  - Limpid and colourless liquid
  - pH ranging between 7.2 and 7.7
  - Density: 1.034
  - Osmotic pressure: 820 mosmoles/kg
  - Sterile solution (by autoclave)
**Toxicological data concerning Diphoterine®**
The tests of innocuousness carried out on Diphoterine® are summarised below:

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular irritation</td>
<td>Non irritant</td>
<td>Test n°1133/4, on rabbits, Safepharm Laboratories Limited, UK, 1987</td>
</tr>
<tr>
<td>In vitro Evaluation of the eye</td>
<td>No cytotoxic or irritant potential to the eye after a short (10 minutes) or prolonged (24 hours) time of contact</td>
<td>Test n°REL/032/05/IRRC/ELB, on human fibroblast cultures, test Integra, Italy, 2005</td>
</tr>
<tr>
<td>Cutaneous irritation</td>
<td>Non irritant</td>
<td>Test n°2005-024, in vitro, Dermal Irritation® test method, Integra, Italy, 2005</td>
</tr>
<tr>
<td>Ocular irritation of a residue of</td>
<td>Non irritant</td>
<td>Test n°6463 TAL, on rabbits, hydrochloric acid, CIT (International Centre of Toxicology), France, 1990</td>
</tr>
<tr>
<td>a washing of an acid with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphoterine®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular irritation of a residue of</td>
<td>Non irritant</td>
<td>Test n°6462 TAL, on rabbits, sodium hydroxide, CIT (International Centre of Toxicology), France, 1990</td>
</tr>
<tr>
<td>a washing a base with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphoterine®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral toxicity</td>
<td>Oral LD₅₀ &gt; 2000 mg/kg ; non toxic, no death, normal evolution of weight, no abnormality at necropsy</td>
<td>Test n°6564 TAR, on rats, CIT (International Centre of Toxicology), France, 1990</td>
</tr>
<tr>
<td>Acute dermal Toxicity</td>
<td>Acute dermal LD₅₀ &gt; 2000 mg/kg; non toxic, no death, no sign of systemic toxicity or dermal irritation, normal evolution of weight, no abnormality at necropsy</td>
<td>Test n°1133/9, on rats, Safepharm Laboratories Limited, UK, 1988</td>
</tr>
<tr>
<td>Sensitisation</td>
<td>Non sensitising</td>
<td>Test n°20030418ST, Magnusson and Kligman method, on Guinea pigs, OECD 406, CERB, France, 2003 (15)</td>
</tr>
<tr>
<td>Mutagenesis</td>
<td>Non mutagenic ; negative Ames test</td>
<td>Test n°29923 MMT, Bacterial reverse mutation Test on Salmonella typhimurium TA 1535, TA 1537, TA98, TA 100et TA 102, Eschherichia Coli WP2 uvrA, CIT (International Centre of Toxicology), France, 2005</td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>Non cytotoxic</td>
<td>Test n°REL/003/06/IRRC/ELB, ISO 10993-5 standard, Integra, Italy, 2006</td>
</tr>
<tr>
<td>Anti-inflammatory potential</td>
<td>Non anti-inflammatory ; no cytotoxic or irritant effect observed on a 3D human epidermis model</td>
<td></td>
</tr>
<tr>
<td>Local tolerance on damaged skin</td>
<td>No irritant or toxic effects</td>
<td>Test n°20080537TL, in the rabbit, CERB Laboratory, France, 2007</td>
</tr>
<tr>
<td>Healthy skin (non-occluded and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>semi-occluded – 24 H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local skin tolerance (occlusive</td>
<td>Non irritant</td>
<td>Test n°1 01-48H, in humans, IDEA Laboratory, France, 2007</td>
</tr>
<tr>
<td>test – 48 H on healthy volunteer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NO SIDE-EFFECTS HAVE BEEN OBSERVED SINCE DIPHOTERINE®
HAS BEEN PUT ON THE MARKET.
The use of DIPHOTERINE® does not present any contraindications.

> PRECAUTIONS FOR USE
To avoid any microbial contamination, keep containers closed. Opened containers in
eyewash stations should only be kept for six months. Do not use after the expiration date
written on the containers.

> ADVERSE EFFECTS
Chemical burns damage living tissues. Diphtherine®'s hypertonicity prevents the penetration
of the tissue (13) and also extracts the chemical. For 1 minute of contact with the chemical,
washing with 500ml of Diphtherine® prevents or minimises the appearance of the burn. If the
contact time is greater than 1 minute, it is possible that a chemical burn will develop. The
osmolarity of a healthy cornea is 420 milliosmoles/L. The osmolarity of a cornea attacked
by a corrosive chemical can reach 2000 milliosmoles/L (not only because of the ionisation
of the chemical substance, but also because of the liberation of electrolytes at the time of
the lysis of the cells).

It is to minimise the osmotic shock that the use of a hypotonic washing solution is
essential and demonstrates very beneficial effects in comparison to water.
Once the corrosive chemical substance is eliminated, the residual osmotic pressure of the
cornea is generally approximately equal to 800 milliosmoles/L. To favourise the most gent-
le return to a physiological state, it may be useful and comfortable to use secondarily, as a
complement to Diphtherine®, a special solution named "Afterwash II" which is isotonic to
tears. This solution is more adapted to this situation than both saline solution alone, which
is hypotonic to tears, and water, whose osmolarity is almost inexistant, creating a second
osmolar traumatism on already potentially damaged tissue.

> WHEN SHOULD DIPHOTERINE® NOT BE USED?
Diphtherine®'s effectiveness is limited on hydrofluoric acid splashes because of the double
corrosive and toxic mechanisms of this acid. Hexafluorine® has been specifically developed
to address these two requirements.
Do not use in the event of splashes of white phosphorus. In the event of these types of
splashes, it is better to use first-aid thermal burn treatment (a water-based gel for example)
on the skin.
Diphtherine® is currently being tested for the treatment of chemical burns due to ingestion
but has not yet been validated. Studies are currently in progress. However, it has already
been tested and classified as non-toxic by oral route.

> CLASSIFICATION OF DIPHOTERINE®
- Washing solution,
- Medical device,
- Class IIa, sterile,
- CE 0459, initial CE certificate obtained: September 1996, renewed January 31, 2007
  after audit
3.1 HEXAFLUORINE®'S MECHANISM OF ACTION

Hexafluorine® is a specific washing solution for ocular and cutaneous hydrofluoric acid (HF) splashes (Figure 3) and fluorides in an acidic medium (e.g.: boron trifluoride). Hexafluorine® is a washing solution with hypertonic and chelating properties.

It thus has two mechanisms of action:
- the mechanical properties of water washing
- additional chemically active and chelating properties which accelerate and optimise the decontamination process
  - Hexafluorine®'s hypertonicity prevents the chemical from penetrating (10) the tissue and creates an inverse flow to pull the chemical to the tissue surface
  - Its neutralising and chelating properties enable it to act both on the corrosive (H+) and toxic (F-) components which are responsible for the particular severity of burns due to this acid

![Figure 3: Hydrofluoric acid mechanism](image)

The photographs in figure 4 highlight Hexafluorine®’s action in vitro on fluoride ions (F−). The chelation of calcium ions by fluoride ions, as much intracellularly at the point of contact as in the circulating blood, explains their toxic effect. Even a limited surface of diffusion can lead to the risk of hypocalcemia with potentially fatal cardiac disorders.

Hexafluorine® by capturing the F− ion, free or precipitated, hinders this toxic mechanism.

![Figure 4: Highlighting of Hexafluorine®’s action on free fluoride ions and on precipitate](image)
3 HEXAFLUORINE®

3.2 - WASHING WITH HEXAFLUORINE®: ADVANTAGES COMPARED TO WATER

3.2.1 - In vitro chemical reactivity

- The pF (fluoride potential) indicates the measure of F⁻ ions like the pH indicates the measure of H⁺ ions. The greater the pF, the lesser the quantity of free F⁻ ions is large. For a pH value greater than 5, the product is not considered to be dangerous (physiological pF).

![Graph: Efficacy of Hexafluorine® on free radical fluoride ions compared to water and a calcium gluconate solution](image)

- As with water, the rapid use of Hexafluorine® is aimed at avoiding the chemical burn due to HF. The more rapidly that Hexafluorine® is used, the shorter the contact with the hydrofluoric acid will be. Thus the risk of a chemical burn developing will be decreased significantly.

![Graph: Efficacy of Hexafluorine® on H⁺ corrosive ions compared to water and a calcium gluconate solution](image)

3.2.2 - Dynamic and physical highlighting of washing effectiveness.

- The OCT-HR technique (Optical Coherence Tomography - High Resolution) allows, on slices of the cornea, to visualize the penetration of the irritating or corrosive chemical substance into the cornea’s interal layers. A recent study (18) has shown the total penetration of 2.5% hydrofluoric acid into the cornea in 240 seconds. This study has shown that Hexafluorine® rapidly stops the penetration of the hydrofluoric acid with a clear cornea after 75 minutes of observation. Comparatively, the corneas washed with water or 1% calcium gluconate are opaque, a phenomena characteristic of a severe HF burn.

![Images: Comparison of corneal penetration with different washing solutions](image)

- HF burn with no washing
- HF burn washed with water
- HF burn washed with 1% calcium gluconate
- HF burn washed with Hexafluorine®

Figure 7: Highlighting of the influence of different washing solutions on the penetration of HF in rabbit eyes ex vivo, 20 seconds of exposure, 25µl of 2.5% HF (grade 2 burn), 15 minutes of washing.
The use of Hexafluorine® permits a rapid neutralisation of the corrosive and toxic potential of HF with a low volume of washing, whereas a progressive addition of water only dilutes the hydrofluoric acid solution. The residual mixture of HF and water remains very aggressive.

Two in vivo experiments were performed (21):

**DEVELOPMENT OF THE BURN**
> The first study was carried out on a cutaneous burn due to 70% HF lasting 20 seconds, in order to observe the comparative histological effects between washing with water, washing with water followed by the topical application of a 2.5% calcium gluconate gel, and washing with Hexafluorine®. The intensity of the reaction was established according to a modified Draize scale.

The main observations of the burn grade after washing were summarised as shown below:

![Graph of burn evolution following different washing methods.](image)

**Figure 8:** Comparison of the efficacy of washing methods following an experimental cutaneous exposure during 10 minutes to 25µl of 70% HF (grade 2 burn).

Washing with water, which does not trap hydrofluoric acid, is not sufficient to stop the evolution of the burn, which quickly becomes a serious burn. The use of calcium gluconate blocks the appearance of the burn, at least during the first 24 hours, but a single application is not sufficient to eliminate all fluoride ions. When the treatment is stopped, the burn re-appears, because the residual rate of free fluorides is still above the toxicity limit. The immediate use of a powerful chelating agent like Hexafluorine® suppresses the action of hydrofluoric acid and does not let any possibility for F⁻ ions to get linked to the calcium into the tissues. The observation of the animals during 6 days does not show any after-effects after a single washing with Hexafluorine® whereas water requires a secondary treatment and calcium gluconate requires multiple applications or injections.
• DEVELOPMENT OF THE CALCEMIA

> In a second in vivo study, the evolution of the development of the calcemia (Figure 7) during 5 days in rats contaminated by 70% hydrofluoric acid.

![Graph of calcium level after a 70% HF burn](image)

*Figure 9: Comparative evolution of the calcium level after decontamination of a cutaneous experimental burn due to 70% HF*

> The analysis of the data shows that washing with water, water + CaCl₂ or water and calcium gluconate have similar results. Statistically, the measures of calcemia carried out between 10 minutes and 1 hour are the same. Significant hypocalcemia can be seen after 4h (for washing with water and washing with water + 10% CaCl₂) and an improvement after 24 h followed by stabilisation. The results clearly show that the calcemia remains normal and stable after washing with Hexafluorine®.

• CASE STUDIES

32 cases of ocular or cutaneous hydrofluoric acid splashes which were washed with Hexafluorine® have been published in the scientific literature. Among them, 5 cases could have presented a lethal risk according to the classification proposed by Dunser (25), but for all the cases the results were the following:

- After each washing, the patient very rapidly noted pain relief, facilitating the decontamination process.
- No after-effects were reported in any of the cases. The loss of work was minimal, one day on average (19, 20, 21).
5 case studies of emergency decontamination with Hexafluorine®(1)

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Splashed by</th>
<th>Affected body surface</th>
<th>Type of washing</th>
<th>Consequences/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HF/HCl bath</td>
<td>Total immersion</td>
<td>Hexafluorine® on the body</td>
<td>Slight burns on the abdomen and the back</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ocular washing with water</td>
<td>Serious burn on the left eye</td>
</tr>
<tr>
<td>1</td>
<td>70% HF vapour</td>
<td>Right cheek</td>
<td>Hexafluorine®</td>
<td>Slight painless erythema. Application the next day with calcium gluconate gel, no lost work time</td>
</tr>
<tr>
<td>1</td>
<td>38% HF</td>
<td>One eye</td>
<td>Hexafluorine®</td>
<td>No burns, no lost work time</td>
</tr>
<tr>
<td>2</td>
<td>5% HF</td>
<td>Body</td>
<td>Hexafluorine®</td>
<td>No burns, no lost work time</td>
</tr>
</tbody>
</table>

SERIES OF 16 CASES AT OUTOKUMPU (AVESTA, various sites, Sweden) (23)

Decontamination with Hexafluorine®

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Splashed with</th>
<th>Affected body surface</th>
<th>Duration of contact</th>
<th>Work loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>70% HF</td>
<td>Left forearm– oral cavity</td>
<td>&lt; 1 min</td>
<td>0 - 1</td>
</tr>
<tr>
<td>1</td>
<td>HF (concentration unknown)</td>
<td>One eye</td>
<td>&lt; 1 min</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>HF/HNO₃ pH1+1</td>
<td>One eye</td>
<td>&lt; 1 min</td>
<td>0 - 0</td>
</tr>
<tr>
<td>1</td>
<td>HF/HNO₃ pH1*</td>
<td>One eye</td>
<td>3 - 5 min</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>HF/HNO₃ pH1+1</td>
<td>Two eyes</td>
<td>&lt; 1 min</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>HF/HNO₃ pH1+1</td>
<td>One thigh</td>
<td>&lt; 1 min</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>HF/HNO₃ pH1+1</td>
<td>Two thighs</td>
<td>1h - 1h:30</td>
<td>2 - 2</td>
</tr>
<tr>
<td>1</td>
<td>HF/HNO₃ pH1*</td>
<td>Face</td>
<td>3 - 5 min</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>HF/HNO₃ pH1+1</td>
<td>Face + oral cavity – Forehead</td>
<td>&lt; 1 min</td>
<td>1 - 1</td>
</tr>
<tr>
<td>3</td>
<td>HF/HNO₃ pH1+1</td>
<td>Forearm– arm + hand – Two elbows</td>
<td>&lt; 1 min</td>
<td>0 - 0 - 1</td>
</tr>
<tr>
<td>1</td>
<td>HF/HNO₃ pH1+1</td>
<td>Wrists</td>
<td>2 h</td>
<td>0</td>
</tr>
</tbody>
</table>

RESULTS
Immediate analgesic effect, no sequelae. In 75% of cases including two splashes with 70% HF, no additional care was required and the average lost work time was less than 1 day (t = 1.1)

HF/HNO₃ mixture: HF 6% and HNO₃ 15%
*preparation including sulphuric acid (H₂SO₄) with an unknown concentration
3 HEXAFLUORINE®

SERIES OF 11 CASES AT THE MANNESMANN PLANT (Remscheid, Germany)

<table>
<thead>
<tr>
<th>Splash</th>
<th>40% HF</th>
<th>6% HF /15% HNO3</th>
<th>40% HF</th>
<th>6% HF / HNO3 15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>% Affected area</td>
<td>1 eye*</td>
<td>1 eye</td>
<td>0.2 − 4.5 − 4.5 − 16.5*</td>
<td>0.2 − 2.25 − 4.5 − 10.5</td>
</tr>
<tr>
<td>First washing (on the site of the accident)</td>
<td>Hexafluorine*</td>
<td>Hexafluorine*</td>
<td>Hexafluorine*</td>
<td>Hexafluorine*</td>
</tr>
<tr>
<td>Second washing (at the infirmary)</td>
<td>Hexafluorine*</td>
<td>Hexafluorine*</td>
<td>Hexafluorine*</td>
<td>Hexafluorine*</td>
</tr>
</tbody>
</table>

RESULTS  
No sequela, no further care required  
No lost work time

* ocular and cutaneous splash with 40% HF

3.3 - WHEN AND HOW SHOULD HEXAFLUORINE® BE USED?

> The use of Hexafluorine® is appropriate in the event of emergency decontamination of splashes with hydrofluoric acid and fluorides in an acid solution.

Performed within the first minute after the splash and using the entire amount of the appropriate product container, the purpose of external washing with Hexafluorine® is to prevent or minimise the appearance of lesions and thus the risks of sequelae.

**WASHING PROTOCOL WITH HEXAFLUORINE®**

Wash first as rapidly as possible within the first minute for optimal efficacy  
and remove clothing and/or contact lenses.  
Continue washing, being sure to use the entire contents of the Hexafluorine® container.

Consult a specialist

**GENERAL INSTRUCTIONS**

Never delay washing  
For optimal effectiveness use an active solution such as Hexafluorine® available at the work site  
If Hexafluorine® is not available, use water then apply locally a specific antidote such as calcium gluconate
FOR OCULAR WASHING:

> Less than one minute of contact with the chemical requires 3 minutes of washing, in other words a 500 ml bottle or a portable eyewash pouch. There is a minimal time period of about 10 seconds before the aggressive chemical begins to penetrate the cornea. For that reason, water can sometimes be effective, in particular with weak corrosive agents. However water, because of its hypotonicity, creates a flux of the chemical from the exterior towards the interior of the cornea. That makes it possible for the corrosive substance to penetrate the anterior chamber more rapidly and deeply [13].

> **Contact lenses:** wearing contact lenses at work stations without protection and with exposure to chemical risk is generally discouraged. It is preferable to wear special protective prescription glasses. Safety goggles or a facial mask, to be placed over corrective lenses may also be used. Prescription glasses worn alone are not sufficient. In the case where contact lenses are worn, it is necessary to remove them as rapidly as possible in order to avoid any overconcentration of the chemical or deterioration of the contact lenses, which will hinder the effectiveness of washing within the first seconds.

IN THE EVENT OF A CUTANEOUS SPLASH

> For a chemical splash on the body and a contact time with the chemical less than one minute, use a 5 litre DAP (Autonomous Portable Shower)

IN THE EVENT OF CHEMICAL CONTACT WITH ORAL MUCOUS MEMBRANES WITHIN THE FIRST MINUTE:

> Possibility of washing with Hexafluorine® and then spitting it out.

### 3.4 - MANAGEMENT OF A CHEMICAL SPLASH WASHED WITH HEXAFLUORINE® AT THE COMPANY MEDICAL DEPARTMENT

3.4.1 – Patient management in the company medical department

Washing with Hexafluorine® performed according to PREVOR’s recommendations, immediately and using the entire contents of the appropriate container, prevents the appearance of burns or considerably decreases their severity.
> IN THE EVENT OF AN OCULAR SPLASH

Ensure that the Hexafluorine® washing has begun within the first minute with a wall-mounted or portable eyewash (500 ml).

If not, for a contact time greater than 1 minute, resume washing with Hexafluorine® and if needed, continue the washing for 3 to 5 times the duration of contact time. HF causes an acid burn from the H⁺ ion and tissue damage and potential systemic toxicity from the F⁻ ion, leading to frequently observed severe eye injuries. Hexafluorine® stops both of these actions. Then use Afterwash IT®, isotonic with human tears, to facilitate a more rapid return to a physiological state.

> IN THE EVENT OF A CUTANEOUS SPLASH

Ensure that washing with Hexafluorine® begun within the first minute.

If not, for a contact time greater than 1 minute, continue washing with Hexafluorine® and if needed, continue washing for 3 to 5 times the duration of contact time to stop the action of the corrosive chemical. All the more reason that in the case of delayed washing, the systemic risk requires management of the patient by a doctor.

• Effects of hydrofluoric acid (23):

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50%</td>
<td>immediate pain and necrosis</td>
</tr>
<tr>
<td>20% - 50%</td>
<td>burn delayed from 1 to 8 hours</td>
</tr>
<tr>
<td>&lt; 20%</td>
<td>pain and necrosis delayed by up to 24h</td>
</tr>
</tbody>
</table>

• Lethal systemic risk with hydrofluoric acid burns (24):

<table>
<thead>
<tr>
<th>Type of burn</th>
<th>Affected surface</th>
<th>Concentration HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burn by contact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 %</td>
<td></td>
<td>anhydrous</td>
</tr>
<tr>
<td>5 %</td>
<td></td>
<td>&gt; 70 %</td>
</tr>
<tr>
<td>7 %</td>
<td></td>
<td>50 - 70 %</td>
</tr>
<tr>
<td>10 %</td>
<td></td>
<td>20 - 50 %</td>
</tr>
<tr>
<td>20 %</td>
<td></td>
<td>&lt; 20 %</td>
</tr>
<tr>
<td>Ingestion of HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation of HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.4.2 – Treatment by a specialist or at the hospital

> OCULAR BURNS

Every hydrofluoric acid ocular burn must be initially and subsequently handled medically because of the frequent disparity between initial appearance and the severity of the sequelae. The treatment of ocular HF burns is similar to the treatment of other chemical burns; specific antidotes can be used according to the company medical protocol and during pre-hospital and hospital management of the injured person.

> CUTANEOUS BURNS

1) Medical Treatment

Generally, after emergency decontamination, protocols recommend the use of specific antidotes: topical, sub-cutaneous, intravenous (Ber block technique), or intra-arterial (for finger and hand burns) such as calcium gluconate or Zéphiram® salts (20). Analgesic treatment may also be prescribed. Medical surveillance of cardiovascular functions may be justified due to the systemic diffusion of HF in relation to the concentration and the total affected body surface area.

2) Additional examinations

Blood tests to be ordered especially if the burn involves more than 1% of the total body surface area (TBSA):
- calcemia
- kalemia
- magnesia
- phosphorenia

---

Case study of a hydrofluoric acid burn (7)

A 45 year old worker, was splashed with a cutaneous 70% HF projection (face, neck, an arm and the abdomen, with a systemic effect which could be lethal, see table, paragraph 3.4), while he was checking a valve. Immediate washing was carried out with water at the accident site for 15 minutes, then with saline solution while being transported to the hospital. The patient received intravenous injections of Ca²⁺ and Mg²⁺ as well as local applications of calcium gluconate gel.

► 1 YEAR OF LOST WORK TIME
3.5 FORMULATION, INNOCUOUSNESS AND CLASSIFICATION OF HEXAFLUORINE®

> FORMULATION AND PROPERTIES OF HEXAFLUORINE®
- Aqueous saline solution containing Hexafluorine®, does not contain phosphates
- Limpid and colourless liquid
- pH ranging between 7.2 and 7.7
- Density: 1.047
- Osmotic pressure: 1030 mosmoles/kg
- Sterile solution (by autoclave)

> INNOCUOUSNESS OF HEXAFLUORINE®
Tests of innocuousness performed on Hexafluorine® are summarised below:

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular irritation</td>
<td>Non-irritating</td>
<td>Test n°133/8, on rabbits, Safepharm Laboratories Limited, UK, 1987</td>
</tr>
<tr>
<td>Cutaneous irritation</td>
<td>Non-irritating</td>
<td>Test n°133/7, on rabbits, Safepharm Laboratories Limited, UK, 1987</td>
</tr>
<tr>
<td>Sensibilisation</td>
<td>Classified non-allergenic</td>
<td>Test n°20040231STC, Magnusson and Klingman method on guinea pigs, CERB, France, 2004</td>
</tr>
<tr>
<td>Toxicity by oral route</td>
<td>Oral LD₅₀ (rat): &gt; 2000 mg/kg; non-toxic, no deaths, normal weight gain, no post-mortem anomalies</td>
<td>Non-toxic (test n°990533ST on rats, CERB, France 2000)</td>
</tr>
</tbody>
</table>
HEXAFLUORINE®

> PRECAUTIONS FOR USE

To avoid any microbial contamination, keep containers closed. Opened containers in eyewash stations should only be kept for six months. Do not use after the expiration date written on the containers.

> ADVERSE EFFECTS

HF ocular burns can lead to significant injuries. Hexafluorine® because of its hypotonicity, stops the penetration and extracts the HF. For 1 minute of contact with hydrofluoric acid, washing with 500ml of Hexafluorine® prevents or minimises the chemical burn. If the duration of contact is more than 1 minute, the chemical burn will appear.

The osmolarity of a healthy cornea is 420 milliosmoles/L. The osmolarity of a cornea attacked by a corrosive chemical can reach 2000 milliosmoles/L (not only because of the ionisation of the chemical substance, but also because of the liberation of electrolytes at the time of the lysis of the cells).

It is to minimise the osmotic shock that the use of a hyperosmolar washing solution is essential and demonstrates very beneficial effects in comparison to water washing.

Once the corrosive chemical substance is eliminated, the residual osmotic pressure of the cornea is generally approximately equal to 800 milliosmoles/L. To encourage the most gentle return to a physiological state, it may be useful and comfortable to use secondarily, as a complement to Hexafluorine®, a special solution named “Afterwash II” which is isotonic to tears. This solution is more adapted to this situation than both saline solution alone, which is hypotonic with tears, and water, whose osmolarity is almost inexistant, creating a second reverse osmolar traumatism on already potentially damaged tissue.

> WHEN SHOULD HEXAFLUORINE® NOT BE USED?

Hexafluorine® is less effective on alkaline solutions. The use of Diphoterine® is much better adapted to such cases. Currently, there is no evaluation program for burns resulting from ingestion, but it has been tested and classified as non-toxic by ingestion.

> CLASSIFICATION OF HEXAFLUORINE®

- Washing solution,
- Medical device
- Class IIa, sterile
- CE 0549, initial CE certificate September 30, 1996, renewed January 31, 2007 after audit
CONCLUSION

Improvement of the management of chemical splashes

Diphoterine® brings a general-purpose response to aggressive chemicals. It improves the management of ocular and cutaneous chemical splashes by pushing back the time of intervention in emergency situations to 1 minute after the splash for optimal effectiveness. When the intervention time is greater than 1 minute, the chemical burn will have already appeared. The delayed use of Diphoterine® will make it possible to stop the chemical’s action on the tissues and to minimise the evolution of the burn, as well as associated pain and inflammation. By limiting the burn, Diphoterine® allows, under better conditions, the application of therapeutic protocols according to the severity of the burn.

Hexafluorine® improves the management of ocular and cutaneous splashes of hydrofluoric acid or fluorides in an acidic medium. Used within the first minute, its effectiveness is optimal. If the contact time is longer than one minute, in addition to Hexafluorine®, apply a treatment based on a chelating fluoride antidote such as calcium gluconate.
BIBLIOGRAPHY


5. Falcy M, Blomet J. Premiers soins en cas de projections ocu- laires, premiers résultats d’enquête (First aid in cases of ocular splashes, preliminary results). DMT 1993, 53, 1st trimester, 33-41


7. Testimonial letters, to be consulted on www.prevor.com


19. Mathieu L, Burgher F, Hall AH. Diphosphatine® chemical splash decontamination solution: skin sensitisation study in the guinea pig. Accepted for publication in Cutaneous and Ocular Toxicology


6

SUMMARY SHEETS
DIPHOTERINE® IN USE

1 NATURE AND PROPERTIES

> Diphotherine® is a washing solution designed for ocular and cutaneous chemical splashes. Set up at the work station and used as first-aid, it allows the minimisation or avoidance of the development of chemical burns, stopping both the effect and the penetration of the irritant and/or corrosive by way of its amphotheric, chelating and hypertonic properties. Diphotherine®, dispensed in specially designed containers, permits and facilitates effective decontamination, reduces pain, the need for secondary care, sequelae and lost work time.

A clinical study carried out in a hospital setting has shown the advantages of even delayed washing with Diphotherine® for the management of ocular chemical burns, combined with a therapeutic protocol aimed at reducing inflammation and at preventing infection while encouraging healing. A published grade IV case likewise developed progressive reepithelialization in less than 21 days and complete and stable healing without surgery after 180 days.

2 HOW SHOULD THIS DEVICE BE USED?

> In the workplace

- Washing within the first minute and as the primary action with the entire Diphotherine® container.

<table>
<thead>
<tr>
<th>SIW</th>
<th>Portable eyewash</th>
<th>Mural eyewash</th>
<th>Micro DAP</th>
<th>Mini DAP</th>
<th>DAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 ml within the first 10 seconds</td>
<td>500 ml within the first minute</td>
<td>500 ml within the first minute</td>
<td>100 ml within the first minute to wash one hand</td>
<td>200 ml within the first minute to wash one arm</td>
<td>5 Litres within the first minute to wash a body</td>
</tr>
</tbody>
</table>

> At the accident and emergency department

* For an ocular splash

- Wash again with 500ml of Diphotherine® followed by a secondary therapeutic protocol.

Based on Roper-Hall classification of ocular chemical burns: prognostic and therapeutic protocol from “Ophtalmologie en urgence” (Emergency Ophthalmology) by Dr Tul, De Nicola, Mann, Miléa and Barale; Elsevier-Masson Editions 2007.

Grade I

Punctuated superficial lacrimal
Hyphaema, chemosis, peribulbar
haemorrhage without ischaemia
No stromal opacity

Out-patient Treatment

- Antibiotic ophthalmic solution
- Cycloplegic ophthalmic solution ± 2% acetic acid ophthalmic solution

Favourable prognosis

Grade II

Partial deepithelialisation
Limbal ischaemia equal to less than
1/3 of the circumference of the limbus
Stromal opacity which obscures the details of the iris

In-patient Treatment

- Anti-inflammatory and antibiotic ophthalmic solution (Ex. Dexamethasone noacyn)
- Cycloplegic ophthalmic solution ± 2% acetic acid ophthalmic solution
- Acetate acid per os (3glycer)
- Symbatrophor ring
- graft

Grade III

Complete deepithelialisation
Limbal ischaemia between 1/3 and
1/2 of the circumference of the limbus
Stromal opacity masking the details of the iris

Grade IV

Complete deepithelialisation
Limbal ischaemia greater than 1/2 of
the circumference of the limbus
Opaque stroma
(all layers affected)

Poor prognosis
DIPHOTERINE® IN USE

3 INOCUOUSNESS

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro evaluation of the ocular irritating potential of a medical device (10 min or 24 hours)</td>
<td>Non-cytotoxic or irritating</td>
<td>Test n’REL/032/05/IRRO/ELB, Integra Laboratory test, Italy, 2005</td>
</tr>
<tr>
<td>Cutaneous irritation</td>
<td>Non-irritating</td>
<td>Test n’2005-024, in vitro, Dermal Irritation® test method, Integra Laboratory, Italy, 2005</td>
</tr>
<tr>
<td>Local cutaneous tolerance (occlusive test - 48 h on healthy volunteers)</td>
<td>Non-irritating</td>
<td>Test n’1.01-48h, in humans, IDEA, France, 2007</td>
</tr>
<tr>
<td>Sensitization</td>
<td>Non-allergenic</td>
<td>Test n’20030418ST, CERB, in the guinea pig, OECD 406, France, 2003</td>
</tr>
<tr>
<td>Toxicity by oral route</td>
<td>Non-toxic; oral DL50 &gt; 2000 mg/kg</td>
<td>Test n’6564 TAR, in the rat, CIT Laboratory, France, 1990</td>
</tr>
</tbody>
</table>

> Classification: Sterile medical device, class IIa

> Therapeutic indications:
Washing of ocular and cutaneous chemical splashes (or oral mucous membranes, followed by spitting out).

4 CONTRAINDICATIONS

There are no known negative interactions with the different families of medicines or devices and more specifically with ophthalmic solutions used in chemical burn protocols. Do not use in cases of splashes due to white phosphorous. In these cases please use an emergency treatment specifically designed for thermal burns (such as a hydrogel). Diphtherine® is currently being tested for the treatment of chemical digestive burns but has not yet been validated. However, it has already been tested and classified as non-toxic if swallowed.

Diphtherine® has a limited effect on hydrofluoric acid splashes due to the double corrosive and toxic mechanism of this acid. Washing with Hexafluorine® is better adapted to these two requirements.

> Side effects

No side effects have been reported by our vigilance system.
Washing with Diphtherine® may cause temporary ocular discomfort. The secondary use of the solution Afterwash II®, isotonic with tears, brings about a more rapid return to a physiological state.

> Precautions for use

To avoid any microbial contamination, keep containers closed. Do not use after the expiry date which appears on the container. Products for single use only.

> Manufacturer's name and address

PREVOR
Anticipate and Save
Technologie Laboratoire & Clinical Risk Management

Moulin de Verville - F95760 Valmondois
Tel : +33130347676
www.prevor.com
**HEXAFLUORINE® IN USE**

### 1 NATURE AND PROPERTIES

**Hexafluorine®** is a washing solution designed specifically for ocular and cutaneous chemical splashes due to hydrofluoric acid (HF) and due to fluorides in an acid medium. Set up at the workplace and used as first-aid, it allows the minimisation or avoidance of the burn's appearance, stopping the corrosive and toxic effects of solutions containing HF and by avoiding the penetration of the tissues by way of its chelating and hypertonic properties. Hexafluorine®, dispensed in specially designed containers, permits and facilitates effective decontamination, reduces pain, the need for secondary care, sequelae (after-effects) and lost work time.

![HF burn washed with tap water](image1)

![HF burn washed with 1% calcium gluconate](image2)

![HF burn washed with Hexafluorine®](image3)

<table>
<thead>
<tr>
<th>Kinetics of decontamination of hydrofluoric acid detected by the Optical Coherence Tomography Technique</th>
</tr>
</thead>
</table>

**Opaque cornea = burn**

**Transparent cornea = no burn**

### 2 HOW SHOULD THIS DEVICE BE USED?

**In the workplace**

- Washing in the first minute and as the primary action with the entire container of Hexafluorine®.
- Specific antidotes, such as calcium gluconate may be used according to the protocol established by the doctor in charge. This is especially important in cases of delayed or insufficient washing, when the burn has already developed.

**At the accident and emergency department**


#### Portable eyewash

- 500 ml within the first minute

#### Mural eyewash

- 500 ml within the first minute

#### DAP

- 5 Litres within the first minute to wash an entire body

#### Grade I

- Punctuated superficial keratitis
- Hyperhaemia, chemosis, perilimitic haemorrhage without ischaemia
- No stromal opacity

**Out-patient Treatment**

- Antibiotic ophthalmic solution
- Cycloplegic ophthalmic solution

**Favourable prognosis**

#### Grade II

- Partial de-epithelialization
- Limbic ischaemia equal to less than 1/3 of the circumference of the limbus
- Stromal opacity which discloses the details of the iris

**In-patient Treatment**

- Anti-inflammatory and antibiotic ophthalmic solution (Ex: Dexamethasone neomycin)
- Cycloplegic ophthalmic solution
- ± 2 % ascorbic acid ophthalmic solution
- Ascorbic acid per os (3g/day)
- Symblepharon ring ± graft

**Grade IV**

- Complete de-epithelialization
- Limbic ischaemia greater than 1/2 of the circumference of the limbus
- Opaque stroma (all layers affected)

**Poor prognosis**
**HEXAFLUORINE® IN USE**

- For a cutaneous splash
  The use of specific topical antidotes, such as calcium gluconate or Zephiran® salts, by subcutaneous injections, or intravenous (Beir Block technique), by intra-arterial injections (for fingers or the hand) is recommended in the scientific literature. This may be combined with a symptomatic analgesic treatment. Monitoring of cardiovascular functions may be justified by the systemic diffusion in relation to the cutaneous surface area affected and the concentration.
  If the burn surpasses 1% of the surface of the body, complementary analyses should be requested: calcemia, kalaemia, serum magnesemia, phosphatemia.

  > **Classification:** medical device, class IIA
  > **Therapeutic indications**
    Washing of ocular and cutaneous splashes due to hydrofluoric acid and fluorides in an acidic medium.

  > **Name and address of the manufacturer:**
    PREVOR
    Sociology Laboratory & Clinical Lab Management
    Moulin de Verville - F95760 Valmondois
    Tel: +33130347676
    www.prevor.com

### 3 INNOCUOUSNESS

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### 4 CONTRAINDICATIONS

There are no known negative interactions with the different families of medicines or devices and more specifically with ophthalmic solutions used in specific chemical burn protocols.

At this time there is no evaluation program for burns due to swallowing. However, Hexafluorine® has been classified as non-toxic by ingestion.

Hexafluorine® has a reduced effect on alkaline substances. Washing with Diphotérine® is much better adapted in this type of situation.

  > **Side effects**
    Our vigilance system has not highlighted any side effects.
    Hypertonic ocular washing with Hexafluorine® may leave a temporary sensation of ocular discomfort. The secondary use of the solution Afterwash II®, isotonic with tears, brings about a more rapid return to a physiological state.

  > **Precautions for use**
    To avoid any microbial contamination, keep containers closed.
    Do not use after the expiry date which appears on the containers.
    Products for single use only.
**VIGILANCE SYSTEM FEEDBACK**

**MANAGEMENT OF A CHEMICAL BURN**

Please complete this form and return it either by email (www.prevoir.com), or by fax (+33 130347670).

The gathering of this information will allow us to enrich our data base concerning the management and the consequences of chemical burns.

**INFORMATION CONCERNING THE ACCIDENT VICTIM**

<table>
<thead>
<tr>
<th>Gender</th>
<th>F</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age:</td>
<td>years old</td>
<td></td>
</tr>
<tr>
<td>Job/Post:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**INFORMATION CONCERNING THE CHEMICAL SUBSTANCE**

Name of the chemical: 

Chemical class: □ acid □ base  □ pH of the solution  □ oxidiser □ reducing agent □ Solvent □ other (specify):  

Product concentration:  

Temperature: □ cold □ hot (°C = …….)  

Chemical splashed under pressure: □ (P = ……..)  

Physical appearance: □ liquid □ solid □ gas

**ACCIDENT DETAILS**

Date:  

Time:  

How?: □ work □ do-it-yourself □ in the home □ attack  

Type of splash: □ ocular □ facial □ neck □ arm □ forearm □ hand □ thigh □ leg □ foot □ anterior thorax □ anterior abdomen □ posterior thorax □ posterior abdomen □ other (specify):  

Quantity of substance:  

Sub-cutaneous penetration: □ yes □ no □ by pression □ wound □ Pre-existing dermatosis

Ocular antecedents (specify):  

**EMERGENCY WASHING IN THE WORKPLACE**

Date:  

Time:  

Time lapsed between the splash and the beginning of the washing process:  

Nature of the primary washing:  

Nature of secondary washing:  

Place: □ Company □ Infirmary □ Ambulance

Quantity / packaging:  

Quantity / packaging:  

Length of washing:  

Length of washing:  

Additional Information:  

..................................................................................................................................................  

..................................................................................................................................................  

..................................................................................................................................................
VIGILANCE SYSTEM FEEDBACK

MANAGEMENT OF A CHEMICAL BURN

PATIENT FOLLOW-UP BY A SPECIALIST OR AT THE HOSPITAL

Date: ........................................ Time: ........................................

Initial clinical observation: ........................................................................................................

What was the medical protocol applied? ....................................................................................

Washing? □ YES □ NO

• If yes: what was the nature of the washing? ...........................................................................

Quantity/ type of container: ........................................................................................................

Length of the washing: ................................................................................................................

pH measurement? □ YES: Value before washing, pH = ...... value after washing, pH = ...... □ NO

Washing resumed? □ YES □ NO

• If yes: type of washing:

  Quantity/ type of container: ........................................................................................................

  Length of washing: .....................................................................................................................

  Description of secondary treatment: ..........................................................................................


DETAILED

□ Short term Observation date (day/month/year): .................................................................

Eye: □ visual acuity: Right eye: ...... Left eye: ...... Binocular: ........

  • grade: □ absence of visible lesion □ I □ II □ III □ IV

  • Total time needed for reepithelialization: ..........................................................

  • Complications: .......................................................................................................................

  • Graft date: .............................................................................................................................

Skin: □ Total time needed for reepithelialization: .................................................

  • Complications: .......................................................................................................................

  • Graft date: .............................................................................................................................

  • Healing quality: ......................................................................................................................

□ Middle term Observation date (day/month/year): .............................................................

Eye: □ visual acuity: Right eye: ...... Left eye: ...... Binocular: ........

  • grade: □ absence of visible lesion □ I □ II □ III □ IV

  • Total time needed for reepithelialization: ..........................................................

  • Complications: .......................................................................................................................

  • Graft date: .............................................................................................................................

Skin: □ Total time needed for reepithelialization: .........................................................

  • Complications: .......................................................................................................................

  • Graft date: .............................................................................................................................

  • Healing quality: ......................................................................................................................

□ Long term Observation date (day/month/year): ..........................................................

Eye: □ visual acuity: Right eye: ...... Left eye: ...... Binocular: ........

  • Final healing quality: ..............................................................................................................

Skin: □ Total length of time needed for total reepithelialization: ...........................................
PRACTICAL SOLUTIONS AND TOOLS FOR CHEMICAL RISK MANAGEMENT AND PREVENTION

www.prevor.com

Emergency washing of chemical splashes

Management of accidental chemical spills

Chemical risk management training for professionals in the field of prevention

Technical manuals and training sessions for chemical risk comprehension, management and prevention
PRACTICAL SOLUTIONS AND TOOLS FOR CHEMICAL RISK MANAGEMENT AND PREVENTION

- Emergency washing of chemical splashes
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- Technical manuals and training sessions for chemical risk comprehension, management and prevention

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