

Report

Diphoterine for alkali chemical splashes to the skin at alumina refineries

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Conflicts of interest

Dr Donoghue is the Chief Medical Officer of Alcoa of Australia, which operates the refineries at which Diphoterine was implemented, but he has no affiliation or financial involvement with Prevor, the manufacturer of Diphoterine.

Introduction

Diphoterine is an amphoteric hypertonic chelating solution used to decontaminate and irrigate chemical splashes of the skin and eyes.¹ It was developed in France and is manufactured by Prevor.² It has very low toxicity with oral and dermal rat LD₅₀s greater than 2000 mg/kg.¹ It has been shown to have low irritancy and has not caused sensitization in experimental animal studies.^{1,3} Diphoterine has been shown *in vitro* to neutralize acids and bases.¹ It is water soluble.¹

Diphoterine irrigation of experimental hydrochloric acid skin splashes in rats resulted in better wound outcomes at 7 d compared with irrigation with normal saline or calcium gluconate. Serum concentrations of substance P were lower at 6 and 48 h for rats irrigated with Diphoterine compared with rats irrigated with normal saline or calcium gluconate.⁴

Diphoterine has been reported as giving prompt relief from the eye and skin symptoms induced by CS “Tear gas” in volunteer French Gendarmes.⁵

Abstract

Background Diphoterine is a commercially available amphoteric, hypertonic, chelating solution used to decontaminate and irrigate chemical splashes. The aim of this study was to evaluate the implementation of Diphoterine at three alumina refineries. This is the largest case series reported to date.

Methods One hundred eighty cases of alkali splashes to the skin were evaluated clinically. Two groups were compared; those who had applied Diphoterine first and those who had applied water first.

Results There were no signs of chemical burn in 52.9% of the group who applied Diphoterine first compared with 21.4% of the group who applied water first. Only 7.9% of the group who applied Diphoterine first had blisters or more severe signs compared with 23.8% of the group who applied water first. The differences were statistically significant ($P < 0.001$). After implementation of Diphoterine the “first aid” injury rate for chemical burns fell 24.7% (95% CI 0.5–43.0%).

Conclusions Applying Diphoterine first was associated with significantly better outcomes following alkali skin splashes than applying water first.

A case series of 24 workers treated with Diphoterine shortly after chemical splash in a German metallurgical plant reported no sequelae and no further treatment required. There were 11 cases of acid splash to the eyes, 8 cases of acid splash to the skin, 4 cases of alkali splash to the eyes and 1 case of alkali splash to the skin.⁶

A case series of 66 patients presenting to a hospital with alkali splash to the eyes found that Diphoterine treatment resulted in a shorter time to corneal re-epithelialization than did treatment with “physiological solution.”⁷

Diphoterine irrigation following alkali application to *ex vivo* rabbit eyes resulted in a greater decline in pH within the anterior chamber than was achieved by irrigation with water, normal saline, or phosphate buffer solution.⁸

Alcoa of Australia operates three alumina refineries in Western Australia at Kwinana, Pinjarra, and Wagerup. These three refineries employ about 3000 people and produce about 13% of the world’s alumina. Much of the Bayer alumina refining process involves strong alkali solutions (primarily sodium hydroxide), which have the potential to

cause chemical burns if the skin is splashed. There are many engineering and administrative controls to reduce the likelihood of splashes occurring, but the possibility still exists that they will occur. Therefore, it is important to provide the best first aid available for chemical splashes. Traditionally, this has involved deployment of emergency showers and emergency eyewash stations in close proximity to any areas of risk. Employees and contractors have been trained for many years to respond to skin splashes by immediately removing contaminated clothing and showering for 20 min. All cases are required to report to the onsite medical centers for assessment. All reported skin splashes are logged in Alcoa's Environment Health and Safety Incident Management System (EHSIMS), which triggers a safety investigation and corrective actions. Employees and contractors have been trained to call the plant emergency number for emergency medical response by onsite ambulance if they sustain or witness a large skin splash.

Following review of the published reports in 2003 and discussion with occupational health and safety staff from alumina refineries in the United States and South America, Alcoa of Australia sought approval of Diphoterine by the Therapeutics Goods Administration of the Australian Government. This was granted in December 2005 and the product was imported in 2006. Alcoa of Australia then decided to implement Diphoterine at its three alumina refineries in Western Australia. To evaluate the effectiveness of the program, a clinical case series was undertaken and injury data were interrogated. The objective of the clinical case series was to determine if the clinical severity of chemical burns were any different when Diphoterine was applied first following chemical splash, compared to when water was applied first. This comparison was made possible when the Diphoterine program was introduced because some employees chose to use Diphoterine first, whilst others chose to apply water first. This is the largest clinical case series reported to date. The objective of the injury rate analysis was to determine if there were any differences in the injury rates for chemical burns before and after the introduction of Diphoterine.

Materials and methods

Diphoterine was first applied in Australia for a chemical splash at the Pinjarra alumina refinery on May 11, 2006. Over the ensuing 8 months, all employees and contractors working in the operational areas of all three refineries were trained in the use of Diphoterine and issued with a 100 ml personal aerosol can, belt, and carrying pouch. Employees and contractors were trained to respond to skin splashes by immediately removing contaminated clothing and applying Diphoterine from their personal can. They were instructed to discharge the entire

contents of the can and to seek assistance from nearby colleagues if necessary to spray larger splashes with multiple cans. They were specifically advised that there was no need to shower before applying Diphoterine and that they had to shower only if they did not have access to enough Diphoterine to cover the affected skin promptly. The instruction to call the plant emergency number for emergency medical response by onsite ambulance if they sustained or witnessed a large skin splash remained unchanged. The ambulances and medical centers were equipped with 5 l canisters of Diphoterine and a large supply of 100 ml cans. The program became mandatory on February 01, 2007. The clinical case series began on October 01, 2006, and ended on February 29, 2008.

All injuries and specifically any chemical splashes (whether injury occurs or not) are required to be reported to the onsite medical centers and logged in Alcoa's EHSIMS.

Clinical case series

During the clinical case series, all cases reporting the use of Diphoterine for chemical splashes were assessed using a standardized one page form and received conventional treatment for any injury. The assessments were made by emergency response officers, occupational health nurses, or plant physicians in the onsite medical centers. Assessments were made 24 h per day, 7 d per week. For each case, the following data were obtained: date and time of clinical assessment, date and time of chemical splash, name of the chemical and estimated time elapsed before the first application of Diphoterine. The subject was asked if water was also used for irrigation and if so whether this was before or after applying Diphoterine. The person undertaking the clinical assessment was asked to draw on a body surface area diagram, the area of skin that was splashed by the chemical. He/she was also asked to answer yes or no to the following questions:

- 1 Is there any redness (erythema) of the skin where the chemical splash occurred?
- 2 Is there any blistering of the skin where the chemical splash occurred?
- 3 Are there any signs of more severe burns?

The answers to these questions were used to assess the severity of the outcome. Severity was graded 1–4 where 1 indicated no signs of a burn, 2 indicated erythema only, 3 indicated blisters were the most serious sign, and 4 indicated signs of more severe burns.

All of these case details were entered into an Excel file spreadsheet. Where the clinical assessments listed a range for the "Estimated time elapsed before the first application of Diphoterine" the upper bound of the range was selected. For example, if "2–3 min" was stated, a value of 3 min was entered into the spreadsheet. Where "a few minutes" was stated, a value of 5 min was entered into the spreadsheet. When analyzing the data two groups were formed, those who had applied Diphoterine first and those who had applied water first,

before using Diphoterine. The “Diphoterine first” group comprised those who had applied water after Diphoterine and those who had said they had not applied water – just Diphoterine. The percentage of body surface area skin splashed by a chemical was estimated visually from the shaded areas on the body surface area diagram. Where a cross was used instead of a shaded area, it was assumed this was a small area and a value of 0.25% body surface area was entered.

Normal clinical follow-up of cases took place depending on the severity of the burns. The study did not attempt to evaluate any possible delayed responses and does not present any clinical assessment data beyond 24 h from the time of the splash.

Environment Health and Safety Incident Management System was interrogated to determine the number of cases reported during the clinical case series timeframe that were potentially eligible to have been studied.

This involved downloading cases using two strategies:

- 1 All cases with a “Nature of Injury” recorded as “Burn (Chemical)” that occurred during the timeframe at any of the three refineries were downloaded from EHSIMS into an Excel file. This spreadsheet was then restricted to cases which did not list “Eye” as the “Body part”, and further restricted by deleting “Deactivated” cases (i.e., cases not substantiated following investigation). Two cases were removed because the “Contact Agent” was acid, not alkali.
- 2 All cases that occurred during the timeframe at any of the three refineries were downloaded from EHSIMS into an Excel file. This spreadsheet was then restricted to cases which did not list “Eye” as the “Body part”, and further restricted to cases which listed the “Contact Agent” as “Caustic...” or “Liquor” and further restricted to cases which did not list “Burn (Chemical)” as the “Nature of Injury”. This spreadsheet was then reviewed and further restricted to cases which gave a history of a chemical splash to the skin of an employee or contractor in the “What Occurred” narrative. There were no deactivated cases to remove from this file.

The two spreadsheets therefore contained any cases that involved employees or contractors in a “Burn (Chemical)” to the skin because of an alkali contact agent, or a splash to the skin of any material with the word “Caustic” included in the “Contact Agent” description or a splash to the skin of “Liquor”. There was no duplication of cases in these two files.

Injury rate analysis

Environment Health and Safety Incident Management System was also interrogated to establish data for two timeframes, one prior to and one after implementation of Diphoterine. The two timeframes were:

Before: May 01, 2005 to April 30, 2006 inclusive.

After: May 01, 2007 to April 30, 2008 inclusive.

Seasonal effects were controlled by selecting the same dates for different years.

For each of these two timeframes, cases were downloaded from EHSIMS using two strategies similar to those listed above. Specifically:

- 1 All cases with a “Nature of Injury” recorded as “Burn (Chemical)” that occurred during the relevant timeframe at any of the three refineries were downloaded from EHSIMS into an Excel file. This spreadsheet was then restricted to cases which did not list “Eye” as the “Body part”, and further restricted to cases involving employees not contractors, and further restricted by deleting “Deactivated” cases (i.e., cases not substantiated following investigation).
- 2 All cases that occurred during the relevant timeframe at any of the three refineries were downloaded from EHSIMS into an Excel file. This spreadsheet was then restricted to cases which did not list “Eye” as the “Body part”, and further restricted to cases involving employees not contractors, and further restricted to cases which listed the “Contact Agent” as “Caustic...” or “Liquor” and further restricted to cases which did not list “Burn (Chemical)” as the “Nature of Injury”. This spreadsheet was then reviewed and further restricted to cases which gave a history of a chemical splash to the skin of an employee in the “What Occurred” narrative. There were no deactivated cases to remove from this file.

The two spreadsheets therefore contained any cases that involved employees (not contractors) in a “Burn (Chemical)” to the skin because of any contact agent (acid or alkali), or a splash to the skin of any material with the word “Caustic” included in the “Contact Agent” description or a splash to the skin of “Liquor.” There was no duplication of cases in these files. The case data for the before and after analyses came from administrative data and were not derived from the clinical assessments.

Environment Health and Safety Incident Management System was also interrogated to determine the number of hours worked by employees (not contractors) at the three refineries during the relevant timeframes. Contractors were not included in the injury rates analysis because the Alcoa EHSIMS database does not record worker-hours for contractors, only for employees. This lack of “denominator” data for contractors meant that it was not possible to calculate injury rates for contractors.

All EHSIMS case types are classified according to the criteria of the US Occupational Safety and Health Administration (OSHA).

Statistical methods

Histograms of the following variables were positively skewed, necessitating the use of nonparametric methods:

- 1 Time elapsed from the chemical splash to the clinical assessment.
- 2 Time elapsed from the chemical splash to the application of Diphoterine.

3 Percentage of body surface area splashed by chemical.

For each of these variables the differences between the two groups ("Diphoterine first" and "water first") were assessed by the Mann–Whitney *U* test.

Cross-tabulation of outcome severity by group ("Diphoterine first" and "water first") was undertaken. The difference in the outcome severity categorization by group was assessed using the Chi Square test. Because more than 20% of the cells had expected counts less than 5, severity categories 3 and 4 were amalgamated to resolve this issue.

Injury rate ratios were generated from injury rates calculated for the periods before and after implementation of Diphoterine.

The 95% confidence intervals for the injury rate ratios were derived using the equations of Kirkwood and Sterne.⁹ All other statistical analyses were undertaken using SPSS 14.0 (SPSS Inc, Chicago, Illinois, USA).

Results

Clinical case series

In total, 197 cases were studied in the clinical case series. However, 11 cases were removed because the clinical assessment occurred more than 24 h after the chemical splash. In addition, two cases were removed because the chemical was acid not alkali and another three cases were removed because the chemical type was not stated. One case was removed because there was no record of the effects on the skin. Therefore, a total of 17 cases were removed leaving 180.

In total, there were 318 cases that were potentially eligible to have been studied during the clinical case series timeframe of October 01, 2006 to February 29, 2008. These comprised 1 "Lost Work Day" case (LWD), 7 "Restricted Work Day" cases (RWD), 9 "Medical Treatment" cases (MT), 207 "First Aid" cases (FA) and 94 "Injury Free Event" cases (IFE).

Therefore, the clinical case series included 180 out of 318 (56.6%) potentially eligible cases. Figure 1 shows the derivation of the clinical case series study population. It is important to note that potentially eligible cases did not necessarily apply Diphoterine, especially in the first 4 months of the 17 month clinical series when it was not yet mandatory. Consequently, the proportion of eligible cases is probably higher than 56.6%.

Table 1 lists results for the following variables:

1. Time elapsed from the chemical splash to the clinical assessment.
2. Time elapsed from the chemical splash to the application of Diphoterine.
3. Percentage of body surface area splashed by chemical.

The results are listed for the two groups – those who applied Diphoterine first and those who applied water first. There were no statistically significant differences

between the groups for time elapsed from the chemical splash to the clinical assessment ($P = 0.496$) or for body surface area splashed by the chemical ($P = 0.233$). As expected, there was a statistically significant difference between the groups for time elapsed from the chemical splash to the application of Diphoterine ($P < 0.001$). More time elapsed for the water first group, because they were, by definition, applying water first. The Diphoterine first group applied Diphoterine within a median time of 1 minute from the time of the chemical splash, whereas the water first group applied Diphoterine within a median time of 5 min from the time of the chemical splash. It is likely that both groups initiated first aid treatment in a similar timeframe, be that Diphoterine first, or water first, because there was a high spatial density of emergency showers throughout the refineries. It is therefore unlikely that there was a meaningful difference between the groups in terms of the length of time that alkali was on the surface of the skin. The median size of chemical splashes was fairly small at about 1%, but some large skin splashes did occur, up to a maximum of 38%.

Table 2 gives the number and percentage of cases in each severity group. There were no signs of a chemical burn in 52.9% of the group who applied Diphoterine first. There were no signs of a chemical burn in only 21.4% of the group who applied water first. Only 7.9% of the group who applied Diphoterine first had blisters or more severe signs. However, 23.8% of the group who applied water first had blisters or more severe signs. The difference in the outcome severity categorization by group was statistically significant ($P < 0.001$).

Injury rate analysis

In the period before implementation of Diphoterine (May 01, 2005 to April 30, 2006 inclusive), there were a total of 140 cases amongst employees (not contractors) comprising 1 MT case, 112 FA cases, and 27 IFE cases. During this period, employees worked 5 944 593 h. Therefore, the total case rate was 4.71 per 200 000 h worked.

In the period after implementation of Diphoterine (May 01, 2007 to April 30, 2008 inclusive), there were a total of 126 cases amongst employees (not contractors) comprising 1 RWD case, 4 MT cases, 88 FA cases, and 33 IFE cases. During this period, employees worked 6 202 230 h. Therefore, the total case rate was 4.06 per 200 000 h worked.

There was therefore a 13.7% reduction in total cases after the implementation of Diphoterine. However, this was not statistically significant. The rate ratio was 0.863 (95% CI 0.678–1.098).

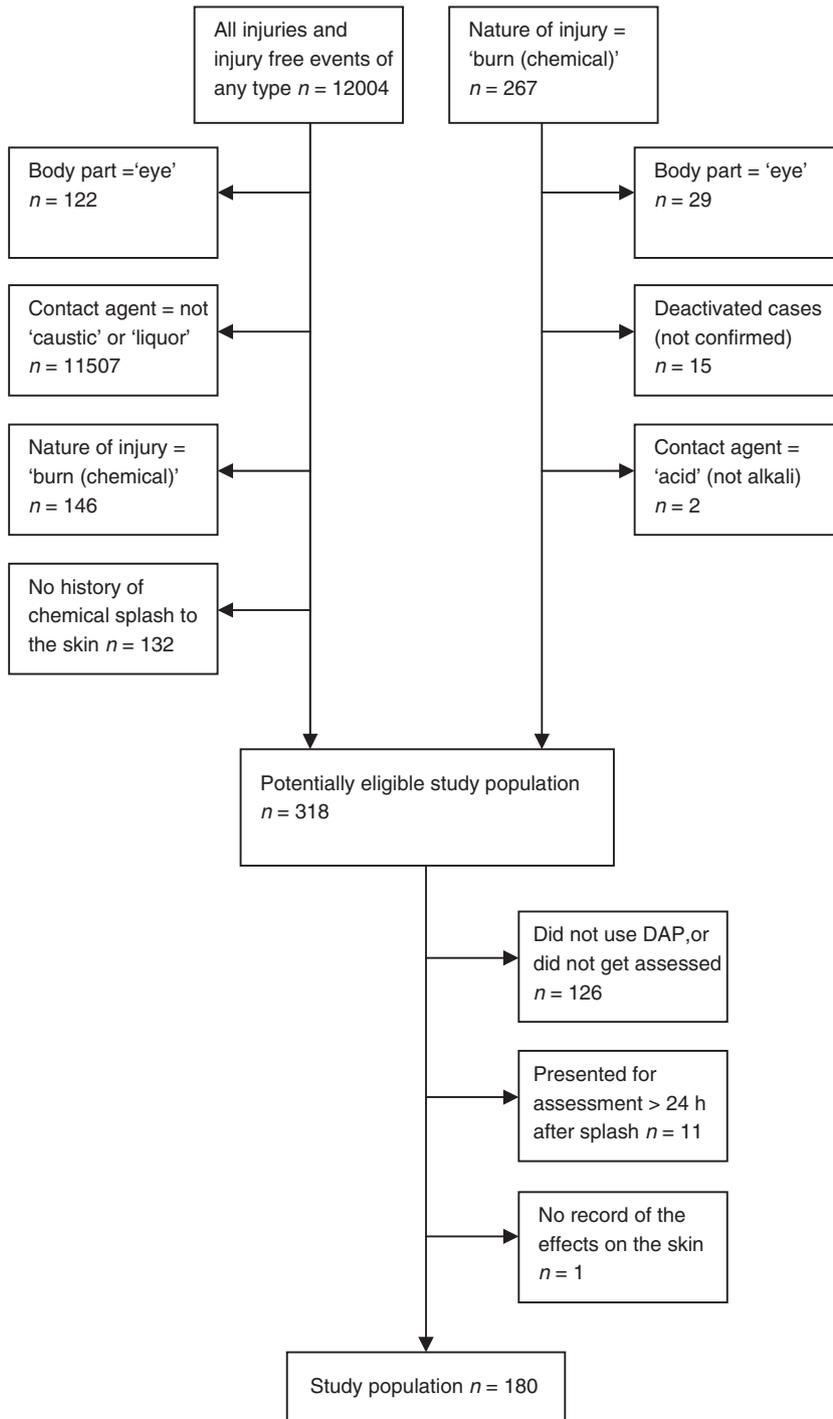


Figure 1 Derivation of clinical case series study population: in the period October 01, 2006 to February 29, 2008. DAP, diphoterine

Table 3 gives the rates and rate ratios for IFE cases, FA cases, and all injuries combined (FA + MT + RWD + LWD). The IFE rate ratio was 1.172 (95% CI 0.706–1.947), indicating a nonstatistically significant increase in IFE cases following implementation of Diphoterine. The FA rate ratio was 0.753 (95% CI 0.570–0.995), indicating a statistically significant

decrease in FA cases following implementation of Diphoterine. The all injury rate ratio was 0.789 (95% CI 0.600–1.038), indicating a nonstatistically significant decrease in all injury cases following implementation of Diphoterine. The numbers of MT and RWD cases were too small to calculate confidence intervals. There were no LWD cases.

Table 1 Clinical case variables – for the group that applied DAP first and for the group that applied water first

	Time splash to assessment (min)		Time splash to DAP (min)		Body surface area (%)	
	DAP first	Water first	DAP first	Water first	DAP first	Water first
<i>n</i>	135	41	135	42	138	42
Median	25	30	1.0	5.0	0.75	1.0
Mean	89	66	2.9	11	1.6	2.9
95% CI	45–134	0–135	1.7–4.1	7.0–15	1.1–2.0	0.98–4.8
SD	260	220	6.9	13	2.7	6.2
Range	0–1410	0–1430	0.0–60	0.0–45	0.10–18	0.10–38
<i>P</i> -value	0.496		<0.001		0.233	

DAP, diphoterine.

Table 2 Number of cases (%) in each severity category – for the group that applied DAP first and for the group that applied water first

Severity (associated signs)	DAP first	Water first
1 (no signs)	73 (52.9%)	9 (21.4%)
2 (erythema)	54 (39.1%)	23 (54.8%)
3 (blisters)	10 (7.2%)	8 (19.0%)
4 (more severe)	1 (0.7%)	2 (4.8%)
Total	138 (100%)	42 (100%)

P < 0.001 when severity categories 3 and 4 are combined. DAP, diphoterine.

Comment

The use of Diphoterine first was associated with significantly better outcomes following alkali skin splashes than the use of water first. There were no signs of chemical burn in 52.9% of the group who applied Diphoterine first when compared with 21.4% of the group who applied water first. Only 7.9% of the group who applied

Diphoterine first had blisters or more severe signs when compared with 23.8% of the group who applied water first. The difference in the outcome severity categorization by group was statistically significant (*P* < 0.001). It was possible that people confronted with a larger, potentially more serious splash might have tended to use water first, trusting what they were familiar with. However, the difference between the two groups in median percentage body surface area splashed by alkali was small and not statistically significant, making this unlikely. It was also possible that there might have been a difference between the two groups in the time elapsed from the splashes occurring to the clinical assessments being undertaken. This might have resulted in a difference in the observed severity of the burns, with for example; erythema resolving in cases taking longer to present for clinical assessment. However, the difference between the two groups in the time elapsed between the splashes occurring and the clinical assessments being undertaken was small and not statistically significant, making this unlikely. It is important to note that the staff undertaking the clinical assessments were not blinded to the nature of the chemical exposure, or to whether Diphoterine had been used first. This could potentially have introduced bias, although it seems unlikely that this would have resulted in the magnitude of differences in severity outcomes that were observed between the two groups.

Following implementation of Diphoterine, there was a 21.1% decrease in the injury rate from chemical splashes and a 17.2% increase in the IFE rate – for cases where there were no signs of skin damage observed. These changes in rates did not reach statistical significance, however, the 24.7% decrease in the FA rate was statistically significant. These observations are consistent with the better clinical outcomes observed using Diphoterine. It seems most likely that implementing Diphoterine has reduced the severity of chemical burns and has resulted in more cases being registered as IFE cases – where there has been no harm carried out at all. Another possibility is that the renewed focus on chemical burns resulting from

Table 3 Chemical burn injury rates before and after implementation of diphoterine

	IFE		FA		FA + MT + RWD + LWD	
	Before	After	Before	After	Before	After
<i>n</i>	27	33	112	88	113	93
Person-hours	5 944 593	6 202 230	5 944 593	6 202 230	5 944 593	6 202 230
Rate	0.91	1.06	3.77	2.84	3.80	3.00
Rate ratio (95% CI)	1.172 (0.706–1.947)		0.753 (0.570–0.995)		0.789 (0.600–1.038)	

IFE, injury free event cases; FA, first aid cases; MT, medical treatment cases; RWD, restricted work day cases; LWD, lost work day cases.

the implementation of Diphoterine has improved behavioral safety, with a reduction in the underlying frequency and severity of splashes. This may have contributed, but the improved clinical outcomes observed in the clinical series are likely to have been an important contributor – and perhaps the main reason for the improvement in injury rate. The possibility that changes in personnel might have affected the injury rates for chemical burns, perhaps because of a lack of experience in the job, is unlikely, given that the percentage of employee turnover during the study period was quite low and stable: 5% in 2005, 6% in 2006, and 7% in 2007 and 2008. There were no significant changes in the refineries processes or work procedures during the study period, which could have affected the injury rates for chemical burns.

There was only one RWD case and no LWD cases in the before and after analyses – showing that although there has been further improvement, there was already effective first aid management in place with no serious cases of skin burn.

The improved outcomes seen with the use of Diphoterine first, suggest we had to reinforce the message to the workforce about the efficacy of Diphoterine and encourage people to have confidence in using Diphoterine first. After decades of using water for irrigation of alkali splashes, it is understandable that some people are reluctant to change.

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