PREVOR
ANTICIPATE AND SAVE
*Toxicology Laboratory & Chemical Risk Management*

# Diphoterine® solution advantages for chemical splashes management

## Informative review







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# This review is the consensus of a global expert panel

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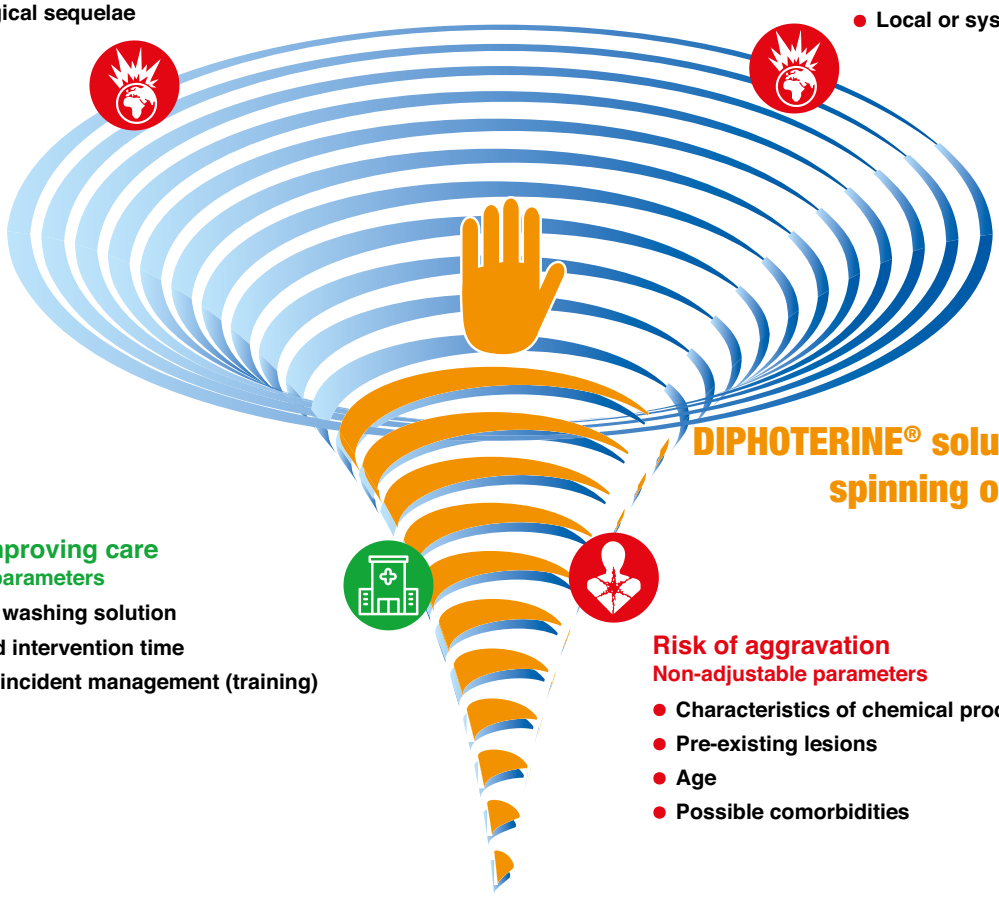
# If we are not careful
# chemical accidents can spiral out of control

### Socio-economical sequelae

- Cost of hospitalisation
- Incapacity to continue working
- Psychological sequelae

### Health sequelae

- Reduction or loss of visual acuity
- Psychological sequelea
- Aesthetic sequelae
- Local or systemic infection



**DIPHOTERINE® solution stops the spiral spinning out of control**

### Factors improving care

**Adjustable parameters**

- Quality of washing solution
- Decreased intervention time
- Improved incident management (training)

### Risk of aggravation

**Non-adjustable parameters**

- Characteristics of chemical product
- Pre-existing lesions
- Age
- Possible comorbidities

### Accident location

- Industrial & professional environment
- Domestic accident
- Assault

Water allows mechanical removal of chemicals from the lesion's surface. In case of a chemical splash with a concentrated corrosive, whether by accident or a deliberate attack, water washing is not enough.
Diphoterine® solution removes chemicals from the lesion's surface, and also extracts what has already penetrated inside the tissues.
This report summarises clinical and experimental studies that have been conducted during the last ten years. The purpose is, on one hand, to compare the differences between mechanical and a combined mechanical and chemical decontamination.
On the other hand, this document includes the feedback of some users of Diphoterine® solution such as the SAMUR of Madrid (do find below the original version as well as the English version).

**SAMUR's feedback highlights Diphoterine® solution's benefits in emergency:**

✓ **Relieves pain** ✓ **Simplifies emergency** ✓ **Reduces lesion severity**

Health, Safety and emergencies MADRID

Directorate-General of Emergencies and Civil Protection

Executive management SAMUR-Civil Protection

MADRID September 8th 2017

Report on the use of Diphoterine® in the SAMUR - Civil protection service

SAMUR - Civil Protection - incorporated this product in 2007. We do not have usage data from 2007 to 2012 because there was no specific code to collect cases in which it could have been used.

In 2012, we introduced a new code (2.41), which includes all interventions in case of spray aggression, which represents a large part of cases encountered.

Since 2012, we have had 370 cases for which we used Diphoterine® by spraying and on 6 occasions against hydrochloric acid, sulfuric acid and other undetermined corrosive substances.

In all cases, follow-up and progression were very good, with no serious eye or skin lesions, except for one patient who died due to massive ingestion of corrosive liquid.

In terms of equipping Diphoterine® in ambulances, responding to chemical risks occurred in 2008. Previously in 2007, it had been incorporated into staffing of the logistic upport team (Victor), in the form of Diphoterine® shower (green fire extinguisher).

The incorporation of Diphoterine® in our department came after a study requested by the CNP (National Police Corps) on the treatment of chemical burns following attacks with incendiary devices containing chemical components.

The reasons we chose this product were as follows:

- Quickly applicable solution right from the first moment of attention, easy to use,

- Effective, since practically all cases treated were carried out without subsequent lesions and in many cases without need for hospital transfer (spray),

- Occupies little space and, of course, less volume compared to water that should be transported to achieve the same "neutralizing" effect. With water, the effect is actually more of a mechanical one than chemical neutralization. In our case, we do not have bottled water for these uses or others in ambulances.

- Does not cause side effects.

salud, seguridad y emergencias | MADRID

*Dirección General de Emergencias y Protección Civil*
*Subdirección General SAMUR – Protección Civil*

Madrid, 8 de septiembre de 2017

**Informe sobre el uso de Diphoterine® en el servicio SAMUR- Protección Civil**

SAMUR – Protección Civil incorporó este producto en 2007. No disponemos de datos de uso de 2007 a 2012 dado que no existía un código específico que reuniera los casos susceptibles de su empleo.

En 2012 incorporamos un código nuevo (2.41) que recoge todas las intervenciones en caso de agresión por spray que supone mucho de los casos atendidos.

Desde 2012 hemos atendido 370 casos en los que hemos utilizado la diphoterine® en caso de spray, y en 6 ocasiones en casos de ácido clorhídrico, ácido sulfúrico y otras sustancias corrosivas sin determinar.
En todos ellos el seguimiento y evolución fue muy buena, sin que a los pacientes les quedaran lesiones graves ni en ojos ni en la piel, a excepción de un paciente que falleció por una ingesta masiva de líquido corrosivo.

Con respecto a la incorporación de la diphoterine® en las ambulancias como dotación ante riesgos químicos se produce en 2008. Antes, en 2007, había sido incorporada a la dotación del equipo de apoyo logístico de guardia (Víctor), en forma de ducha de diphoterine® (extintor verde).

La incorporación de la diphoterine® en nuestro Servicio vino tras un estudio, solicitado por el CNP (Cuerpo Nacional de Policía), sobre el tratamiento de las quemaduras químicas en ataques con artefactos incendiarios con componentes químicos.

Las razones por las que se apostó por este producto fueron las siguientes:

- ✓ Solución rápidamente aplicable en el primer momento de la atención, fácil de usar.
- ✓ Eficaz, ya que prácticamente todos los casos atendidos, han cursado sin lesiones posteriores y, en muchos casos, sin necesidad de traslado hospitalario (spray)
- ✓ Ocupa poco espacio y, desde luego, menor en proporción al volumen de agua que se debería llevar para conseguir el mismo efecto de "neutralización". En el agua realmente el efecto es por arrastre más que neutralización química. En nuestro caso no disponemos de agua envasada para estos usos y otros en las ambulancias.
- ✓ No provoca efectos secundarios

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# SUMMARY

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# INTRODUCTION

**Chemical lesions are caused by irritating and corrosive products[1, 2].**

These are mainly strong acids and alkalis, the best known being sulfuric acid and sodium hydroxide, and powerful oxidants and reducers, such as hydrogen peroxide, chromium trioxide, lithium, sodium, and hydrazine. Solvents or chelating agents are also irritating. Certain chemicals, such as titanium tetrachloride or acyl chloride, can react with water and release acids, such as hydrochloric acid.

Depending on the nature, strength, and concentration, the action of irritants and corrosives on the eye or skin will be more or less fast and deep. For example, 2N concentrated sodium hydroxide (pH 14) fully diffuses the cornea in 36 seconds[3]. When contact time and the affected surface area increase, combined with previous parameters, the lesion caused will be partially reversible or irreversible with permanent sequelae.

Chemical splashes can occur at home while gardening or doing house hold tasks, or more frequently in a professional environment (chemical industry, pharmaceutical industry, police departement). In fact the law enforcement services (police department, military agents …) is a field that is deeply impacted by chemical lesions. In battlefield condition, the speed and the ease of decontamination are crucial to allow the law enforcement agents to be operational as fast as possible.

**Decontamination solution must:**
- **be polyvalent, can be used whatever nature of chemical,**
- **be easy and safe to use for both skin and eyes,**
- **reduce pain so that the operator/worker can resume work shortly after incident.**

It has been shown that Diphoterine® solution can meet all of those criteria. In fact, multiple studies have shown that Diphoterine® solution is polyvalent and therefore can be used on strong alkalis and acids[20,35], tear gas[33,34],… Moreover, Diphoterine® is an aqueous and active solution which allows to remove mechanically the product from the surface of the body and stop its diffusion inside the tissues.
In an article published in 2015 Brvar *et al*[34] found that use of Diphoterine® solution, before or after the exposure to chlorobenzylidene malononitrile (CS = tear gas), decreased pain significantly. Police agents can therefore be operational faster than those who did not use Diphoterine® solution.
In a study published in 2017, Fortin *et al*[42] showed that the pain felt by the victim after a chemical splash whether by an acid, an alkali, an oxidant or a reducer is significantly decreased after the use of Diphoterine® solution.
In another study that took place in three alumina refineries in Australia[29], Donoghue *et al* showed that the use of Diphoterine® solution reduces the lesion's severity. The number of patients needing medical treatment was decreased by 25% in those refineries since the implementation of Diphoterine® solution.
Moreover, given the fact that **Diphoterine® solution is polyvalent and safe,** it can be used in all circumstances for both eye and skin lesions. This simplifies emergency and can shorten the time between the chemical splash and first aid.

[1] Maibach HI, Hall AH, Chemical Skin Injury, Ed. Springer, 2014, ISBN 978-3-642-39778-3.

[2] Schrage NF, Burgher F *et al.* Chemical Ocular Burns, Ed. Springer, 2011, ISBN 978-3-642-14549-0.

[3] Spoeler *et al.* Dynamic analysis of chemical eye burns. Journal of Biomedical Optics, 2007 July/August, 12, 4, 1-6.

[4] https://en.wikipedia.org/wiki/Acid_throwing

[5] Milton R, Mathieu L, Hall AH, Maibach HI. Chemical assault and skin/eye burns: two representative cases, report from the Acid Survivors Foundation, and literature review. Burns, 2010, 36(6), 924-32.

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[7] Naomi J. Anderson, MPH *et al.* Psychiatric Diagnoses After Hospitalization With Work-Related Burn Injuries in Washington State. Journal of Burn Care & Research, 2011, 369-378.

[8] O'Neill TB, Rawlins J, Rea S, Wood F. Complex chemical burns following a mass casualty chemical plant incident: How optimal planning and organisation can make a difference. Burns), 2012, 38, 713-718.

[9] Thenard LJ, Gay-Lussac JL. Sur l'acide fluorique. Mémoire. Ann. Chem. Phys. 1809, 69, 204.

[10] Schrage NF, Abu Sabah S, Hermanns L, Panfil C, Dutescu RM. Irrigation with phosphate-buffered saline causes corneal calcification during treatment of ocular burns. Burns. 2019, doi: 10.1016/j.burns.2019.04.022.

[11] https://www.arznei-telegramm.de/html/htmlcontainer.php3?produktid=039_01&artikel=1304039_01k

In recent years, chemical assaults have increased in developed countries, although this phenomenon is more common in poor countries, such as Bangladesh[5]. This is also the case in the UK where several hundred cases are reported each year, sometimes between rival gangs of adolescents[6], and have pushed the authorities to inquire about the care to be provided to victims.

The victim can experience severe sequelae, the treatment of which is expensive, and psychological suffering[7]. Chemical assaults are intended to mutilate and disfigure. They are extremely disabling and they limit the a return to normal social life.

Today, the entire scientific community agrees[8] that the first things you should do if you are witness or victim of a chemical splash are: undress and remove protective lenses and shower as quickly as possible, and then consult a specialist for medical care according to severity of lesions caused by the chemical.

Although washing the body, parts that have been exposed, with water is a huge advantage compared to the absence of washing, today, after many historical attempts, the understanding of the mechanisms of action of chemicals on the eye and the skin, coupled with the characterisation of lesions severity has improved washing with water and allowed other solutions to be developed.

For example, in 1809, Thenard and Gay Lussac[9] tried to limit the effects of hydrofluoric acid with a diluted potash solution. The myth of neutralisation has stuck with the idea of adding a thermal burn for acid/alkali neutralisation which resulted in the development of borate and phosphate buffers. However, the effectiveness of borates is limited, and phosphates have a toxic potential and induce corneal calcification[10]; this led the European Medicines Agency to issue a warning in late 2012 reported by journals[11].

Chemical concepts with balancing possibilities include amphoteric concepts with water as the main representative.

PREVOR Laboratory naturally developed Diphoterine® solution and Previn® solution (German version of Diphoterine® solution) based on the amphoteric concept.

**Diphoterine® solution is a sterile eye and skin washing solution in case of contact with chemicals. It is an aqueous hypertonic, and amphoteric solution, it is therefore safe and effective. It is classified as IIa by European Directive 93/42/EEC for medical devices.**

The safety of Diphoterine® solution was assessed according to the ISO10993 standard based on the rules set by the European Directive. Each year, the risk-benefit analysis is re-assessed and the conformity of the firm is examined during annual audits carried out by the notified body GMED (CE0459) designated by the competent authorities. Diphoterine® solution is non-irritating, non-cytotoxic, non-sensitising and non-toxic[12] (see detailed results in appendix 1). Diphoterine® solution follows Z358.1 American ANSI standard and EN European 15154 standard describing safety shower and eyewash unit not connected to the water network.

A study on ocular application in healthy volunteers, without chemical burn, compared to phosphate buffer did not reveal any adverse effects[13].

Diphoterine® solution contains the same active compound as Previn® solution and works according to the same mechanism; it is therefore considered equivalent and only the pH stabiliser differs. Clinical data acquired for both solutions gives similar results.

The first comparative clinical study[14] on the effectiveness of a hypertonic amphoteric washing solution compared to saline solution was carried out in Martinique in the late 2000s when there were recurring and increasing ammonia attacks on the eyes due to local beliefs.

[12] Hall AH, Cavallini M, Mathieu L, Maibach HI. Safety of dermal diphoterine application: an active decontamination solution for chemical splash injuries, Cutan Ocul Toxicol, 2009, 28(4), 149-156.

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[15] Gérard M, Merle H, Chiambaretta F, Rigal D, Schrage NF. An amphoteric rinse used in the emergency treatment of a serious ocular burn. Burns, 2002, 28, 670-673.

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[18] Cavallini M, de Broccard F, Corsi MM, Fassati LR, Baruffaldi Preis FW. Serum pro-inflammatory cytokines and chemical acid burns in rats, Annals of burns and fire disasters, 2004, XVII, 2, 1-5.

[19] Gao H, Liao X, Li W. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. Selection of decontaminants for experimental phenol burn wounds, [Article in Chinese], 2015, 33(12), 915-917.

This before-and-after study showed that, despite late treatment several hours after the splash, re-epithelialization time is significantly reduced when first and second degree burns are washed with Diphoterine® solution. A severe case of chemical eye burn, which was not included in the study, healed in 180 days without surgery[15].

**Different clinical results obtained from case reports and comparative studies carried out in several countries (including a multicentric study) show the advantage of using Diphoterine® solution in immediate or delayed use.**

- **Immediate use on site as first aid,** where the appearance or development of the chemical lesion has been prevented or limited. The action of the chemical is stopped. Little or no lesion is observed and the pain is stopped. Following a medical examination the exposed worker can quickly return to work at his workstation.
- **Use in ambulances and fire brigade vehicles,** where management time is usually around 15 to 30 minutes. In this case, the chemical burn has time to develop as it can appear in the first minute. With hypertonic washing, the chemical's diffusion is stopped along with the pain as the chemical burn process is halted by the amphoteric action minimising secondary care.
- **Use in hospital environment,** where time before treatment can be much longer, from over 30 minutes up to several hours. The burn is well developed, and lesions are substantial; however, their progress can still, even after several hours, be halted by washing with Diphoterine® solution which is not the case for water or saline solution. Care and surgical procedures can then be performed on stabilised tissue, and the overall care of the patient is facilitated.

All clinical results obtained or provided are summarised in the two appendices (2 and 3).

Experimentally, comparative assessment on animals[16] in ocular application helps to demonstrate versatile efficiency of Previn® solution and its effectiveness compared to buffer solutions. On an *in vivo* burn lesion with concentrated hydrochloric acid[17,18], washing with Diphoterine® solution proves to be more effective than saline solution in stopping acid action on the skin: pain and inflammation are significantly reduced. Similar results have been recently obtained on an *in vivo* 90% phenol lesion in rats[19]. The biopsy analysis of the skin shows that the burn is severe after water washing, less severe but existing with 75% ethanol and PEG400, and very light with Diphoterine® solution. Biomarkers' level (such as alanine aminotransferase , creatine kinase, bilirubin and serum creatinine...) in the Diphoterine® solution group are lower than the other 3 groups; statistical significant differences are observed compared to the water group ($p < 0.05$).

Two international systematic reviews[20,21] recently showed the benefit of using Prevor solutions instead of water or saline solution, thus showing the way to a much more favourable risk-benefit safety and effectiveness balance for hypertonic amphoteric solutions. The convergent results obtained, whether in an industrial environment, during first aid, or in hospital environment, have led various countries and international scientific communities[22], such as France[23], UK[24], Germany[25], South Africa[26], Slovenia[27], Canada[28] and Australia[29], to include Diphoterine® and Previn® solutions in their consensus, health guidelines, and treatment database.

Diphoterine® solution washes chemical exposures but doesn't reconstruct the tissue that was already damaged. It limits or avoids the progression of the lesion and prepares skin and eye tissue conditions for better natural healing process and appropriate medical care for skin and eyes.

**If water was the 20th Century first aid washing for chemical splashes**
**Diphoterine® solution is the 21st Century first aid for decontamination of chemical emergencies.**

[20] Lynn DD, Zukin LM, Dellavalle R. The safety and efficacy of Diphoterine for ocular and cutaneous burns in humans. CutanOcul Toxicol, 2017, 36(2), 185-192.

[21] Lewis CJ, Al-Mousawi A, Jha A, Allison KP. Is it time for a change in the approach to chemical burns? The role of Diphoterine® in the management of cutaneous and ocular chemical injuries. J Plast Reconstr Aesthet Surg, 2017, 70(5), 563-567.

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[23] Bourges JL. Urgences en Ophtalmologie. Ed. Masson. 2018. Chapitre 5.1.5. Brûlures oculaires. Merle H, Gerard M. 254-268.
Merle H. Mesnard C. Ocular Burns [Brûlures chimiques]. Encyclopédie Médicale Chirurgicale. French, 2020, 37, 21-208-A-05.

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[28] Gravel S, Dub J, Sylvestre C. Learning tool for a cost-based management of occupational health and safety measures. Perspectives interdisciplinaires sur le travail et la santé, 2020, 22-1.

[29] Alkali chemical burn (grout) Guidelines for immediate intervention. Endorsed by ANZBA.

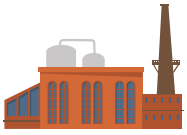
# Main properties of Diphoterine® solution

**Diphoterine® solution**

✓ Polyvalent ✓ Active ✓ Safe

1. Reduces lesion severity
2. Simplifies emergency
3. Rapid intervention
4. Available everywhere, portable & transportable
5. Removes risk of hypothermia
6. Relieves pain
7. Reduces maintenance and installation costs
8. Increases intervention margin
9. Immediate use in all circumstances

# Expected results of Diphoterine® washing





| Use | Emergency – On site<br>Within 1 min | Emergency or Pre hospital<br>Within 30 min | Hospital<br>Within 24 hours |
|---|---|---|---|
| **Effectiveness** | Quickly stops pain<br>No serious lesion and redness disappears without treatment | Stops pain without analgesic<br>Initial restoration within few hours | Less hospital care days<br>Reduces need for surgery<br>Stops pain without analgesic |
| **Logistics** | Portability and ease of use<br>Eye: 500 mL<br>Skin: 100 mL, 200 mL, 5 L | Portability and ease of use<br>Eye: 500 mL<br>Skin: 100 mL, 200 mL, 5 L | Portability and ease of use<br>Eye: 500 mL<br>Skin: 100 mL, 200 mL, 5 L |
| **Less costs compared to water** | Prevents need for hospital treatment | Strongly reduces need for care<br>Avoids surgery | Reduces treatment costs by 50%<br>Significantly reduces need for surgery |

# Main results in immediate use, mainly in industrial environment

| Data | Clinical data type | No. of cases | Site | Results* for Diphoterine® solution compared with water |
|---|---|---|---|---|
| Donoghue[30] | Comparative study | 180 (138 D / 42 W) | Skin | No burn in 52.9% of cases washed with Diphoterine® solution against 21.4% for water. Burns in 7.9% of cases with Diphoterine® solution against 23.8% with water ($p < 0.001$). |
| Konrad[31] | Comparative study | 42 cases including 3 eye and skin (11 P / 11 AA / 4 W) | Eye/ skin | Work stoppages were significantly reduced with Previn® solution 0.18 ± 0.4 days compared to water 8 ± 8.12 days and acetic acid 2.91 ± 4.25 days. Cases washed with Previn® solution did not require secondary care. Whereas 75% of cases washed with water and 25% of cases washed with acetic acid needed medical care. |
| Nehles[32] | Case series | 24 (P) | Eye/ skin | No sequelae, no need for secondary care, no work stoppage. |
| Cavallini[33] | Comparative study | 25 (D/W) | Skin | The initial skin pH is 4.88, after application of 70% glycolic acid, pH value dropped to 0.7. After washing: for the water group (1 min), the pH reached 3.4 and for the group that used Diphoterine® pH reached 4.03. The difference in pH increase is significantly better with Diphoterine® solution ($p < 0.001$). |
| Viala[34] | Comparative study | 5 (D) | Eye/ skin | Five French gendarmes entered a standard CS exposure training room. They developed classic eye and skin symptoms. In turn, they each had their eyes and face pre-washed with Diphoterine® solution, or were washed post-exposure, or no washing was performed to observe symptoms' progress. The gendarmes who entered the CS chamber without prior application of Diphoterine® solution developed the expected symptoms of excessive tearing, eye irritation, and blepharospam. Following post-exposure decontamination with Diphoterine® solution, these effects quickly stopped in four of them who were quickly operational. When Diphoterine® solution was applied to the eyes and face before entering the CS chamber, the expected symptoms did not occur. |
| Bvrar[35] | Comparative study | 22 6 CS / 8 D pre-exposure / 8 D post-exposure | Eye | Pain felt in the CS cloud was significantly lower in the group pre-exposed to Diphoterine® solution (5.6 ± 1.1; $p = 0.01$) than in the CS group without decontamination (9.7 ± 0.5) and in the group washed with Diphoterine® solution post-exposure (9.1 ± 0.4) where it was similar. The time between CS exposure and arrival at the control point for the group pre-exposed to Diphoterine® solution (1.26 ± 0.44 min) was significantly shorter than in the CS group (2.28 ± 0.25 min; $p = 0.04$) and in the group post-exposed to Diphoterine® solution (2.30 ± 0.48 min; $p = 0.02$) where there was no difference. Residual pain at the control point in the group pre-exposed to D (1.1 ± 0.4) and in the group post-exposed to Diphoterine® solution was similar with a significantly lower level than in the CS group (2.3 ± 0.5, $p = 0.02$). |
| Simon[36] | Comparative study | 375 (170 D/205 W) | Eye/ skin | The percentage of chemical splashes that did not result in any sequelae (52%) was significantly lower ($p < 0.05$) from that observed for washing with water (33%). A significant difference ($p < 0.05$) was observed between the percentage of cases (0%) that caused a work stoppage following washing with Diphoterine® solution and that observed with water (3.4%). |
| Girard[37] | Comparative study | 175 | Eye/ skin | No work stoppage and almost no need for secondary care. |

** Diphoterine® solution = D; Previn® solution = P; AA = Acetic acid; W = Water; CS = Chlorobenzylidene malononitrile,which is a tear gas.*

[30] Donoghue AM. Diphoterine for alkali chemical splashes to the skin at alumina refineries. Int J Dermatol, 2010, 49(8), 894-900.

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[32] Nehles J, Hall AH, Blomet J, Mathieu L. Diphoterine for emergent decontamination of skin/eye chemical splashes: 24 cases. Cutan Ocul Toxicol, 2006, 25(4), 249-258.

[33] Cavallini M, Puggioni V, Gazzola R. Evaluation of cutaneous pH after chemical peel and its correction with amphoteric solutions. J of Plastic Dermatol, 2010, 6(2), 145-147.

[34] Viala B, Blomet J, Mathieu L, Hall AH. Prevention of CS «tear gas» eye and skin effects and active decontamination with Diphoterine: preliminary studies in 5 French Gendarmes. J Emerg Med, 2005, 29(1), 5-8.

[35] Brvar M Chlorobenzylidene malononitrile tear gas exposure: Rinsing with amphoteric, hypertonic, and chelating solution. Human and Experimental Toxicology 2015, 1-6.

[36] Simon F. Comparaison eau/Diphotérine® : lavage de plus de 600 projections chimiques sur 7 ans sur le site ATOCHEM SAINT-AVOLD. Poster. 2000. Congress of the French Society for the Study and Treatment of Burns.

[37] Girard M. Étude comparative de l'efficacité des premiers soins dans les brûlures sur 185 accidents. Annales du congrès de la Baule sur la prise en charge des brûlures chimiques, 1997, 99-102.

# Main results obtained in pre-hospital and hospital use

| Reference | Clinical data type | No. of cases | Average management time | Site | Results |
|---|---|---|---|---|---|
| Kulkarni-Jeffery[38] | Case series Comparison | 65<br>9 W+D<br>56 W | W 12.11 (5-120) versus W+D 10 (10-15)" | Skin | This study compares the interest of Diphoterine® solution as a secondary washing at the hospital.<br>The water group has a healing average of 13.65 days against 4 days for Diphoterine® solution ($p < 0.01$).<br>The water group has an average work stoppage time of 17 days against 5 days for Diphoterine® solution ($p = 0.14$)<br>Costs in the water group are 13.223 INR (205 USD) against 7150 INR (111 USD) in group D ($p = 0.50$).<br>Significant decrease in pain in the Diphoterine® solution group compared to the water group ($p < 0.001$). |
| SAMUR Spain[39] | Case series | 370 (D) | Within 30 min | Eye skin | Favourable progression of patients with non-severe burns.<br>Quick and easy use in an environment where water is not necessarily available. |
| Gérard[40] | Case-report | 1 (D) | 1 hour | Eye | Initial severe fourth degree burn. Healed in 180 days without surgery. |
| Merle[41] | Comparative clinical study | 66<br>104 burned eyes<br>(48 NaCl/56 D) | 5.8 ± 8.9 (D) | Eye | For first and second degree burns, re-epithelialisation time is shorter with Diphoterine® solution [1.9 ± 1 days against 11.1 ± 1.4 days ($p = 10^{-7}$) and 5.6 ± 4.9 days against 10 ± 9.2 days ($p = 0.02$)]. |
| Yoshimura[42] | Case series | 1 (W)<br>2 (W+D) | 30 min | Eye/ Skin | Since the delay between the splash of the chemical and the arrival at the hospital is often long, the SAMU (EMS) is an important element in the emergency chain. Equipping the ambulance with Diphoterine® solution would make it possible to limit exposure time. |
| Fortin[43] | Case series | 34 (D) | 1-555 min (median = 77.5) | Eye/ mouth | Significant reduction of pain, from 7 to 1 on visual analogue scale (VAS). |
| Verbelen[44] | Comparative clinical study (D against W) | 112<br>46 D+H/<br>66 W | Up to 24 hours | Skin | Need for surgery decreased from 41 % to 11 % ($p < 0.0001$)<br>and hospitalisation time reduced from 7.7 days to 3.4 days ($p = 0.031$) |
| Zack-Williams[45] | Case series Comparison (D against W) | 131<br>47 D/<br>84 W | 0.5 days for D<br>2.55 days W<br>($p < 0.004$) | Skin | Significant decrease in pH for Diphoterine® solution compared to water: 1.076 against 0.4 ($p < 0.05$).<br>No significant difference in healing time, need for surgery, or length of hospitalisation. |
| Schrage[46] | Comparative clinical study | 1495 cases<br>P versus W or saline or other washings | Up to several hours | Eye | The frequency of corrosive chemical eye burns was comparatively high despite tightening of occupational health and safety regulations over the past 30 years. The severity of corrosive chemical eye burns has been dramatically decreased since the introduction of Previn® solution for initial and secondary washing. A new protocol for immediate Previn® solution use by the Cologne Fire Brigade and secondary Previn® solution washing in hospital has reduced the frequency of severe corrosive chemical eye burns to less than 60% as compared to the period of 1988-2005 when other washing solutions were used. Anecdotally, patients treated with Diphoterine® solution had lower analgesic demand. This will be explored in detail in a follow-up study in due course. |
| Schrage[46a] | Comparative clinical study of strong corrosive exposures | 676<br>(227 P / 199 W / 136 NaCl / 114 Ringer) | Not precised | Eye | It is never too late to wash. Taking Previn® solution in first and secondary washing is the best choice concerning the resulting lower grade of eye burns. This will lower significantly the rates of non-healing grade III and IV eye burns. This has been observed on a large population if Previn® solution is used.<br>Lower time in hospital after changing the protocol (1 day Median less).<br>By introduction of this protocol in Cologne, the overall rate of severe eye burns has been reduced to 25%. |

** Diphoterine® solution = D; Previn® solution = P; H = Hexafluorine® solution (specific for hydrofluoric acid).*

[38] Kulkarni P, Jeffery S. The effects of the use of Diphoterine® solution on chemical burns in the Tarapur industrial complex, India. Burns Open. 2018. 2, 2, 104-107.
[39] Mediavilla JJ et al. Actuación santaria en incidentes NRBQ. Sociedad Española de Medicina de Urgencias de interés científico por SEMES. ISBN 978-987-639-025-5.
[40] Gérard M, Merle H, Chiambaretta F, Rigal D, Schrage NF. An amphoteric rinse used in the emergency treatment of a serious ocular burn, Burns. 2002, 28, 670-673.
[41] Merle H, Donnio A, Ayeboua L, Michel F, Thomas F, Ketterle J, et al. Alkali ocular burns in Martinique (French West Indies) Evaluation of the use of an amphoteric solution as the rinsing product. Burns. 2005, 31(2), 205-11.
[42] Yoshimura Y. Lesiones Químicas: Una Nueva Visión. XVIII Congreso Nacional de Salud en el Trabajo. 2014. Mérida - México.
[43] Fortin JL, Fontaine M, Bodson L, Depil-Duval A, Bitar MP, Macher JM, Paulin P, Ravat F, Hall AH. Use of an Amphoteric Solution in Eye, Skin and Oral Chemical Exposures: Retrospective Multicenter Clinical Case Series. Fortin et al., J ClinToxicol 2017, 7, 343.
[44] Verbelen J, Hoeksema H, Claes K, Monstrey S. Chemical injury experience with an advanced approach. British Burns Association Congress. 2018. Awarded Best oral presentation.
[45] Zack-Williams SDL, Ahmad Z, Moiemen NS. The clinical efficacy of Diphoterine® in the management of cutaneous chemical burns: a 2-year evaluation study. In: Z. A, editor.: Ann Burns Fire Disasters, 2015, 31, 28(1), 9–12.
[46] Wiesner N, Dutescu RM, Uthoff D, Kottek A, Reim M, Schrage NF. First aid therapy for corrosive chemical eye burns: results of a 30-year longitudinal study with two different decontamination concepts. Graefes Arch Clin Exp Ophthalmol. 2019, 257, 1795-1803.

# Published reviews: from industry to hospital

| | | |
|---|---|---|
| Lynn and al.<br>Skin - Eye | This is a review regarding the safety and effectiveness of Diphoterine® solution for treating chemical skin and eye burns in humans. Published data must have included Diphoterine® solution in the treatment of chemical burns on the skin or eyes as well as meet other specified criteria. Acceptable studies had to use either a quantitative (e.g. number of work days lost) or qualitative (e.g. level of erythema) approach when measuring cutaneous or ocular lesion outcomes.<br>The results show Diphoterine® solution is safe and highly effective in improving healing time, healing sequelae, and pain management of chemical burns on the skin and eyes of humans. Outcomes are significantly improved when compared to water or an equivalent physiological solution. "We recommend that this product be readily available to emergency responders and companies who expose their employees to hazardous chemical substances in order to improve healing sequelae, pain management, and lost work days from these kind of burns". | Department of Dermatology, Veterans Affairs Hospital, Denver, Colorado, USA |
| Lewis and al.<br>Skin - Eye | This is a case report of combined ocular and cutaneous acid burn treated with Diphoterine® solution, together with a review of the current supporting literature.<br>On the basis of the evidence available supporting the role of Diphoterine® and Hexafluorine® solutions, "we propose that these amphoteric solutions would be suitable additions to the first aid management of chemical burns laid out in the JRCALC* guidelines by paramedics, as would lavage with room-temperature isotonic solutions such as Hartmann's solution or saline if amphoteric solutions are not available. Furthermore, we believe that these products should be available for use in UK emergency departments for the treatment of complex chemical lesions under the guidance of plastic and burn surgeons". | Department of Plastic Surgery, Newcastle, UK |

Lynn DD, Zukin LM, Dellavalle R. The safety and efficacy of Diphoterine for ocular and cutaneous burns in humans. Cutan Ocul Toxicol, 2017, 36(2), 185-192.

Lewis CJ, Al-Mousawi A, Jha A, Allison KP. Is it time for a change in the approach to chemical burns? The role of Diphoterine® in the management of cutaneous and ocular chemical injuries. J Plast Reconstr Aesthet Surg, 2017, 70(5), 563-567.

*JRCALC guidelines = The Joint Royal Colleges Ambulance Liaison Committee guidelines.

# I

# Evidence that water is just not enough

Pictures Dr Kulkarni.

When an attacker uses a liquid corrosive, he intends to injure and disfigure his victim causing suffering. In order for the victim to have irreversible, mutilating and blinding wounds, the attacker uses very aggressive and highly concentrated chemicals, such as sulfuric acid, ammonia or sodium hydroxide. The attacker and the victim know that washing with water does not work, creating a climate of fear, that of being disfigured (See Figure 1).

Figure 1: Woman disfigured with acid attack in UK.

**Physical[47], psychological[48,49] and social[50] consequences for chemical assault victims are indeed very serious and invalidating.**

## I.1 Mass casualty chemical plant lesion in Australia

In Autralia[50] in 2012, a pipeline containing 100% sulfuric acid had burst in the plant and had showered workers with the concentrated acid. The four workers were immediately taken to safety showers, however the garments were not removed. They suffered severe burns on legs, some required amputations and they also had severe burns on the back and the hands even with water washing.

[47] Milton R, Mathieu L, Hall AH, Maibach HI.Chemical assault and skin/eye burns: two representative cases, report from the Acid Survivors Foundation, and literature review. Burns, 2010, 36(6),924-932.

[48] Mannan A, Ghani S, Clarke A, et al. Psychosocial outcomes derived from an acid burned population in Bangladesh, and comparison with Western norms. Burns, 2006, 32, 235-241.

[49] Naomi J. Anderson, MPH, David K. Bonauto, MD, MPH, Darrin Adams, BA. Psychiatric Diagnoses After Hospitalization With Work-Related Burn Injuries in Washington State. Journal of Burn Care & Research. 2011, 369-378.

[50] Rahzani K, Taleghani F, NikbakhtNasrabadi A. Disfiguring burns and the experienced reactions in Iran: consequences and strategies-a qualitative study. Burns, 2009, 35(6), 875-881.

[51] O'Neill TB, Rawlins J, Rea S, Wood F. Complex chemical burns following a mass casualty chemical plant incident: How optimal planning and organisation can make a difference. Burns, 2012, 38, 713-718.

## I.2 Review about water washing effectiveness

In 2006, Hall and Maibach[52] also conducted a literature review on the effectiveness of water decontamination of ocular and cutaneous chemical splashes. Their literature review leads to the following conclusion:

**"From this review, it is clear that although chemical burn lesions represent a small portion of total burn lesions, the human economic impact is significant. Although immediate water decontamination has generally been shown to decrease the severity of chemical skin / eye burns, it is also obvious that it does not prevent such burns from developing, nor does it always prevent the need for lost work time, hospitalisation, burn center / unit admission, the requirement for surgical treatment, and sequelae. Significant sequelae and death can occur following chemical splashes, even when water decontamination is done on a timely basis. If water is all you have, then water is what you should use. If water decontamination was done in a timely manner and with low concentrations of toxicants, you might have no burns, but this cannot be determined from the available data".**

## I.3 Examples of Case reports from Brazil and China

### I.3.1 A chemical lesion with 63% nitric acid, Brazil [53]

Here is a chemical lesion with 63% nitric acid (Figure 2). Only water was used as washing solution. It's possible to see the xantocromic reaction. The ulcer needed to be opened. Bad evolution (Figures 3 and 4).

Figure 2: Chemical lesion.

Figures 3 and 4: Bad evolution due to 63% nitric acid.

### I.3.2 A chemical lesion with sulfuric acid, China[54]

After a chemical splash of sulfuric acid ($H_2SO_4$), the victim was washed for 10 mins with water, he was still left with 33% TBSA burns. The victim was hospitalised for 58 days for treatment and surgery.

Figure 5: Male, burnt by splashing of $H_2SO_4$ in face, head and body.

[52] Hall AH, Maibach HI. Water decontamination of chemical Skin/Eye splashes. Cutaneous and Ocular Toxicology, 2006, 25, 67-83.

[53] Yoshimura Y. Lesiones Químicas: Una Nueva Visión. XVIII Congreso Nacional de Salud en el Trabajo. 2014. Mérida - México.

[54] Wen J. Occup Health & Emerg Rescue, 2017, 35(1), 2.

# II

# Properties of Diphoterine® solution & expected results

**Diphoterine® solution**

✓ Polyvalent ✓ Active ✓ Safe

1. Reduces lesion severity
2. Simplifies emergency
3. Rapid intervention
4. Available everywhere, portable & transportable
5. Removes risk of hypothermia
6. Relieves pain
7. Reduces maintenance and installation costs
8. Increases intervention margin
9. Immediate use in all circumstances

# III

# Interest in using Diphoterine® solution


# III - Interest in using Diphoterine® solution

**Diphoterine® solution is able to provide a set of properties that can be used alone or in combination, depending on the splashed chemical irritant/corrosive agent.**

Experimentally, it is possible to mimic how this set of properties can play together and understand each effect. Here is the example of sodium hydroxide (soda)[55].

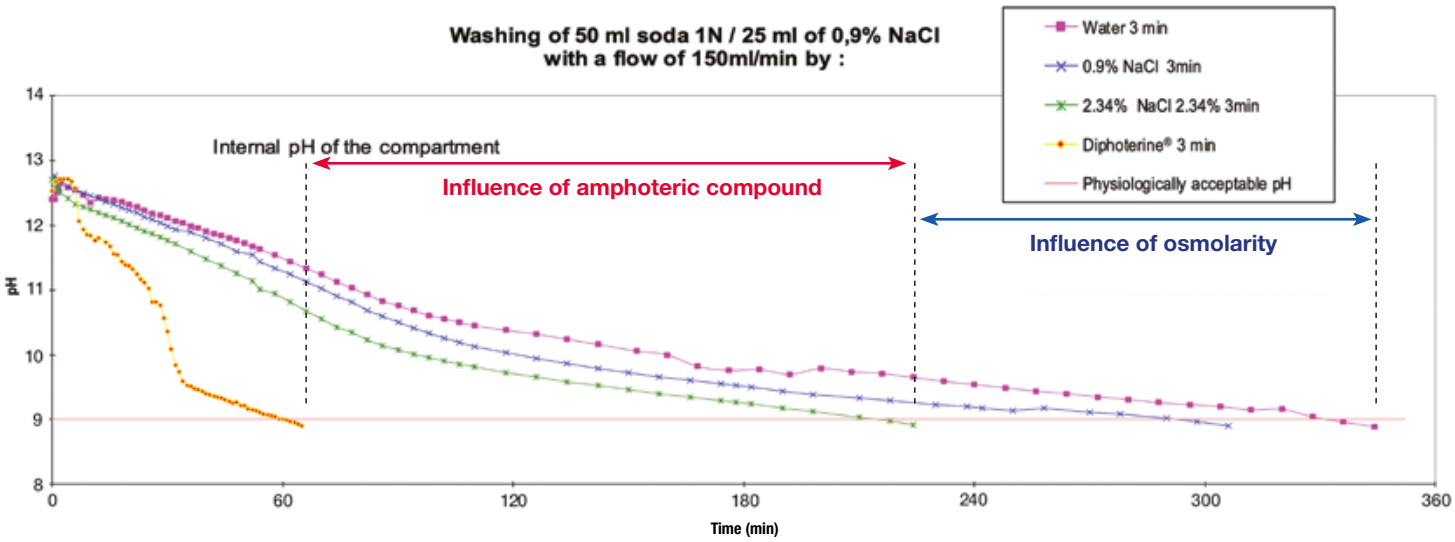



Figure 6: Influence of osmotic pressure and amphoteric properties on washing effectiveness.

## III.1 Diphoterine® solution is a water-based solution – Mechanical washing

**Diphoterine® solution is a water-based solution that can remove chemical at the surface of the tissue as water does mechanically.**

## III.2 Diphoterine® solution is also hypertonic and amphoteric

### III.2.1 - Diphoterine® solution is hypertonic – Stops or limits diffusion and removes chemicals

**Diphoterine® solution limits the diffusion of chemicals through the skin and the eye.**

If there is a movement of liquid from the outside to the inside, there is a risk of edema with swelling of tissues and creation of space where inflammatory cells in reaction to the lesion will migrate and colonize these spaces and hinder the wound healing process. This phenomenon is called the Wash-In effect: this is the case regarding hypotonic solutions such as water and normal saline solution (Figure 7) which is isotonic to blood but hypotonic to eyes.

[55] Mathieu L, Burgher F, Blomet J. Comparative evaluation of the active eye and skin chemical splash decontamination solutions Diphoterine and Hexafluorine with water and other rinsing solutions: Effects on burn severity and healing. JCHAS. 2007, 14, 4, 32-39.

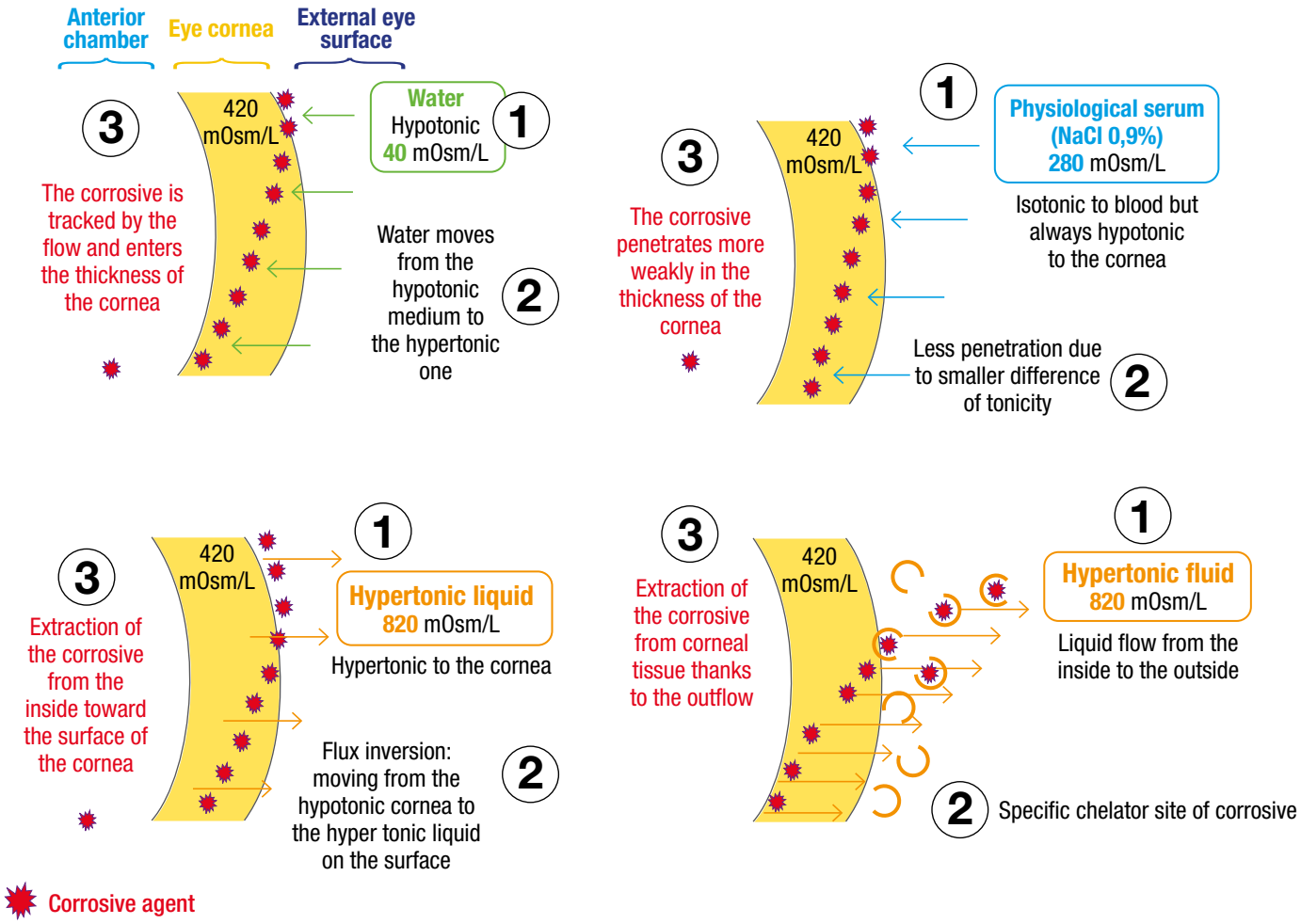



Figure 7: Importance of hypertonicity to stop diffusion of chemicals.

As Diphoterine® solution is hypertonic (about 820 mosmoles/kg), it limits or avoids penetration of irritant and corrosives by creating a flux from the inside to the outside of the cornea and skin.

### III.2.2 - Diphoterine® solution is amphoteric – Acts on chemicals

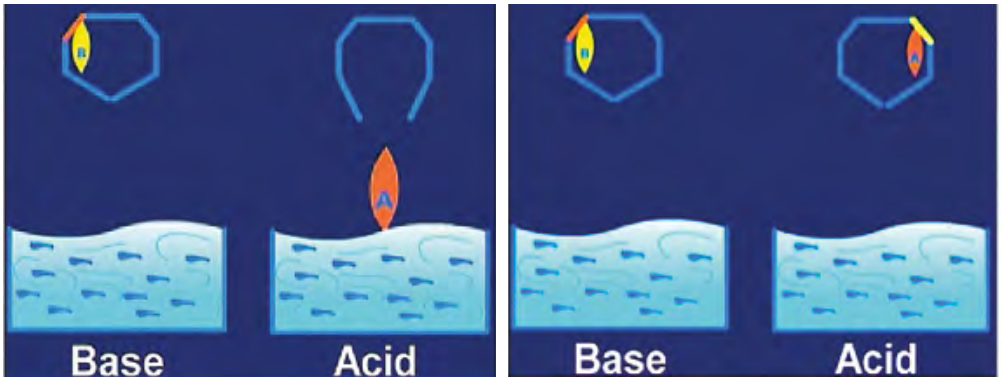



Figure 8: Interest for amphoteric agent to act on chemicals.

Diphoterine® solution can stop or limit chemical aggressiveness.
As for example, it can mitigate pH to acceptable physiological values (Figure 8).

### III.2.3 - Diphoterine® solution effectiveness

**The combination of its three properties (water based, hypertonic and amphoteric solution) allows Diphoterine® solution to bring out the amount of chemical that would have penetrated but would not have reacted yet, thus allowing pain reduction and less need for analge analgesics[56].**

Decrease in pH was observed after an alkali burn in case of:
- an ex vivo experience using caustic soda[57] (Figure 9)
- an in vivo experimental ammonia burn[58]
- two clinical studies one on chemical peeling[59] and the other on hospital burden of chemical burns in Birmingham[60], UK.

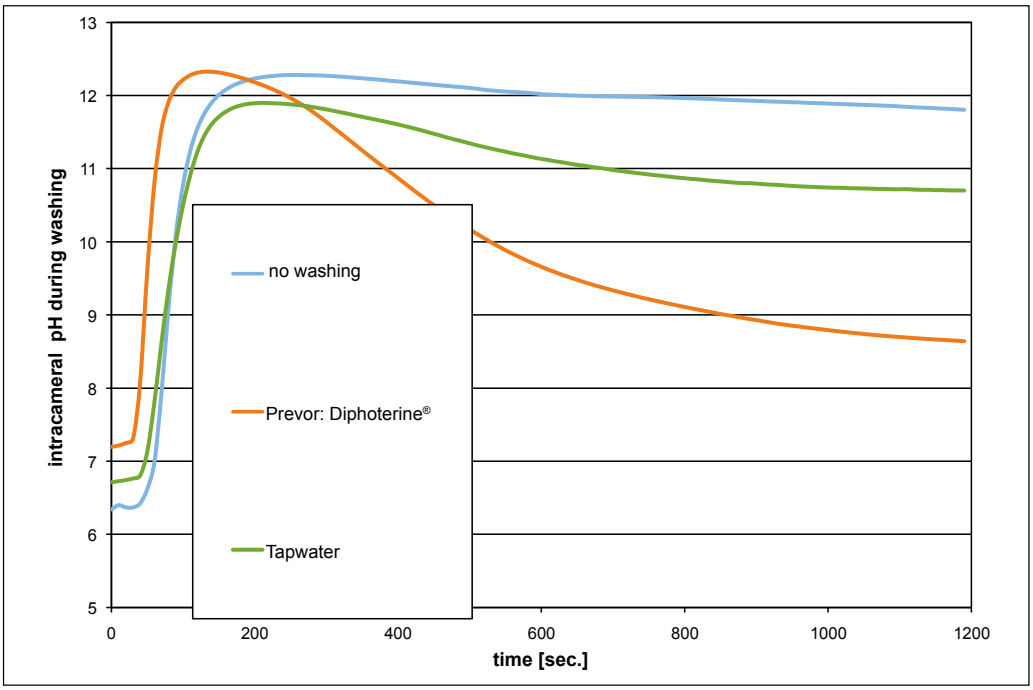



Figure 9: Decrease of intracameral pH with Diphoterine® solution versus no washing and tap water washing. (after ocular contamination with 2N NaOH solution).

## III.3 Results regarding health

### III.3.1 - Interest in immediate action (emergency, on site)

#### III.3.1.1 - Study at Alcoa, Australia – Less severe burns and less need for care

In 2010, Donoghue[61] published a study on the management of 180 burns with base chemical exposures in an industrial environment in Australia.

**Diphoterine® solution as first washing showed significantly better results (p <0.001) than decontamination with water as first washing: no signs of chemical burn in 52.9% cases compared to 21.4%, only 7.9% of cases had blister or more severe signs of burns compared to 21.4% of cases for water. Following the implementation of Diphoterine® solution, the rate of chemical lesions requiring first aid decreased by about a quarter.**

[56] Fortin JL, Fontaine M, Bodson L, Depil-Duval A, Bitar MP, Macher JM, Paulin P, Ravat F, Hall AH. Use of an Amphoteric Solution in Eye, Skin and Oral Chemical Exposures: Retrospective Multicenter Clinical Case Series. Fortin and al., J ClinToxicol, 2017, 7, 343.

[57] Schrage NF, eye burns [Augenverätzungen] [German], Augenheilkunde, 2015, 126-144.

[58] Gérard M, Josset P, Louis V, Ménérath JM, Blomet J, Merle H. Is there a delay for ocular external washing in the treatment of an ocular burn due to ammonia? Comparison of the rinsing solutions: saline solution and Diphoterine® solution [Existe-il un délai pour le lavage oculaire externe dans le traitement d'une brûlure oculaire par l'ammoniaque? Comparaison de deux solutions de lavage : sérum physiologique and Diphotérine® solution] [French], J Fr Ophtalmol, 2000, 5, 449-458.

[59] Cavallini M, Puggioni V, Gazzola R. Evaluation of cutaneous pH after chemical peel and its correction with amphoteric solutions. J Plastic Dermatol, 2010, 6(2), 145-147.

[60] Zack-Williams S.D.L., Ahmad Z., Moiemen N.S. The clinical efficacy of Diphoterine® solution in the management of cutaneous chemical burns: a 2-year evaluation study. Ann Burns Fire Disasters, 2015 31, 28(1), 9-12.

[61] Donoghue AM. Diphoterine® solution for alkali chemical splashes to the skin at alumina refineries. Int J Dermatol, 2010, 49(8), 894-900.

### III.3.1.2 - Policemen, study in France and Solvenia – Study in order to maintain operational capacity

Two studies[62,63] about "tear gas exposures" (more specifically chlorobenzylidene malononitrile – CS) in France and Slovenia.

**Preventive and post exposure use of Diphoterine® solution makes it possible to remain operational after CS tear gas exposure.**

**For the study in Slovenia (See table 1, Figure 10), law enforcement officials refused to make a group decontaminated with water because water amplifies the burning sensation after ocular CS exposure.**

| Group (number of police officers) | Pain level inside CS* cloud (0–10 points) | Time interval between CS* exposure and arrival at the ready for action checkpoint (min) | Residual pain at the ready for action checkpoint (0–10 points) |
|---|---|---|---|
| CS group (6) | 9.7 ± 0.5 | 2:28 ± 0:25 | 2.3 ± 0.5 |
| Pre exposure group (8) | 5.6 ± 1.1[a] | 1:26 ± 0:44[a] | 1.1 ± 0.4[a] |
| Post exposure group (8) | 9.1 ± 0. 4 | 2:30 ± 0:48 | 1.4 ± 0.7[a] |

*CS: chlorobenzylidene malononitrile.
[a]$p < 0.05$.

Table 1: Pain level and time interval between exposure and arrival at the "ready for action" checkpoint in 22 police officers treated with amphoteric, hypertonic, and chelating solution before and after tear gas (CS) exposure.

Figure 10: CS* exposure by running for 20s through a CS* cloud prepared with eight CS* hand grenades during regular police training.

**CS: chlorobenzylidenemalononitrile.*
*Picture from publication reference 62.*

[62] Viala B, Blomet J, Mathieu L, Hall AH. Prevention of CS «tear gas» eye and skin effects and active decontamination with Diphoterine® solution: preliminary studies in 5 French Gendarmes. J Emerg Med, 2005, 29(1), 5-8.

[63] Brvar M Chlorobenzylidenemalononitrile tear gas exposure: Rinsing with amphoteric, hypertonic, and chelating solution. Human and Experimental Toxicology, 2015, 1-6.

### III.3.2 - Interest in delayed action (pre-hospital)

**When Diphoterine® solution is used as delayed washing, it:**
- **stops pain compared to water washing**
- **reduces need for analgesic and hospitalisation.**

See letter from SAMUR, Madrid, Spain, page 3 and following case reports from SAMU, Sao Paulo, Brazil.

#### III.3.2.1 - On skin (SAMU, Sao Paulo, Brazil)

- A chemical burn due to 20% caustic soda, SAMU, Brazil.

This case report deals with maintenance involving product containing 20% caustic sodium hydroxide (NaOH).
When handling a drum of 200 litres, together with another employee, pallet and barrel slipped and slapped the bottom in the soil, splashing the product over the employee. Evolution with hyperemia and local lesion of half the face, neck, thorax and left side of the abdomen (about 4% of the Total Body Surface Area - TBSA).

**First washing was performed with soap and water and did not reduce pain (Figures 11 and 12).**

Figures 11 and 12: Superficial lesions developing after water washing.

**SAMU of Cubatao was called for help and immediately reacted, started decontamination using 200 mL Diphoterine® solution and reported pain reduction.**
**Intervention delay before Diphoterine® solution was 30 minutes.**
**Washing with Diphoterine® solution allowed immediate disappearance of local hyperemia and victim returned immediately to work (Figures 13 and 14).**
**Seen for medical consultation the day after the accident, the victim did not complain.**

Figures 13 and 14: Patient after Diphoterine® solution decontamination.

### III.3.2.2 - On eyes

• Ocular chemical burn with hydrochloric acid (SAMU, Sao Paulo, Brazil)

Patient was performing domestic work cleaning floor with muriatic acid (hydrochloric acid), with unknown concentration, when she suffered a splash in her left eye.

**The victim washed her eye with water but after 40 minutes, she called the SAMU of Cubatao because worsening of pain (Figure 15).**

**Within minutes the SAMU performed copious irrigation of Diphoterine® solution LIS* and Mini DAP for about 30 minutes (Figure 16), there was reduction of bipalpebral edema with reduced local pain.**

The victim had ophthalmologic evaluation and medicated with antibiotic, cyclopegic and local corticosteroid.
After 4 days (Figure 17), she came to the SAMU to thank for care; further, corneal ulcer evolution could be seen, without clouding or further complications.
Figure 18 shows the eye evolution after 5 days, completely healed. After 15 days, she had no further treatment. This case demonstrates that the emergency services conducted by SAMU on chemical emergencies, can bring a great benefit to patients, with reduction of pain, sequelae and faster recovery.

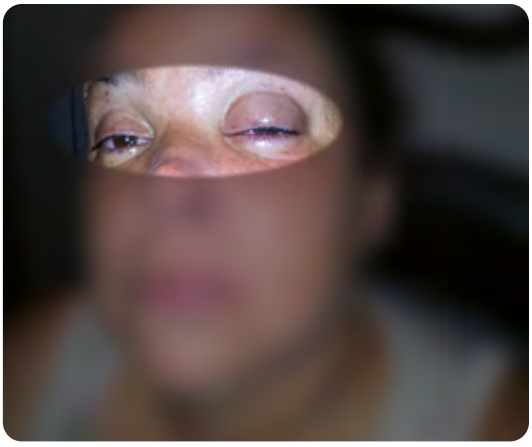


Figure 15: First care into the ambulance.

Figure 16: After decontamination with Diphoterine® solution.

Figure 17: After 4 days.

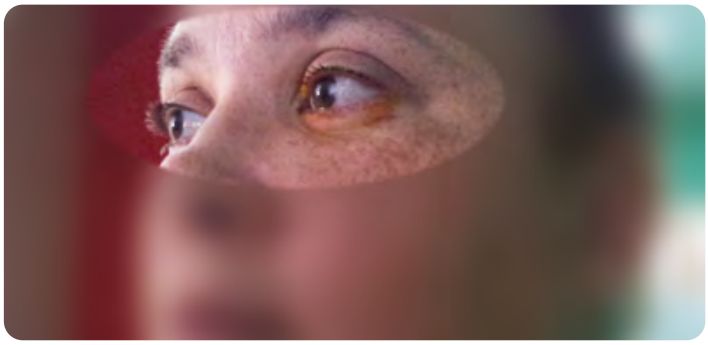


Figure 18: After 5 days.

**Since the delay between chemical splash and arrival at the hospital is often long, the SAMU (EMS) is an important element in the emergency chain. Equipping the ambulance with Diphoterine® solution would make it possible to limit the exposure time.**

*LIS: Lav'œil Individuel Stérilisé (FR) = SIEW = Sterile Individual Eye Wash (EN)

### III.3.3 - Interest in delayed washing (hospital) on skin and eyes

**Diphoterine® solution compared to water stops pain, reduces need for surgery and reduces hospital care and stay.**

#### III.3.3.1 - Retrospective multicentric study, France and Belgium

Fortin and al[64] conducted a retrospective study of 34 cases from several reporting centers use of Diphoterine® solution for eye, skin or oral chemical exposure decontamination. The following data were retrieved: exposure circumstances (workplace, domestic, deliberate assault), chemical nature and pH, exposure type, initial clinical signs, clinical signs after flushing, initial and final visual acuity, analog scale (VAS) pain ratings, consulting specialist physicians' conclusions.

**Results:** 58.8% of the 34 cases were occupational exposures, 29.4% were domestic, 5.9% occurred in schools, and 5.9% were deliberate chemical assaults. Concerning involved chemicals, 11 were basic substances, 11 were acidic, 1 was an oxidizing substance, 2 were solvents, and 9 were miscellaneous substances. There were 21 ocular exposures, 8 cutaneous exposures, 4 mixed (ocular/cutaneous), and 1 oral exposure. Initial clinical findings in ocular exposures were: pain, blepharospasm, hyperemia, palpebral edema, excessive tearing, and blurred vision. Of cutaneous exposures, 1 was a deep necrotic lesion and 7 were superficial. Median (IQR) VAS before flushing with Diphoterine® solution was 7; VAS after ocular or skin flushing was 1.

**Conclusion:** The earliest application is still the best but, even if used with delay, application of amphoteric solution to the eye or skin reduces pain intensity associated with chemical lesion. While randomized clinical trials are lacking, early use of amphoteric solution appears to reduce sequelae.

#### III.3.3.2 - Retrospective clinical study in Martinique, France – Decreased time for re-epithelialization and less complication

In 2005, Merle[65] published a clinical study on the pre-hospital and hospital care of ocular chemical splashes by base. This study compares washing with 0.9% physiological saline and Diphoterine® solution.

**The study shows a significant reduction in re-epithelialization time when washing with Diphoterine® solution for Grade I and Grade II, a similar trend for Grade III. No case in Grade IV after washing with Diphoterine® solution. There is also less complication with washing with Diphoterine® solution compared to saline solution (Table 2).**

| Data | Total (n = 104) | Physiological solution (n = 48) | Diphoterine* (n = 56) | p-value |
|---|---|---|---|---|
| Grade 1 | 52 (50%) | 17 (35.4%) | 35 (62.5%) | 0.002 |
| Grade 2 | 32 (30.8%) | 16 (33.3%) | 16 (28.6%) | |
| Grade 3 | 12 (11.5%) | 7 (14.6%) | 5 (8.9%) | |
| Grade 4 | 8 (7.7%) | 8 (16.7%) | 0 | |
| Eyelid burns | 44 (42.3%) | 29 (60.4%) | 15 (26.8%) | 0.0005 |
| Delay of first irrigation (min) | 53 ± 142 | 76.3 ± 177 | 33± 100 | 0.009 |
| Delay of second irrigation (h) | 4.7 ± 7.3 | 3.5 ± 4.7 | 5.8 ± 8.9 | 0.57 NS |
| Time elapsed to re-epithelialization (days) | 9 ±14.2 | 16.3 ± 18. | 3.7 ±5 | $10^{-7}$ |
| Final visual acuity | 20/22 ± 20/70 | 20/25 ± 20/70 | 20/20 ± 20/200 | 0.01 |
| Complications | | | | |
| Corneal opacity | 9 (8.7%) | 7 (14.5%) | 2 (3.5%) | 0.03 |
| Perforation | 3 (2.9%) | 2 (4.1%) | 1 (1.8%) | |

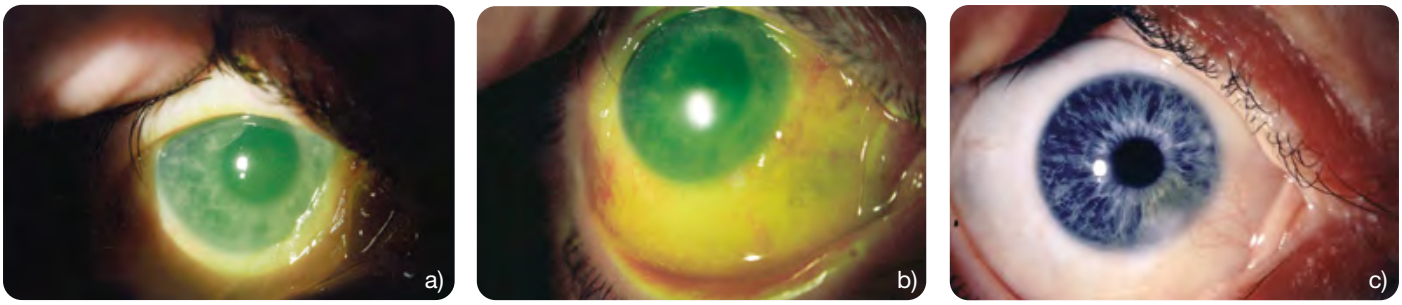
n: number of eyes, NS: no significant

Table 2: Overall characteristics of ocular burns.

[64] Fortin JL, Fontaine M, Bodson L, Depil-Duval A, Bitar MP, Macher JM, Paulin P, Ravat F and Hall AH. Use of an Amphoteric Solution in Eye, Skin and Oral Chemical Exposures: Retrospective Multicenter Clinical Case Series. J Clin Toxicol, 2017, 7, 2.

[65] Merle H, Donnio A, Ayeboua L, Michel F, Thomas F, Ketterle. J, et al. Alkali ocular burns in Martinique (French West Indies) Evaluation of the use of an amphoteric solution as the rinsing product. Burns. 2005, 31(2), 205-211.

**Considering it is an ocular grade IV lesion, this case is remarkable as re-epithelialisation took place within 21 days and complete healing within 180 days without graft.**




Figures19: a) Initial examination of the right eye after washing with Diphoterine® solution (1h after accident): importance of stromal oedema. b) Initial examination of the right eye after washing with Diphoterine® solution (1h after accident): conjunctival and 360° limbal ischemia; scleral necrosis on the infero-nasal region. c) Final examination of the right eye: total re-epithelialisation of the cornea; stable neovascularization in the infero-nasal region; visual acuity: 14/20.

### III.3.3.3 - Retrospective clinical study in Cologne, Germany

**Previn® solution (german version of Diphoterine® solution) is significantly better as first aid or secondary washing compared to all other washing solutions on strong corrosives such acids, bases, calciferous agents and detergents.**

In a retrospective study[66, 67] on 1495 cases washing with Previn® (Diphoterine®) solution[68, 69] over 30 years at Merheim clinic in Cologne, data analysis showed that when Previn® solution is used as a first aid or as a secondary washing on strong corrosives, the severity of lesions is significantly decreased.

The involved strong corrosives are acids (sulfuric acid, hydrochloric acid, pickling agents, formic acid or nitric acid), bases (sodium hydroxide, potassium hydroxide, drain pipe cleaner or ammonia), calciferous agents (lime, cement or plaster) or detergents (cleaning agent, laundry detergent, surfactant, or benzalkonium chloride).

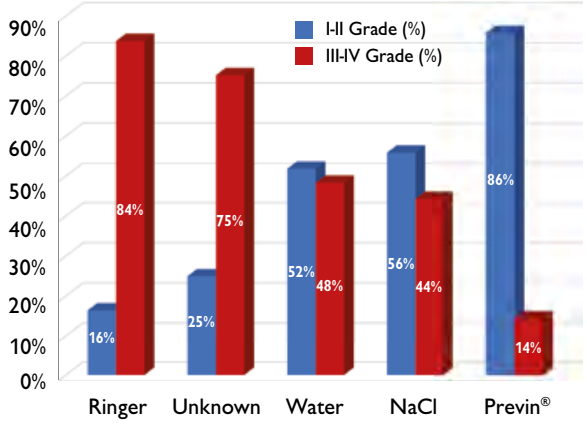



Figure 20a

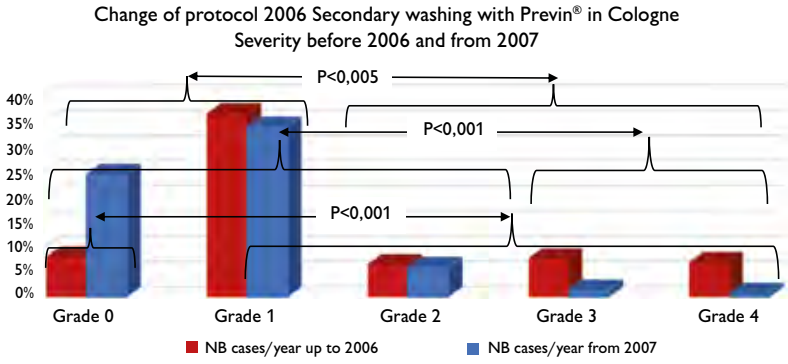



Figure 20b

Figure 20a: Measurement of the first washing effectiveness on corrosive ocular burns; Previn® solution significantly better compared to all decontaminating products.
Figure 20b: Measurement of the secondary washing effectiveness; Previn® solution significantly better compared to all decontaminating products.

**"Less severe burns represent both a social and economic benefit, preventing disabled persons and providing financial advantages for our Department and the hospital".**

*N. Schrage, Director of the Ophthalmology Hospital in Cologne (Germany)*

[66] Gérard M, Merle H, Chiambaretta F, Rigal D, Schrage NF . An amphoteric rinse used in the emergency treatment of a serious ocular burn. Burns, 2002, 28, 670-673.

[67] Gérard M, Merle H, Ayeboua L, Richer R. Etude prospective des brûlures oculaires par bases au CHU de Fort de France. J Fr. Ophtalmol, 1999, 22, 8, 834-847.

[68] Wiesner N, Dutescu RM, Uthoff D, Kottek A, Reim M, Schrage NF. First aid therapy for corrosive chemical eye burns: results of a 30-year longitudinal study with two different decontamination concepts. Graefes Arch Clin Exp Ophthalmol, 2019 May 30. doi: 10.1007/s00417-019-04350-x.

[69] Schrage N, Edelmann C, Wiesner N, Uthoff D. Research on first aid and early treatment of chemical eye burns. SOG congress 2019, Oral presentation, Interlaken, Switzerland.

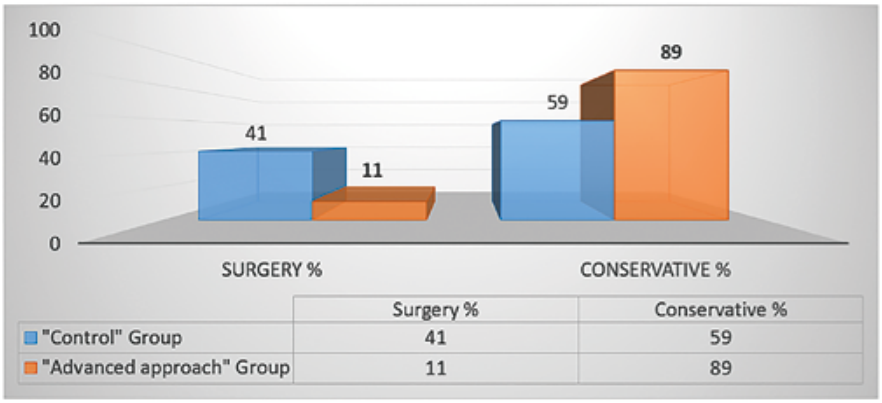
### III.3.3.4 - Retrospective clinical study in Gent, Belgium - Reduces need for surgery and reduces hospital care

The Burn Center in the University Hospital of Gent, Belgium, carried out a monocentric retrospective study on chemical burns' management between the 1st of January 2008 and the 31st of December 2015.

**This study revealed that patients who were decontaminated with either Diphoterine® or Hexafluorine® solutions (46 patients), according to indication, required significantly less surgery ($p < 0.0001$) and had significantly shorter hospital stays ($p = 0.031$) when compared to the patient group where only washing with water was performed (66 patients).**
**Even in case of delayed washing good results were observed.**

**RETROSPECTIVE STUDY UZ-GENT: RESULTS**

- **Statistics (Mann-Whitney Test) revealed significantly less surgery ($p < 0.0001$) in the "Advanced approach" group (5 operations) when compared to the "Control" group (43 operations).**



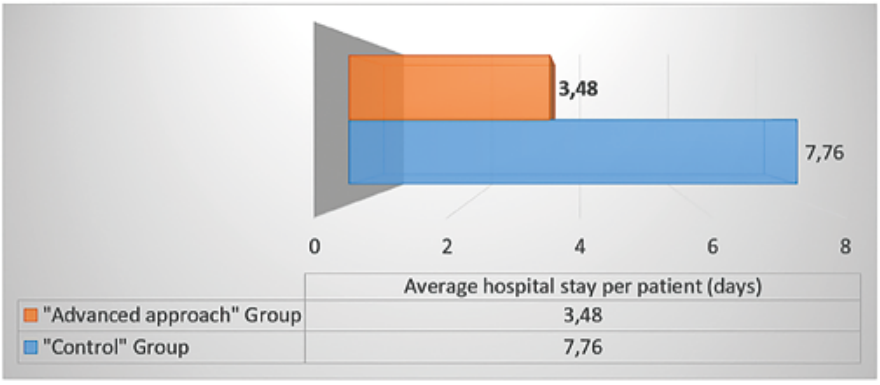

| | Surgery % | Conservative % |
|---|---|---|
| "Control" Group | 41 | 59 |
| "Advanced approach" Group | 11 | 89 |

Figure 21: Need for surgery.

Universitair Ziekenhuis Gent

**RETROSPECTIVE STUDY UZ-GENT: RESULTS**

- **Within the population of hospitalized patients, statistics (Mann-Whitney Test) revealed a significantly shorter hospital stay ($p=0.031$) in the "Advanced approach" group when compared to the "Control" group.**




| | Average hospital stay per patient (days) |
|---|---|
| "Advanced approach" Group | 3,48 |
| "Control" Group | 7,76 |

Figure 22: Duration of hospital stay (in days).

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* Verbelen J, Hoeksema H, Claes K, Monstrey S. Chemical injury experience with an advanced approach. British Burns Association Congress, 2018. Awarded Best oral presentation. *(Note 43 page 11).*

### III.3.3.5 - Clinical study in India – less pain, less surgery, less hospitalisation cost

**Previous to the clinical assessment on chemical skin lesions[70] (see page 11), analysis of all chemical skin/eye exposures was done at Tarapur Ashirwad Clinic Boisar, India[71].**

During the 10 months study, they registered 110 cases of chemical burns in industries. 100% of the patients were men. 71 cases washed with water only on site (plant), 31 cases washed with polyvalent, hypertonic and amphoteric solution only (at the clinic), 8 cases with water first and polyvalent solution upon arrival at the clinic. The clinic being situated 10min away from the industrial area, in 32 cases, patients came to the clinic without first washing with water at the accident site. After study duration of 6 months (70 cases), they noticed that some elements could help improve outcome, so they were introduced from December onwards (40 cases):

- Pain factor upon arrival versus pain factor when leaving the clinic (after use of water or polyvalent, hypertonic and amphoteric solution),

- Visual acuity upon arrival versus visual acuity when leaving the clinic (after use of water or polyvalent, hypertonic and amphoteric solution).

There were 62 ocular, 48 dermal splashes. No patient has shown any side-effects / allergic reaction after using polyvalent solution. These clinical preliminary results show that chemical burns classical management can be improved.

**The number of work days lost and hospitalisation costs when decontaminated with polyvalent, hypertonic and amphoteric solution are about a ¼ of the ones with water ($p < 0,01$). Victims decontaminated with polyvalent, hypertonic and amphoteric solution present pain decrease before/after significantly different from those washed with water ($p < 0,001$). Visual acuity was also improved ($p < 0,0005$). Average cost of hospitalisation with Diphoterine® solution is significantly less important than with water ($p < 0.01$).**

## Lost work time

| All | Water | Diphoterine® solution | *p* |
|---|---|---|---|
| Work days lost | 10,41±18,12 | 2,42±2,31 | < 0.01 |
| Number of cases | 71 | 31 | |

## Pain improvement

| All | Water | Diphoterine® solution | *p* |
|---|---|---|---|
| Average pain decrease (scale 1 to 10) assessment of pain before/after washing | 2,12 ± 0,86 | 3,67 ± 0,65 | < 0.001 |
| Number of cases | 26 | 12 | |

## Visual acuity

| Visual acuity before VS after washing with | Water | Diphoterine® solution |
|---|---|---|
| No improvement | 13 | 2 |
| Improvement of 1 acuity threshold **e.g. 6/9 to 6/6** | 3 | 8 |
| Improvement of 2 acuity thresholds **e.g. 6/12 to 6/6** | 0 | 2 |
| **Total cases** | **16** | **12** |

*($p < 0,0005$)*

## Hospital costs

| All | Water | Diphoterine® solution | *p* |
|---|---|---|---|
| Average cost of hospitalisation post accident (INR)* | 8085±12449 | 2065±2108 | < 0.01 |
| Number of cases | 71 | 31 | |

[70] Kulkarni P, Jeffery S. The effects of the use of Diphoterine® solution on chemical burns in the Tarapur industrial complex, India. Burns Open. 2018, 2, 2, 104-107.

[71] Kulkarni P. Latest First Aid Solution to manage chemical burns. Presented at the Nordic Burn Meeting 2016 congress. Awarded best poster at NBM 2016 congress.

*INR = Indian rupee

### III.3.3.6 - Review on corrosive attacks in the UK – Recommended decontamination strategy for hospital and prehospital managment

In 2019, following the increase of acid attacks in the UK since 2014, Lewis and al[72] conducted a review on the changing epidemiology of corrosive attacks in the UK and currently employed management strategies.

This study analyses closely the history of chemical aggression and the fact that corrosive products are preferably used. It highlights the fact that such aggression is a way to dehumanise the victim, and at the same time, for the perpetrator, it is much more easier (no physical contact, no observation of the consequences) and cheaper. All these may heighten moral disengagement and reduce the perpetrator's sense of moral responsability.

Another view addressed by this publication is the psychological after-effects and the importance of offering psychological support to the victims, which should begin early during admission.

The study concludes by advocating decontamination strategy, for pre-hospital and hospital, that includes the use of Diphoterine® or Hexafluorine® solutions (Figure 23).

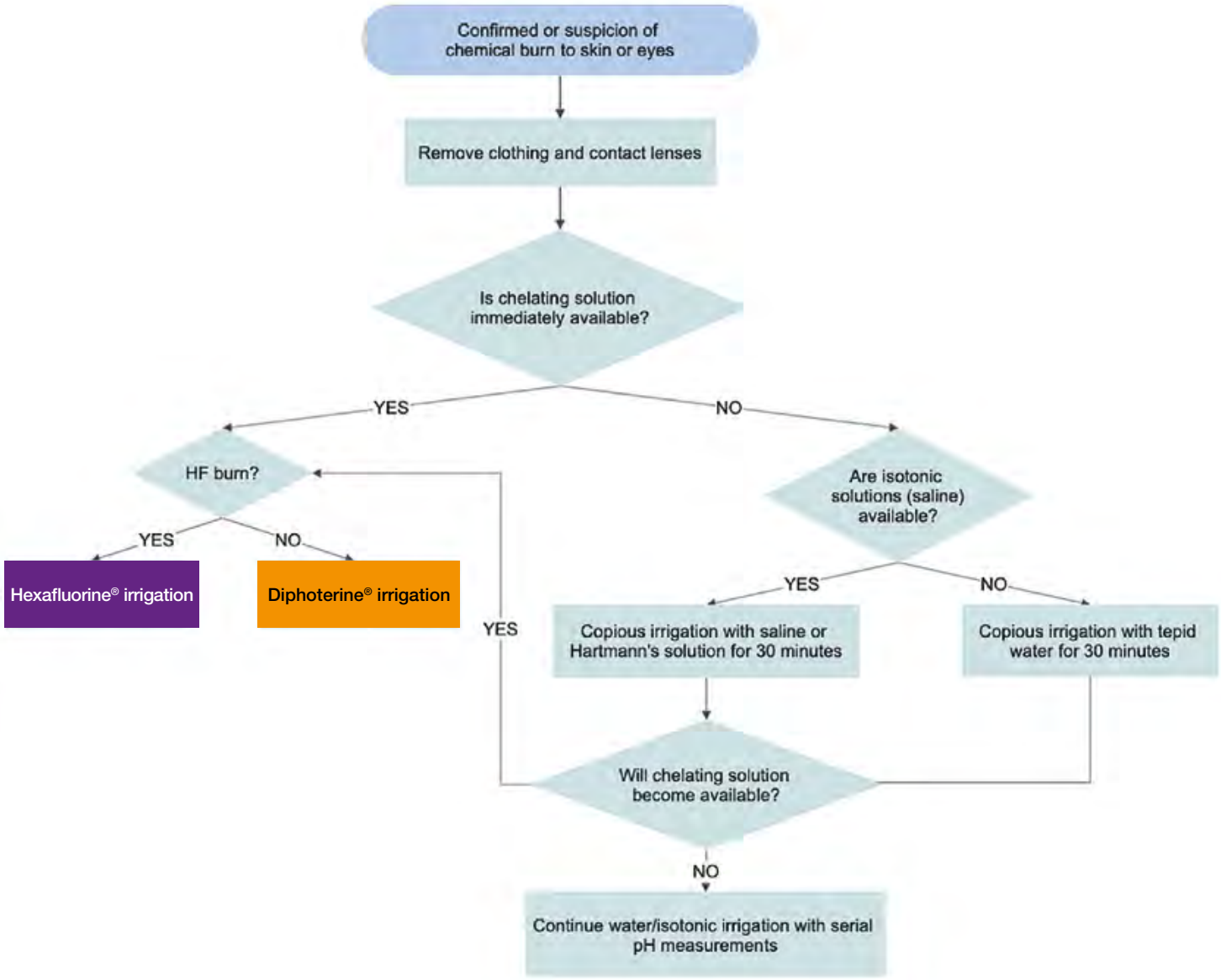



Figure 23: An algorithm for emergency decontamination of chemical lesions to the skin and eye.

[72] Lewis CJ, Hodgkinson EL, Allison KP. Corrosive attacks in the UK – Psychosocial perspectives and decontamination strategies. Burns. 2020, Feb, 46(1), 213-218.

## Conclusion

These clinical preliminary results show that chemical burns classical management can be improved. The number of days off work and hospitalisation costs when decontaminated with Diphoterine® solution are about ¼ of the ones with water ($p < 0.01$). Victims decontaminated with Diphoterine® solution present pain change before/after significantly different from those washed with water ($p < 0.001$). Visual acuity was also improved ($p < 0.0005$). Further results will be presented in due time including more patients.

# III.4 - Practical advantages of Diphoterine® solution

## III.4.1 - Minimises volume for decontamination

Decontamination with Diphoterine® solution requires a small washing volume of 500 mL for an eye with a delay within the first minute. To decontaminate the skin, spray with 100 or 200 mL within the first minute or use a 5 L portable shower for a complete body.

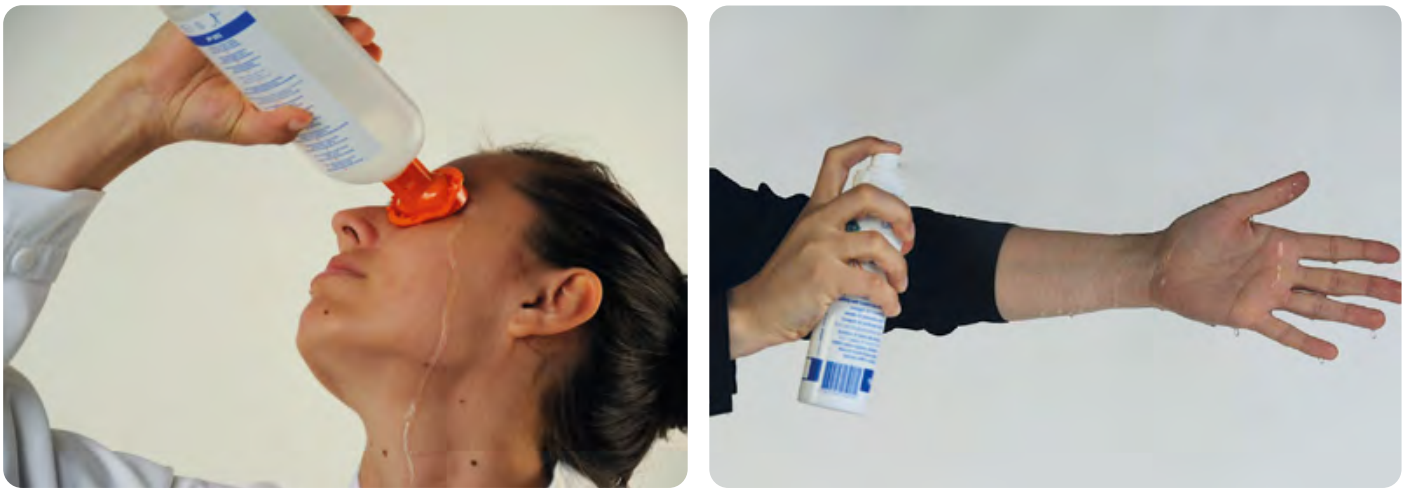


Figure 24: Self-decontamination of an ocular exposure with 500 mL of Diphoterine® solution or a skin exposure with a 100/200 mL spray within a minute.

## III.4.2 - Easy to find space in the vehicle


Figure 25: Sprays and individual eyewashes ready for use in an ambulance, SAMU, Brazil.

### III.4.3 - Portable

Figures 26 and 27: Eyewash carried on belt for self ocular decontamination with Diphoterine® solution.

### III.4.4 - Simple use in case of mass casualties

Figure 28: Mass casualty.

Figure 29: Decontamination of complete body with an autonomous portable shower (DAP).

# III.5 - Remarkable case reports

## III.5.1 - Immediate use as first aid in industries

When used as first aid and directly after the splash, Diphoterine® solution can prevent or limit chemical agent diffusion and stop the lesion process. Here are some of the testimonies[73] delivered by industries (see table 3) from various fields, chemical manufacturing, industrial equipment manufacturing, stainless steel, rescuers as SAMUR in Spain, nuclear industry, printing field, pharmaceutical industry, metallurgy, hygiene products, metals, school/university, water industry.

More than 50 firms gave a testimony involving 64 victims of specified accidents and 8 firms reported testimonies of «Everyday» use and the benefit observed for workers. 16 accidents involved strong acids, 25 accidents involved strong alkalis. There were 37 eye exposures and 35 skin exposures with 8 combined eye and skin exposures.

Firms have described the advantages below:

- Decrease in secondary care
- Decreased pain during washing
- Decrease in severity of burn lesions
- Decrease in sequelae
- Decrease in lost time at work

| Country | Chemicals | Nb of cases | Exposed area | Results |
|---|---|---|---|---|
| Peru | 36% Hydrochloric acid | 1 | Face | No cutaneous lesion |
| Mexico | 30% Hydrochloric acid | 1 | Left arm | No cutaneous lesion |
| Venezuela | Sulfuric acid | 2 | 1 hand, 1 drop on scalp | No marks after a few days |
| France | Trichloroethane | 1 | Eye | No secondary care |
| China | 65% Nitric Acid | 1 | Arm | No abnormality, no secondary care, no worktime loss |
| Israel | Phosphoric Acid | 1 | Eyes | Delayed washing (6 minutes), no burn lesion |
| Germany | 100% Nitric Acid | 1 | Hand | No sequelae, no worktime loss |
| Germany | Concentrated Sulfuric Acid | 1 | Face | No sequelae, no worktime loss |
| France | 98% Sulfuric Acid | Several | | No more accidents, only benign incidents with no sequelae and no worktime loss |
| Belgium | 96% Sulfuric Acid | 1 | Face, forearms, back | Face and forearms washed with Diphoterine® solution = no lesion. Back was not washed: several burn lesions |
| Germany | 96% Sulfuric Acid | 1 | Face, neck | No sequelae, no worktime loss |
| France | Concentrated Sulfuric Acid | 1 | Face | Little secondary care, no sequelae |
| France | Sulfuric Acid | 1 | Hand | Fast relief, no cutaneous irritation |
| France | 98% Sulfuric Acid | 1 | Face, eyelids | No secondary care, no worktime loss |
| Uganda | 30% Potassium hydroxide | 2 | Hands | Reduction of skin irritation |
| Ireland | 50% Caustic soda | 1 | Face | No major effects, back to work immediately |
| Spain | Caustic soda | 1 | 2 Forearms | Delayed washing, fast disappearance of symptoms |
| France | Concentrated Caustic Soda | 1 | Face, arm, foot | Face and arm immediately washed with Diphoterine® solution, foot washed 15 min later. 1st grade burn lesions on face and arm and 2nd grade lesion on foot |

Table 3: Testimonies and benefits for workers from industries using Diphoterine® solution.

[73] Testimony letters from industrial users.

### III.5.2 - Latex in eyes - Diphoterine® solution versus water

On August 24th 2013 at 9:15 pm, in the Emergency Department of Montbéliard Hospital, France, a 58-year-old gardener came with face edema, watery eyes, bilateral blepharospasm and atrocious eye pain (VAS* = 8/10). In the late afternoon, he manipulated a latex plant Euphorbia Lathyris (Figure 30) whose latex is used to scare moles. He presented an inflammatory reaction of the face to latex, after rubbing his eyes with his hands which was impregnated with latex.

**Before going to the hospital, The victim did an eyewash with saline solution and then took oral morphine tablet that did not amend the eye irritation and severe pain. At 9.40 pm, a new eye wash with physiological saline was done without success. Faced with the ineffectiveness at 10:00 pm, a peripheral venous line was placed with infusion of Paracetamol 1 g + Solumedrol (Corticoids) 1 g + Polaramine 5 mg IV.**

Figure 30: Euphorbia Lathyris (Euphorbia)
Sample brought by the patient for identification

Faced with total ineffectiveness of usual therapeutics, being in a therapeutic stalemate and reminding himself that the physician had a sample of a 500 mL bottle of Diphoterine® solution available (at that time the hospital did not have Diphoterine® solution), he therefore decided to use 250 mL of Diphoterine® solution in each eye (Figure 31).

Figure 31: Diphoterine® solution ocular washing 2013.08.24 – 8:45 pm
*(Picture: Dr Bitar – CHBM)*

**VAS = Visual Analogue Scale is a way of measuring how likely people are.*

## Evolution of pain (VAS)

Beginning of Diphoterine® solution washing

0.9% NaCl solution to re-establish the osmotic tonicity

| Time | 10:40 pm | 10:43 pm | 10:45 pm | 10:49 pm | 10:51 pm | 10:59 pm | 11:05 pm |
|---|---|---|---|---|---|---|---|
| VAS(/10) | 10 | 6 | 6 | 5 | 5 | 5 | 4 |

Bilateral blepharospam disappearance

Ocular hyperhemia disappearance

Ophthalmological check-up
Moderated conjunctival suffering
Treatment by Maxidrol®, Optiva®

| Time | 11:35 pm | 11:47 pm | 11:56 pm | 00:00 am | 08:51 am | 10:00 am |
|---|---|---|---|---|---|---|
| VAS(/10) | 10 | 6 | 6 | 5 | 5 | 5 |

Hospitalisation at the reception medical unit

Figure 32: Follow-up of Euphorbia burn patient

**During washing blepharospasm quickly disappeared. There was practically no pain. The following morning an ophthalmological examination showed that the patient had only a slight conjunctival lesion (Figures 32).**

2013.08.24 – 10:40 pm: Blepharospasm

2013.08.24 – 10:40 pm: Blepharospasm

2013.08.24 – 10:45 pm: Resolution of blepharospasm during ocular washing with Diphoterine® solution

*(Picture: Dr Bitar – CHBM)*

*(Picture Dr N'Guedia - CHBM)*

Figure 33: Pictures of the Euphorbia burn patient, during and after Diphoterine® solution washing.

A completely different evolution with a similar case in an ophthalmology department in 2009 in Chelmsford, Essex where the patient despite, a 3-day hospitalisation, washing with 8 liters of physiological saline, did not prevent the evolution to deeper corneal lesions. Pain management required 3 days of morphine treatment.

### III.5.3 - Management of a child, Emergency Department, Burn Center, Liege, Belgium[74, 75]

An 18 months old child was splashed with caustic soda on his right leg.

**The young victim arrived at the burn centre one hour after the accident. Delayed decontamination with Diphoterine® solution was performed. 2 weeks later, the wound started good healing (Figures 34).**


Figures 34: Evolution of the chemical lesion after decontamination with Diphoterine® solution – Child's exposure to caustic soda.

### III.5.4 - Severe mucuous burn, Emergency Department, France

On April 3rd 2016, at the emergency department of Lons-le-Saunier Hospital in France, a 21-year-old man with buccal and lingual chemical lesion showed up at 12:15.
The victim had accidentally ingested ammonia from an unidentified water bottle.
The initial pain was assessed at 3:10 pm.

As the hospital emergency department did not have Diphoterine® solution, the emergency physician called the intensive care anesthetist on duty at St-Luc-St-Joseph Burn Center in Lyon for measures to be taken.

The same intensive care anesthetist called the emergency physician specialised in toxicology for advice. The latter suggested washing the victim's mouth with Diphoterine® solution.

Relationship with a pharmacist on duty at a hospital equipped with Diphoterine® solution was established for an immediate transfer of 2 bottles of Diphoterine® solution.

A taxi was sent to collect these 2 bottles at this hospital 200 km away!

**Mouthwash with Diphoterine® solution started at 08:15 pm (8 hours and 15 minutes after ingestion of ammonia) according to the following protocol: 5 mouth washes performed successively, keeping the Diphoterine® solution in the mouth without swallowing it for 3 minutes. This resulted in a reduction in pain and the absence of lesion.**

[74] Jacquemin D, Is delayed decontamination with Diphoterine® solution useful in chemical injuries? Asia Pacific Association of Medical Toxicology, Poster, Singapore, 2016.

[75] Jacquemin D, Chemical Skin injury, 2014, Springer Ed., Chapter 4.9, Clinical data review, 157-170.


*Ammonia ingestion*
*Buccal and lingual chemical lesion*
*04.03.2016 – 08:15 pm –*
*Picture: CH Lons le Saunier*

*Ammonia ingestion*
*Buccal and lingual chemical lesion*
*04.03.2016 – 08:45 pm–*
*Picture: CH Lons le Saunier*

Figures 35: Evolution of patient's mouth lesions, return to normal appearance after mouth decontamination with Diphoterine® solution.

Pictures of the lingual lesions at the beginning of washing (08:15 pm) and at the end of washing (08:45 pm).

At the end of 5 mouth washes, macroscopic appearance of the tongue was normal.

Patient was seen for monitoring the next day in the emergency department, there was no lesion and food taste perception was normal.

### III.5.5 - Highly concentrated sulfuric acid, China

**Here two cases of exposure to sulfuric acid ($H_2SO_4$) in China[76] respectively washed with water (Figure 36) or with Diphoterine® solution (Figure 37). Severe burns appeared after washing with water while the patient decontaminated with Diphoterine® solution only presented superficial erythema.**


Figure 36: Patient: Male, burnt by $H_2SO_4$ splash on face, head, and body.

**Though the victim was washed for 10 mins with water, he was still left with 33% 2nd degree burns and was hospitalised 58 days for treatment and surgery.**

Figure 37: Patient: Male, splashed by highly concentrated $H_2SO_4$ on arm.

**The victim immediately decontaminated himself with Diphoterine® solution. 2 hours later he came to hospital. Upon medical examination in the facility infirmary, there were no clinical findings other than mild, painless erythema of the exposed area.**

[76] Wen J. Occup Health & Emerg Rescue. 2017, 35(1), 2.

### III.5.6 - Fall in a tank of 30% sulfuric acid during 20 minutes, Belgium

This 38 year old man was victim of an industrial injury[77]. He fell in a tank containing 30% sulfuric acid. He remained submerged during 20 minutes until co-workers got him out with a rope. He was wearing safety devices, clothes, helmet and glasses and got undressed out of the tank. He was soaked with a fire hose at the place of the accident. He was showered with Diphoterine® solution at the infirmary. At the burn center, the victim presented with chemical lesions which remained painful.

**He received a second Diphoterine® solution shower until pain disappeared.**

Twelve hours later, lesions were painless, and the intensity of erythema and depth of chemical lesions were reduced. He left hospital the day after admission.

Figure 38a: Chemical burn of face and neck.

Figure 38b: Chemical burn of forearm.

Figure 38c: After decontamination with Diphoterine® solution.

**After decontamination using Diphoterine® solution, the victim had painless lesions. The intensity of erythema and depth of chemical lesions were also decreased. The patient was discharged the day after.**

[77] Jacquemin D, Chapter Clinical data review 4.9, Chemical Skin Injury, Ed. Springer, ISBN 978-3-642-39778-3

### III.5.7 - Chemical and thermal lesion with 68% nitric acid, Brazil

The worker[78] doing a nitric acid duct maintenance that was supposed to be depressurized. When opening the valve, he received a jet of steam containing acid. The victim was washed with water within few seconds and then went to the medical infirmary, where he was decontaminated with Diphoterine® solution during 10 minutes.

**Even with a delayed decontamination with Diphoterine® solution, the victim recovered well after 30 days and returned to work.**


Figures 39a, b, c: Pictures taken of the patient on the day of the accident post decontamination with Diphoterine® solution.


Figures 40a, b, c: 11 days after decontamination.


Figures 41a, b, c: 17 days after decontamination.

[78] Yoshimura Y, Diphoterine® Solution for Skin and Eye Chemical Splash Decontamination: Case Series and Comparison with a Case Decontaminated with Water only. Under publication.

### III.5.8 - Chemical lesion due to 98% sulfuric acid, France

A worker[79] was splashed with 98% sulfuric acid ($H_2SO_4$). Water decontamination was delayed for approximately 5 minutes and and the victim developed 3rd degree burns and edema of the face, neck, right ear, and external auditory canal.


Figure 42a: 24 hours after 98% $H_2SO_4$ exposure. 3rd degree burns of the face, neck and ear with significant edema.
© Dr Belliard's pictures


Figure 42b: 72 hours after 98% $H_2SO_4$ exposure. Burn lesions have improved and edema has resolved. An exudative lesion is apparent in the auditory canal.
© Dr Belliard's pictures


Figure 42c: 29 days after 98% $H_2SO_4$ exposure. The burn lesions are almost completely resolved.
© Dr Belliard's pictures

**At 72 hours, edema had resolved. By 29 days, wound healing was nearly complete.**

Diphoterine® solution decontamination began 15 minutes later, resulting in pain relief from acid inactivation stopping the lesion process. Four hours later, 48-hour intermittent Diphoterine® solution application was performed depending on patient's pain.

[79] Mathieu L, Fosse C, Bigaigon-Cantineau J, Burgher F, Coudouel H, Belliard B, Hall AH, Blomet J, Maibach HI, Experimental evaluation of chemical burns and their decontamination: the case of sulfuric acid 62nd IAOH Conference Occucon-Delhi, 1st to 4th February, 2012, New Delhi, India.

# IV
# Conclusion

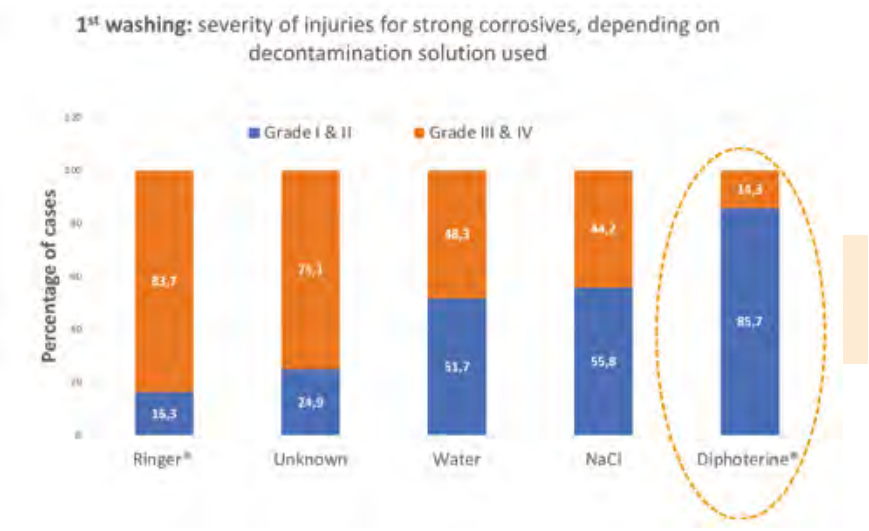
**All of these data show that Diphoterine® solution has an interest for industries, pre-hospital and hospitals. It can stop lesion evolution, it can reduce pain, the need for secondary care and eventually surgery.**
**All the studies show that there is less need for care and costs reduction for pre-hospital teams (such as emergency services and fire brigades) as well as hospital organisation. Furthermore recent reviews, Lynn *et al.* and Lewis *et al.* have shown that there is increase in benefits and reduction in lesions when using Diphoterine® solution.**



# Diphoterine® solution

✓ Polyvalent ✓ Active ✓ Safe

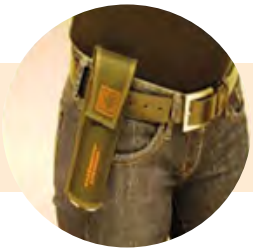
**1** **Reduces lesion severity**



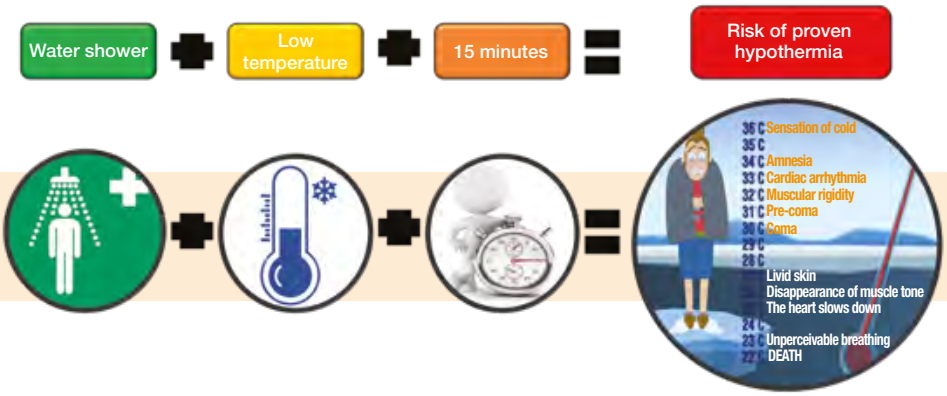

**2** **Symplifies emergency**

**3** **Rapid intervention**

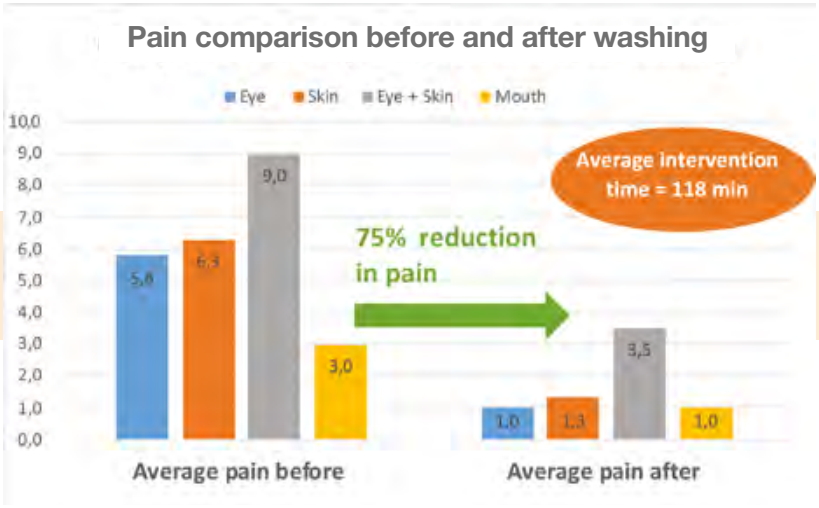
**4** **Available everywhere, portable & transportable**



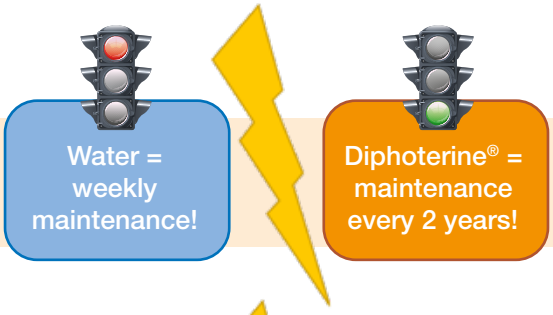
## 5 Removes risk of hypothermia



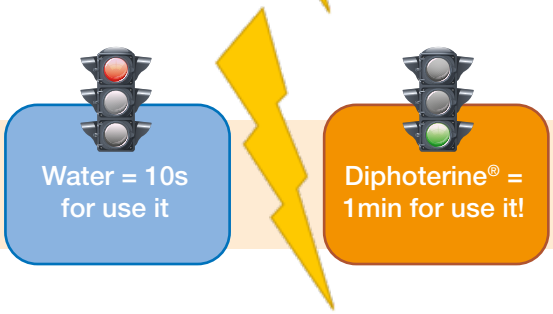

## 6 Relieves pain




## 7 Reduces maintenance and installation costs




## 8 Increases intervention margin




## 9 Immediate use in all circumstances

**Before using Diphoterine® solution**

✓ No need to identify the chemical

✓ No need to check the eye (because no phosphate)

# V
# Appendices


Chemical burns[80, 81] represent up to 10% of burns[82]. They are due to the action of corrosives and irritants on the eye and skin, such as acids and bases, oxidizers and reducing agents, chelators and solvents.

Chemical lesion's mechanism (Figure 1) consists of 3 stages: contact, diffusion and reaction.

Several parameters intervene to explain the potential seriousness of a dangerous skin chemical agent: concentration, hydrophilicity or lipophilicity, power of solvation, viscosity, and amount deposited on the surface of the skin, duration of contact, temperature, pressure... These key points are summarized in Figure 1b.


Figure 1a:
Chemical lesion's mechanism

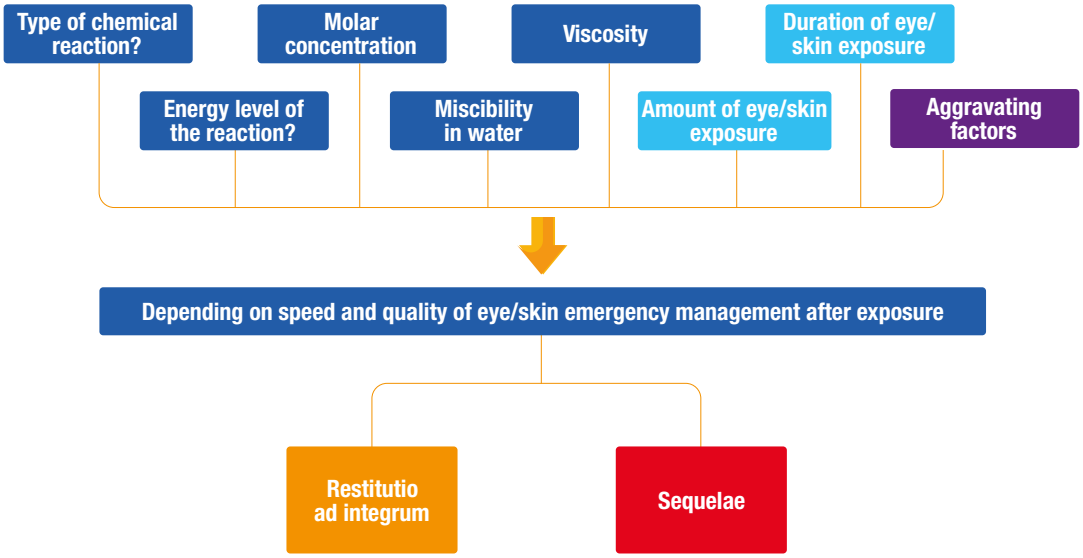



Figure 1b: Key points of chemical lesion and how it can evolve

Deleterious diffusion and reaction can begin within one minute after receiving a chemical splash.

- **Example of sodium hydroxide**

**Here is an example of diffusion of 2 molar (M) sodium hydroxide solution (NaOH) in full cornea within less than 40 seconds using an ex vivo model EVEIT* based on rabbit cornea with OCT**[83] (Figure 2).**

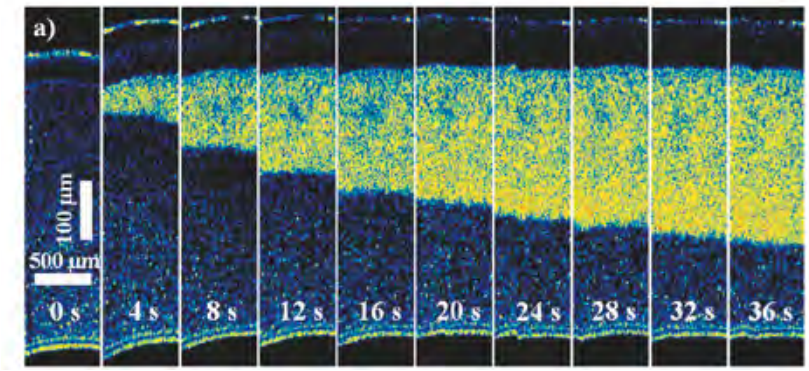



Figure 2: OCT image sequences illustrating corneal tissue damage caused by topical application of 2 molar NaOH

**EVEIT = Ex Vivo Eye Irritation Test, is an ex-vivo model on rabbit corneas kept alive.*
***OCT= Optical Coherence Tomography.*

[80] Schrage NF, Burgher F, Blomet J, Bodson L, Gerard M, Hall AH, Josset P, Mathieu L, Merle H. Chemical Ocular Burns, Ed. Springer, 2011, ISBN 978-3-642-14549-0.

[81] Maibach HI, Hall AH, Chemical Skin Injury, Ed. Springer, 2014, ISBN 978-3-642-39778-3.

[82] Hardwicke J, Hunter T, Staruch R, Moiemen N. Chemical burns: an historical comparison and review of the literature. Burns, 2012, 38(3), 383-7.

[83] Spöler F, Först M, Kurz H, Frentz M, Schrage NF. Dynamic analysis of chemical eye burns using high resolution optical coherence tomography. Journal of Biomedical Optics, 2007, 12(4), 1-6.

This model shows what happens when decontamination occurs (Figure 3):

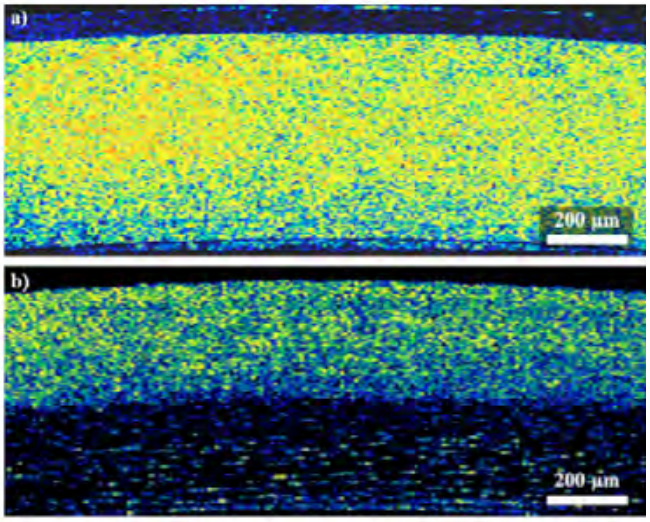



Figure 3: Demonstration of the effectiveness of washing as a first aid treatment after chemical eye burn (1 M NaOH).
a) No washing
b) Decontamination with Previn® solution (Diphoterine® solution) 20 seconds after application of NaOH solution.

**Comparison between Figure 3 a) and 3 b) shows that thanks to Previn® solution washing, NaOH diffusion is stopped which saves the cornea.**

- **Example of ammonia**

**In an experimental burn on rabbit eye due to ammonia[84, 85], edema can be easily observed with creation of spaces that might be colonized by inflammatory cells (Figure 5). The histology of cornea washed with Diphoterine® solution (Figure 6) shows that it is fully preserved without appearance of edema. Whereas when washed with saline solution, which is hypotonic to cornea, edema is present (Figure 4).**

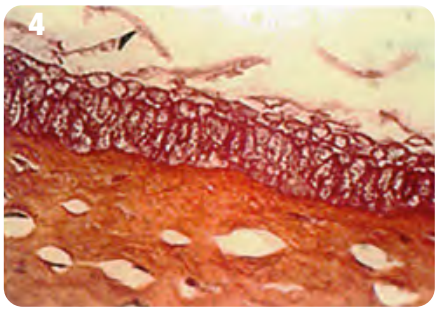



Figure 4: Anatomo-pathological analysis of a cornea burned by ammonia and washed 3 minutes later with physiological saline. Coagulated epithelium. Edematous stroma.


Figure 5: Anatomo-pathological analysis of a cornea burned by ammonia, not having been washed and taken at 5 minutes: oedematous stroma. Normal Descemet's membrane. Endothelial cells destroyed.


Figure 6: Anatomo-pathological analysis of a cornea burnt with ammonia and washed 3 minutes later with Diphoterine® solution: vacuolated and coagulated epithelium. Stroma normal.

[84] Gérard M, Louis V, Merle H, Josset P, Menerath JM, Blomet J. Etude expérimentale sur la pénétration intra-oculaire de l'ammoniaque [Experimental study on the intra-ocular penetration of ammonium hydroxide]; J Fr Ophtalmol. 1999, 22, 10, 1047-1053.

[85] Gérard M, Josset P, Louis V, Menerath JM, Blomet J, Merle H. Is there a delay for the external ocular rinsing in the treatment of an eye burn due to ammonia? Comparison of two rinsing solutions: Physiological serum and Diphoterine®. J Fr Ophtalmologie, 2000, 23, 1-10.

• Example of nitrogen mustard

The absence of stromal edema is observed on an experimental burn[86] on rabbit with nitrogen mustard, a mimic product of yperite (sulfur mustard)[87], known to induce effects by inhalation, severe ocular lesions and cutaneous lesions.

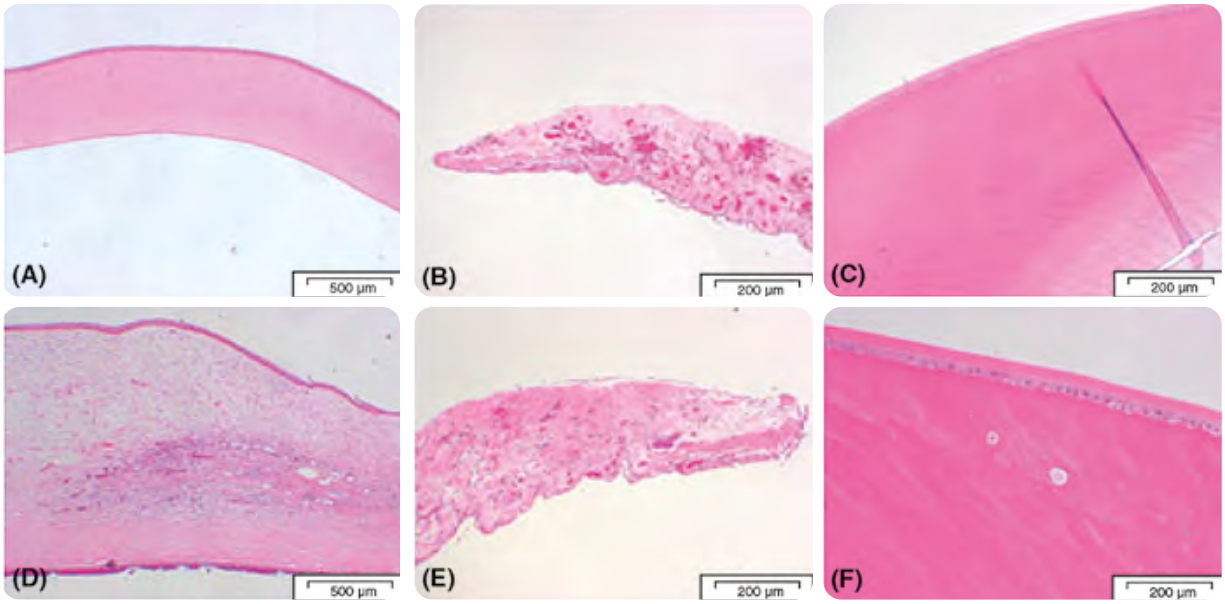
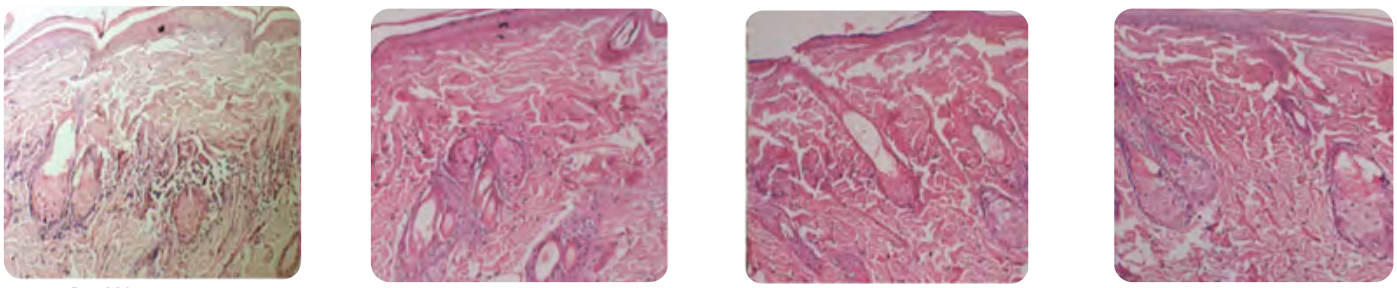



Figure 7: Histology preparations, Cornea (A, D) iris (B, E) and crystalline lens (C, F) lesion at day 22 after exposure to nitrogen mustard. (A-C) Treated with Diphoterine® solution, no damage. (D-F) Treated with saline solution, edema.

• Example of phenol[88]

Similar results were obtained recently on a 90% phenol lesion in rats[89]. The biopsy analysis (Figure 8) of the skin shows a severe lesion after water washing, less severe but existing lesion with 75% ethanol and PEG400, and very light lesion with Diphoterine® solution. The levels of biomarkers (such as alanine aminotransferase, creatine kinase, bilirubin and serum creatinine...) in the Diphoterine® solution group are lower than the other 3 groups, statistical significant differences are observed compared to water group ($p<0,05$).



**A -** Water group

**B -** 75% ethanol group

**C -** PEG 400 group

**D -** Diphoterine® solution group

Figure 8: Images of the wounds of different groups of rats:
**A -** Water group, huge inflammatory infiltration, localized in the sebaceous glands, epithelia of sebaceous glands almost entirely damaged.
**B -** 75% ethanol group, mild inflammatory infiltration, epithelia of sebaceous glands largely damaged.
**C -** Group PEG400, results similar to the ethanol group under a microscope.
**D -** Diphoterine® solution, mild inflammatory infiltration, shallow burn, part of the sebaceous glands survives.

[86] Goverman J, Montecino R, Ibrahim A, Sarhane KA, Tompkins RG, and Fagan SP. Sulfur mustard gas exposure: case report and review of the literature. Ann Burns Fire Disasters, 2014, 27(3), 146-150.

[87] Goldich Y, Barkana Y et al. Use of an amphoteric rinsing solution for the treatment of ocular tissues exposed to nitrogen mustard. Acta Ophthalmol, 2013, 91(1), 35-40.

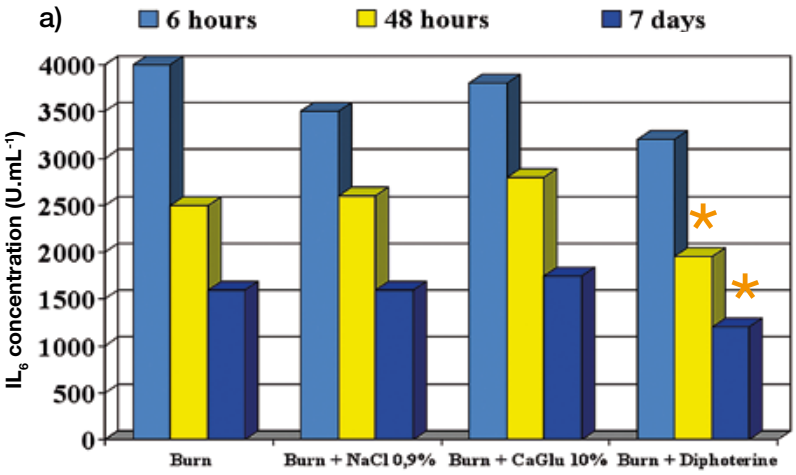
[88] Horch R. Phenol burns and intoxications. Burns, 1994, 20(1), 45-50.

[89] Gao H, Liao X et al. Selection of decontaminants for experimental phenol burn wounds. [Article in Chinese] Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi, 2015, 33(12), 915-917.

- Example of hydrochloric acid

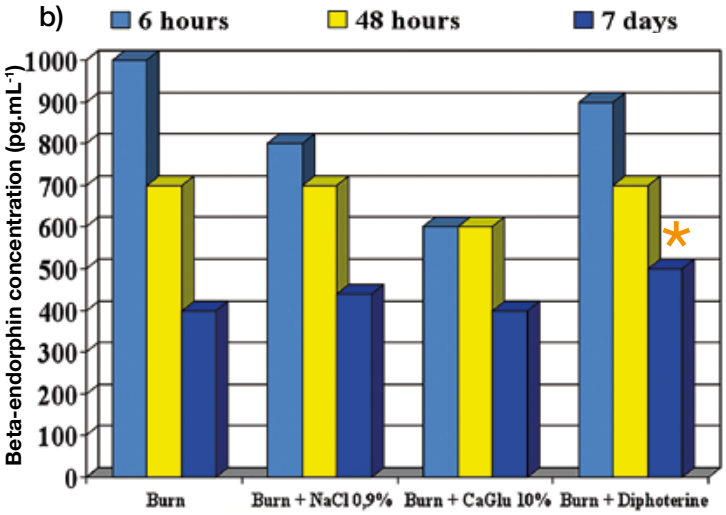
An in vivo prospective, randomized, blind comparative study[90, 91] between saline, calcium gluconate and Diphoterine® solution is performed on a skin lesion due to concentrated hydrochloric acid exposure (Figure 9). Concentrated hydrochloric acid induces lesions, pain and inflammation.

**In case of concentrated hydrochloric acid exposure, immediate skin decontamination with Diphoterine® solution improves the process wound healing with smaller lesions and significantly decreases pain and inflammation.**

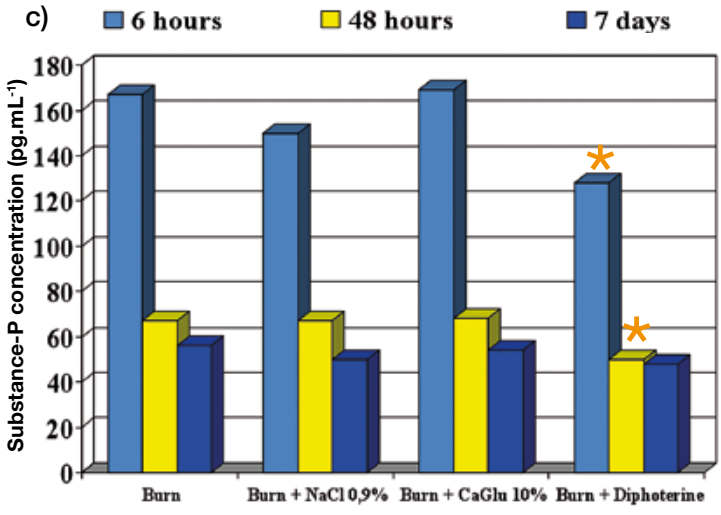



$IL_6$, biomarker of inflammation, is significantly decreased by Diphoterine® solution washing compared to other washing solutions at 48 hours and 7 days ($0.001 < p < 0.05$).

| Washing solution | Size of the lesion at day 7 (mm) |
|---|---|
| Diphoterine® solution | 4 |
| Saline solution | 6 |
| Calcium Gluconate | 9 |
| No washing | 12 |




Beta-endorphin, having analgesic capacity, is significantly decreased with Diphoterine® solution washing compared to no washing or other washing solutions at 7 days ($p<0.05$).




Substance-P, playing a significant role in inflammation, is decreased and significantly different with Diphoterine® solution versus other groups at 6 and 48 hours ($p < 0.05$).

Figure 9: Evolution of a) interleukin-6 ($IL_6$) concentration b) β-endorphin concentration and c) substance-P concentration after decontamination of an in vivo exposure to hydrochloric acid.

[90] Cavallini M, Casati A. A prospective, randomized, blind comparison between saline, calcium gluconate and Diphoterine for washing skin acid injuries in rats: effects on substance P and ß-endorphin release. European Journal of Anaesthesiology, 2004, 21, 389-392.

[91] Cavallini M, de Broccard F, Corsi MM, Fassati LR, Baruffaldi Preis FW. Serum pro-inflammatory cytokines and chemical acid burns in rats. Annals of burns and Fire disasters, 2004, XVII, 2, 1-5.

## 1 - Recommended protocol for maximum effectiveness[92]

For maximum effectiveness, we recommend washing the splash within 60 seconds after exposure with:

- The use of the LPMD bottles (500 mL) for **eye splashes;** use the full bottle content on the affected eye.

- The use of the MICRO / MINI DAP (200 / 100 mL) for **skin splashes** (equal to a face); use the full content on the contaminated area.
  For more extensive skin splashes, we recommend the use of 5 liters portable self contained shower (DAP).

  Effectiveness, is ensured by the active properties of Diphoterine® solution.

- The secondary washing with Afterwash II® solution rapidly restores the physiological balance of the eye, and thus, reduces the unpleasant sensations due to the chemical splash.

## 2 - General recommendations

**Diphoterine® solution must be used as the first solution and as the first response. A preliminary washing with water leads to a delay in the application, and because of this loss of time, the effectiveness of Diphoterine® solution is reduced. If Diphoterine® solution is not available on the place of the splash, never delay washing. Failing that, use water. Do not exceed the expiry date indicated on the packaging. The entire content of each package has to be used in continuous washing in accordance with Prevor's protocol, even if the pain has decreased.**

## 3 - Scope of effectiveness and known limitations of Diphoterine® solution

Diphoterine® solution makes it possible to stop penetration of the chemical and the development of all chemical lesions, except for splashes of hydrofluoric acid and its derivatives on which it has a reduced effect. In this case it is especially recommended to use Hexafluorine® solution, a washing solution for splashes of both hydrofluoric acid and fluorides in an acidic medium.

## 4 - What to do if the lesion has already developed, or if decontamination starts after 60 seconds?

After 60 seconds, depending on the chemical type, the lesion may have already developed. Washing, including on a lesion that has already developed, will improve delivery of secondary care. Diphoterine® solution also appears of interest in cases of delayed washing (after 60 seconds). In this case, it is recommended to continue initial washing by a second decontamination with Diphoterine® solution for a maximum of 15 minutes for an eye splash and 3 to 5 times the contact time for a skin splash.
Based on clinical experiences, pH measurement and/or pain evolution could help the physician to adjust decontamination process and improve patient management.

[92] https://www.prevor.com/en/download-instructions-for-use

## 5 - Upkeep and maintenance

- Do not expose packagings to freezing temperatures.
- Ideally store between 15 to 35°C.
- Replace packagings before expiry date indicated on the cap.
- **No loss of effectiveness when thawed out.**

| Packaging | Upkeep and storage |
|---|---|
| **SIEW** | Does not require special storage except freezing temperatures.<br>Shocks, crushes or significant rubbing may occur when carrying the SIEW, it can be protected with a strengthened holster. |
| **LPD** | Must be stored in a place which is neither exposed to high temperatures nor sunlight. |
| **LPMD** | Should be stored in a dry location, away from sources of intense heat. |
| **MICRO DAP /MINI DAP** | Must be stored in a place which is neither exposed to high temperatures nor sunlight. |
| **DAP** | Does not require special storage except freezing temperatures (in this particular case DAP could be stocked in an anti freeze protective box). |

## 6 - In cases of external auditory canal or buccal mucosa exposure

- If the **auditory canal** is affected, a check-up is needed to verify the integrity of the ear drum before decontamination. Decontaminate if possible with Diphoterine® solution applying carefully with a syringe 500 ml in the ear canal, head tilted on one side to allow the liquid to flow out of the ear. Just as any unilateral ear wash with a liquid at room temperature, light dizziness may result without any serious consequence; it spontaneously regresses after a few minutes.

- If **buccal mucosa** is affected by the splash, the mouth may be washed with Diphoterine® solution and spit out.

## 7 - Safety

| |
|---|
| **Medical Device class IIa (CE 0459)** |
| **Can be used on healthy or damaged eyes, therefore on damaged tissues (eye and skin)** |
| **Sterile (by autoclave)** |
| **Made in France by PREVOR** |
| **Follows Z358.1 American ANSI standard and EN European 15154 standard** |
| **Expiration: 2 years** |
| **Non-toxic ($LD_{50}$ > 2000 mg/kg)** |
| **Non sensitizing** |
| **Non-cytotoxic** |
| **Non-irritant** |
| **Does not contain phosphates** |

Portable eyewash – 50 mL, to be used within the first 10 seconds for optimal results. *Reference SIEW*.*

Spray 100 mL *(Reference MICRO DAP*)* and 200 mL *(Reference MINI DAP*)* for small body surfaces.
Use within the first minute for optimal results.


Mural Eyewash 500 mL *(Reference LPMD*)*. Use within the first minute for optimal results.


500 mL Portable Eyewash *(Reference LPD*)* for pre-hospital and hospital use.


Portable eyewash – 200 mL, *(Reference AFTERWASH II).*
To be used, as secondary washing, after Diphoterine® solution washing in the eyes.
To reestablish the physiological balance of the eye for more comfort.

*SIEW = Sterile Individual Eye Wash (EN) - DAP = Douche Autonome Portable (FR) - LPD = Lave-Œil portable Diphoterine® (FR)
LPMD = Lave-Œil Portable & Mural Diphoterine® (FR)

**Various wall boxes and trolleys are also available to optimise ergonomics and accessibility of our solutions.**
**Use within the first minute for optimal results.**

**Autonomous Portable Shower 5 L for complete body** *(Reference DAP*)*.
**Use within the first minute for optimal results.**

*SIEW = Sterile Individual Eye Wash (EN) - DAP = Douche Autonome Portable (FR) - LPD = Lave-Œil portable Diphoterine® (FR)
LPMD = Lave-Œil Portable & Mural Diphoterine® (FR)

PREVOR works with experts to keep people safe.

# So that a chemical accident remains an incident

***"On the basis of the evidence available supporting the role of Diphoterine® and Hexafluorine® solutions, we propose that these amphoteric solutions would be suitable additions to the first aid management of chemical burns laid out in the JRCALC* guidelines by paramedics, as would washing with room-temperature isotonic solutions such as Hartmann's solution or saline if amphoteric solutions not available. Furthermore, we believe that these products should be available for use in UK emergency departments for the treatment of complex chemical lesions under the guidance of plastic and burn surgeons."***

Lewis CJ, Al-Mousawi A, Jha A, Allison KP. Is it time for a change in the approach to chemical burns? The role of Diphoterine® solution in the management of cutaneous and ocular chemical injuries. J Plast Reconstr Aesthet Surg, 2017 May, 70(5), 563-567. Review.

*JRCALC guidelines = The Joint Royal Colleges Ambulance Liaison Committee guidelines.

## Expected results of Diphoterine® washing


| Use | Emergency – On site<br>Within 1 min | Emergency or Pre hospital<br>Within 30 min | Hospital<br>Within 24 hours |
|---|---|---|---|
| **Effectiveness** | Quickly stops pain<br>No serious lesion and redness disappears without treatment | Stops pain without analgesic<br>Initial restauration within a few hours | Less hospital care days<br>Reduces need for surgery<br>Stops pain without analgesic |
| **Logistics** | Portability and ease of use<br>Eye: 500 mL<br>Skin: 100 mL, 200 mL, 5 L | Portability and ease of use<br>Eye: 500 mL<br>Skin: 100 mL, 200 mL, 5 L | Portability and ease of use<br>Eye: 500 mL<br>Skin: 100 mL, 200 mL, 5 L |
| **Less costs compared to water** | Prevents need for hospital treatment | Strongly reduces need for care<br>Avoids surgery | Reduces treatment costs by 50%<br>Significantly reduces need for surgery |

The earlier Diphoterine® solution is used the better the results. Diphoterine® solution is always better than water.

Chemical lesions represent up to 10% of burns.

They are due to the action of corrosives and irritants on the eye and the skin.

Analysis of all products classified as corrosives or irritants has shown that these products are mostly acids, bases, oxidants, reducing agents, chelators and solvents.

Deleterious diffusion and reaction of irritants/corrosives can begin within one minute after exposure.

As a consequence, washing should be able to remove the chemical from the surface, to stop or limit its diffusion within the eye or the skin and acts on its irritant/corrosive potential.

Zach Williams[1] shows that water washing does not decrease the pH to physiologically acceptable level, because the chemical remains in the tissues despite water washing.

Washing chemical exposures with water removes the chemical from the surface of the eye or skin. But water is hypotonic, so it does not prevent the diffusion of chemicals within the eye or skin and eases the diffusion. Water does not have any action on the chemical potential of irritants and corrosives. This is why lesion can develop following exposures to strong corrosives despite water washing.

Diphoterine® solution as an aqueous hypertonic, amphoteric and safe solution can remove chemicals from the surface of the skin and the eye, can stop or limit diffusion, create a flux from the inside to the outside of the tissues and can act on irritant/corrosive potential by mitigating the pH.

The review summarises most of the experimental and clinical data showing Diphoterine® solution's benefits for management of chemical irritant/corrosive exposures.

In case of chemical splash at workplace[2, 3, 4], washing with Diphoterine® solution as first aid helps to achieve optimal decontamination with prevention or significantly less severe lesion (usually only redness), less need for secondary care and less work stoppage compared to water and/or buffer solutions. Workers can therefore resume work faster.

In case of delayed washing with Diphoterine® solution[1, 5, 6, 7, 8, 9] as first or secondary washing, by rescuers or by professionals at the hospital, even if the chemical's action has already started and damaged the eye or the skin, the remaining chemical within tissues is removed, pH is mitigated and the lesion is halted. As a consequence, pain is significantly decreased or stopped as well as lesion severity and time for reepithelialisation. Furthermore complications and need for surgery are also reduced compared to water and all the other available washing solutions. Treatment and care follow up can be carried out in optimal conditions.

Use of Diphoterine® solution always contributes to decrease lesion severity:

- It allows return to acceptable physiological pH level very quickly in first intention.
- Only limited care is needed 30 minutes onwards.
- Clear advantage is shown under 24 hours for the victim, and the hospital regarding the complexity of care needed.


[1] Zack-Williams SDL et al. Ann Burns Fire Disasters. 2015, 31; 28(1), 9–12.

[2] Donoghue AM. Int J Dermatol. 2010, 49(8), 894-900.

[3] Nehles J et al. Cutan Ocul Toxicol. 2006, 25(4), 249-58.

[4] Schrage N et al. SOG congress 2019, Interlaken, Switzerland.

[5] Fortin JL et al. J ClinToxicol 2017, 7, 343-347.

[6] Merle H et al. Burns. 2005, 31(2), 205-11.

[7] Gérard M et al. Burns 2002, 28, 670-673.

[8] Cavallini M et al. J of Plastic Dermatol. 2010, 6(2), 145-147.

[9] Kulkarni P, Jeffery S. Burns Open. 2018, 2, 2, 104-107.



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**Diphoterine® solution washes and removes chemicals* to limit burns and sequelae.**

*For hydrofluoric acid, use Hexafluorine® solution

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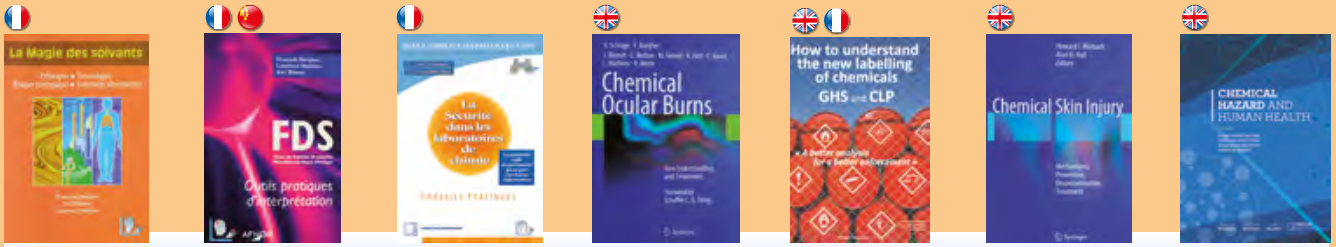


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