MHRA UK PUBLIC ASSESSMENT REPORT

Aqueous cream: contains sodium lauryl sulfate which may cause skin reactions, particularly in children with eczema

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PLAIN-LANGUAGE SUMMARY

KEY MESSAGE: Aqueous cream may cause skin irritation in some people, especially when used as a moisturiser in children with eczema. These skin reactions may be due to an ingredient contained in aqueous cream called sodium lauryl sulfate, or other ingredients such as preservatives.

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK government agency responsible for regulating medicines and medical devices. We continually review the safety of medicines and vaccines in the UK[1], and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. This report discusses a product called aqueous cream, and its risks and benefits when used in children with eczema.

Eczema is a persistent skin condition characterised by symptoms such as dry, itchy, red and swollen areas of skin. These symptoms can flare up at different times, sometimes in response to allergic or irritant triggers. Eczema can be made worse by dryness of the skin, and therefore it is important to keep the affected areas of the skin moistened to promote skin healing and relief of symptoms.

Aqueous cream is used as an emollient (moisturiser) and a 'wash-off' soap substitute to relieve the symptoms of dry skin conditions such as atopic eczema[2]. It has been used for this purpose since the 1950s in adults, children and babies, and is still widely used today (approximately 11 million containers of 100 mL aqueous cream were supplied by hospital and retail pharmacies in the UK in 2012[3]). Aqueous cream is sold over-the-counter in supermarkets and retail pharmacies, and may also be prescribed in larger quantities by a health professional.

As with any medicine, the use of aqueous cream may cause side effects in some individuals. It is known that aqueous cream may be associated with skin reactions in some people when it is used as a leave-on moisturiser. An assessment of children attending a dermatology clinic showed that more than half of the children who used aqueous cream had skin reactions. Following this assessment, all clinical information on the use of aqueous cream in children with eczema was recently reviewed by the MHRA and the Commission on Human Medicines[4]. The findings and recommendations from the review are summarised below.

Results

The review examined information from clinical trials, reported cases, and clinical guidelines.

In the dermatology clinic assessment, 71 children aged 1 – 16 years with atopic eczema were treated with aqueous cream as a leave-on moisturiser. Around 56% of

[1] Suspected side effects to any drug or vaccine can be reported to the MHRA by both healthcare professionals and members of the public via the YellowCard Scheme (http://www.mhra.gov.uk/yellowcard)

[2] There are several different types of eczema – atopic eczema is usually triggered by an allergy or irritant and tends to run in families

[3] Data derived from IMS Health, IMS MIDAS, 01/12/2012, by the MHRA

[4] An independent committee of health professionals and scientists who advise government Ministers on the safety, effectiveness and quality of medicines

uses of aqueous cream were followed by an immediate skin reaction such as burning, stinging, itching and redness, within 20 minutes of application.

Other studies report thinning of the skin and increased loss of water from the skin following application of aqueous cream in some individuals both with and without eczema.

NICE guidelines for managing eczema in children advise that 'aqueous cream is associated with stinging when used as a leave-on emollient but can be used as a wash product', and the National Eczema Society advises that 'if aqueous cream is used as a leave-on emollient it can irritate the skin of children with eczema and make it worse rather than better'.

The irritation associated with aqueous cream is thought to be caused by sodium lauryl sulfate (SLS), which is a component of emulsifying wax (one of the listed ingredients of aqueous cream) and helps to maintain the creamy consistency of aqueous cream. 24 suspected cases of skin reactions[1] associated with emulsifying wax in aqueous cream have been reported to the MHRA since 1988 through the Yellow Card side effect reporting scheme[2].

Other ingredients in aqueous cream, such as preservatives, may also contribute to adverse skin reactions.

Despite the irritant effects reported, in clinical practice aqueous cream has been useful in the treatment of eczema in a very large proportion of patients.

On the basis of the review, aqueous cream labelling and information leaflet will be updated with a warning on the potential of local skin reactions, and SLS will be listed as an ingredient. The following advice and recommendations on the use of aqueous cream have been given for healthcare professionals:

Key advice:

- Aqueous cream contains sodium lauryl sulfate (SLS) which may cause local skin reactions (eg, stinging and contact dermatitis), particularly in children with atopic eczema. Other ingredients such as preservatives may also contribute to skin reactions.

- During an eczema treatment consultation, health professionals should inform patients that skin irritation (such as burning, stinging, itching or redness) may occur if aqueous cream is used as a leave-on emollient, often within 20 minutes of application.

- If a patient has skin irritation (burning, stinging, itching or redness) after the use of aqueous cream, they should discontinue treatment, and talk to their healthcare professional who will be able to advise on suitable alternative treatments.

[1] Data from Drug Analysis Print, MHRA website (http://www.mhra.gov.uk/home/groups/public/documents/sentineldocuments/dap_1359110223225.pdf)
[2] http://www.mhra.gov.uk/yellowcard

1. INTRODUCTION

(See glossary for an explanation of the terms used in this report)

Aqueous cream is a well-established and widely prescribed product used as an emollient and soap substitute in the treatment of dry skin conditions, including atopic eczema. During July – September 2008, compared with the same period in 2004, prescribing of emollients increased by 38% to 2.6 million items and costs increased to £14.1 million. Aqueous cream was the most prescribed emollient product during July – September 2008 (accounting for 493 000 of items) followed by Diprobase cream (351 000 items), E45 cream (341 000 items) and Doublebase gel (304,000 items) (NHS Information Centre report: Atopic eczema – Prescribing guidance and discussion points. 2009).

Like other emollients, aqueous cream relieves skin dryness by providing moisture to the dehydrated skin barrier, improving the flexibility of the skin. However, aqueous cream formulations contain sodium lauryl sulfate (SLS), a known skin irritant. SLS is a component of emulsifying wax, one of the key ingredients of aqueous cream. E45, Diprobase and Doublebase are all SLS-free emollient products.

Acute adverse skin reactions associated with aqueous cream use have been documented in a clinical audit of patients at a paediatric dermatology clinic (Cork et al. 2003). The audit showed that 56% of exposures to aqueous cream were followed by an immediate cutaneous reaction described as a 'stinging' sensation upon application. In this study, aqueous cream elicited a higher level of discomfort than any other product used (see section 3.2, literature review, for further details).

Various studies have been carried out in both children and adults to look at the effects of aqueous cream on skin barrier function and its effect on the stratum corneum (see section 3 for further details). Adverse skin reactions associated with aqueous cream are not limited to children and have been documented in healthy adult volunteers as well as eczema patients. The acute effects of aqueous cream on skin barrier function appear far better documented in literature than the chronic effects, which have not yet been determined.

At the time of this review, the product information for all aqueous cream products stated that care must be taken if the user is allergic to any of the ingredients, but only three stated that skin reactions may occur with use of aqueous cream, and only two listed SLS as an ingredient on the label.

As a consequence of the new publications and the differences between the product information, the MHRA and the Commission on Human Medicines[1] reviewed the use of aqueous cream in eczematous conditions, and the role of SLS in aqueous cream formulations and its impact on the skin. The review evaluated whether additional advice and recommendations on the use of aqueous cream were necessary in light of recent studies and information.

[1] An independent committee of health professionals and scientists who advise government Ministers on the safety, effectiveness and quality of medicines

2. BACKGROUND

Legal and regulatory status of aqueous cream

The formulation of aqueous cream is very well established. Aqueous cream first appeared in the 1958 British Pharmacopoeia. The 1958 formulation also contained SLS and the modern 2013 British Pharmacopoeia formulation remains unchanged compared to the 1958 version (see http://www.pharmacopoeia.co.uk/).

Aqueous cream products are all sold as General Sales List (GSL) status in the UK (ie, they are available in supermarkets, pharmacies, etc), but larger quantities may also be prescribed by health professionals. There are five aqueous cream products currently licensed in the UK (Pinewood, Ayrton Saunders, Thornton and Ross, Ecolab, Boots) which may be marketed under different brands. None of the products caution against using aqueous cream in eczematous or other conditions with damaged or broken skin.

The products all contain the preservative phenoxyethanol, but some contain other additional preservative agents, including parabens, and chlorocresol. All products state the ingredients, however SLS is not always specifically mentioned because it is a sub-component of emulsifying wax used in the formulation.

Atopic eczema and the role of emollients

Atopic eczema is a chronic inflammatory skin condition characterised by an itchy red rash and skin lesions. The condition is most commonly seen in skin creases such as folds of elbows or behind the knees, but can also appear in other areas. The eczema lesions themselves vary in appearance from collections of fluid in the skin (vesicles) to gross thickening of the skin (lichenification) on a background of poorly demarcated redness. Other features such as crusting, scaling, cracking and swelling of the skin can occur. Atopic eczema is associated with other atopic diseases such as hay fever and asthma. People with atopic eczema also have a dry skin tendency, which makes them particularly vulnerable to the drying effects of soaps.

Atopic eczema typically starts in early life, usually in the first months, with around 80% of cases starting before the age of 5 years. The disorder affects both sexes equally. In the UK, 15-20% of school-aged children and 2-10% of adults will be affected by the condition at some stage[1]. Atopic eczema commonly resolves during childhood, but it may persist into adult life, or recur in the teenage or early adult years.

Depending on disease severity, atopic eczema may have a considerable adverse effect on the quality of life of affected individuals and their families (eg, through sleep disturbances due to itching and scratching of skin). Atopic eczema may adversely influence a child's emotional and social development and may predispose to psychological difficulties[1].

Around 20% of people with otherwise typical atopic eczema are not atopic as defined by the presence of positive skin prick test reactions to common environmental allergens, or through blood tests, which detect specific circulating immunoglobulin E (IgE) antibodies. The word 'atopic' in the term 'atopic eczema' is an indicator of the frequent association with atopy and separates this clinical phenotype from the ten or so other forms of eczema such as irritant, allergic contact, discoid, venous, seborrhoeic and photosensitive eczema, which have other causes and distinct patterns (Hoare 2000).

[1] Data from Scottish Intercollegiate Guidelines Network 2011

The terms *atopic eczema* and *atopic dermatitis* are synonymous. The term atopic eczema or just eczema is frequently used in the UK, whereas atopic dermatitis is used more frequently in the US.

According to diagnostic criteria from Williams et al. 1994, atopic eczema should be diagnosed when a child has an itchy skin condition plus three or more of the following:

- visible flexural dermatitis involving the skin creases, such as the bends of the elbows or behind the knees (or visible dermatitis on the cheeks and/or extensor areas in children aged 18 months or under)
- personal history of flexural dermatitis (or dermatitis on the cheeks and/or extensor areas in children aged 18 months or under)
- personal history of dry skin in the last 12 months
- personal history of asthma or allergic rhinitis (or history of atopic disease in a first-degree relative of children aged under 4 years)
- onset of signs and symptoms under the age of 2 years (criterion should not be used in children aged less than 4 years).

In Asian, black Caribbean and black African children, atopic eczema can affect the extensor surfaces rather than the flexures, and discoid (circular) or follicular (around hair follicles) patterns may be more common[1].

NICE guidelines on atopic eczema in children (NICE 2007) recommend that healthcare professionals should use a stepped approach for managing atopic eczema in children. This means tailoring the treatment step to its severity. Emollients should form the basis of atopic eczema management and should always be used, even when the eczema is clear. Management can then be stepped up or down, according to the severity of symptoms, with the addition of the other treatments listed in Table 1.

Table 1. Treatment options for atopic eczema

Mild atopic eczema	**Moderate atopic eczema**	**Severe atopic eczema**
Emollients	Emollients	Emollients
Mild potency topical corticosteroids	Moderate potency topical corticosteroids	Potent topical corticosteroids
	Topical calcineurin inhibitors	Topical calcineurin inhibitors
	Bandages	Bandages
		Phototherapy
		Systemic therapy

To manage dry skin with its shortcomings (eg, an increased loss of water which provides easier access for invading allergens and bacteria through the skin), emollient therapy is widely used to restore the normal protective mechanisms. Emollients (also known as moisturisers) are used to treat or prevent dry, rough, and scaly skin. They work by forming an oily layer on the top of the skin that traps water in the skin. They soften and moisturise the skin and in this way decrease itching and diminish flaking. Many moisturising products also contain ingredients that soften the keratin that holds the top layer of skin cells together (eg, urea, alpha hydroxy acids, and others). These products let the dead skin cells fall off and help the skin retain more water.

[1] NICE guidelines on atopic eczema in children

Emollients have a beneficial effect on eczema by inhibiting loss of water from the skin and restoring the fatty components of the outer layer of the skin, thereby improving the skin barrier. This prevents penetration of allergens, irritants, and organisms, and breaks the itch-scratch cycle, thereby reducing the release of inflammatory active proteins. A good skincare routine using emollients can soothe, moisturise, and protect the skin, thus helping to reduce the need for steroid preparations.

Different emollient formulations such as creams, ointments, and oils are readily available and are summarized in Table 2.

Table 2. Types of emollients

Type	Description
Emollient creams and ointments	Designed to be left on the skin. Creams soak into the skin faster than ointments.
Emollient soap substitutes	Contain emollient ingredients with very mild emulsifiers. They are used instead of soap and other detergents.
Emollient semi-dispersing bath oils	Contain oils and emulsifiers that disperse the oil in the water. This combination has a cleansing effect if gently rubbed over the skin.
Non-dispersing emollient bath oils	Contain oils with no emulsifying agent. The oil forms a layer on the surface of the water which is deposited on the skin on getting out of the bath.
Adjuvant emollient products	Contain additional ingredients such as antipruritics and antiseptics.

3. RESULTS OF REVIEW ON AQUEOUS CREAM

3.1 Overview of guidelines on emollients and aqueous cream use in eczema

Long-term emollient therapy is considered the mainstay of treating atopic eczema, and expert opinions from clinical guidelines support the use of emollients in the treatment of atopic eczema to restore the defective skin barrier. The following guidelines on emollient use have been reviewed (in chronological order, with specific information about aqueous cream highlighted):

Akdis et al.: Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report 2006 *Allergy 2006: 61: 969–987*

The regular use of emollients is important and together with skin hydration, it represents the mainstay of the general management of atopic dermatitis. Emollients should be applied continuously, even if no actual inflammatory skin lesions are obvious. Because different emollients are available, selection criteria, such as the individual skin status, seasonal and climatic conditions, and the time of day, should be considered for optimising the patients' basic treatment. Water-in-oil or oil-in-water emulsions might be substituted to support the skin barrier function. Emollients containing polidocanol are effective in reducing pruritic symptoms. Adjuvant application of topical preparations with urea allows for intensive hydration of the skin, whereas salicylic acid can be added to an emollient for the treatment of chronic hyperkeratotic lesions.

No specific information was included in the guidelines about the use of aqueous cream.

National Institute for Health and Clinical Excellence (NICE): Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years. *London: National Collaborating Centre for Women's and Children's Health; 2007.*

NICE advises that healthcare professionals should offer children with atopic eczema a choice of unperfumed emollients to use every day for moisturising, washing and bathing. This should be suited to the child's needs and preferences, and may include a combination of products or one product for all purposes. Furthermore, leave-on emollients should be prescribed in large quantities (250–500 g weekly) and an alternative emollient should be offered if a particular emollient causes irritation or is not acceptable to a child with atopic eczema. The guidelines also highlight that emollients and/or emollient wash products should be used instead of soaps and detergent-based wash products.

The guidelines also reviewed the available evidence on aqueous cream emollients: an audit of children attending a paediatric dermatology clinic recorded the proportion of immediate cutaneous reactions to emollients (defined as one or more of burning, stinging, itching and redness developing within 20 minutes of application). Aqueous cream was the emollient used by most (71%), which was associated with an immediate cutaneous reaction in 56% of exposures, compared with 18% with other emollients used (details of the other emollients were not reported; n = 100). (Cork 2003)

Based on the above evidence, NICE guidance states: "Aqueous cream is associated with stinging when used as a leave-on emollient but can be used as a wash product."

National Eczema Society: Factsheet on Emollients 2008. *www.eczema.org*
When the skin is very dry, using a combination of the three types of emollients helps to give the best hydration and restore the skin's barrier function to normal. Emollients can be used in combination with other treatments, such as topical steroids and topical calcineurin inhibitors.
In an audit of children attending a paediatric dermatology clinic, using aqueous cream caused irritant reactions in more than fifty percent of the children (Cork 2003).
If aqueous cream is used as a leave-on emollient cream it can irritate the skin of children with eczema and make it worse rather than better.

Primary Care Dermatology Society & British Association of Dermatologists (BAD): Guidelines for the management of atopic eczema 2009. *Volume 39, Oct 2009. http://www.bad.org.uk/*
Emollients should be applied as liberally and frequently as possible. Ideally, emollients should be applied every 4 hours or at least 3–4 times per day. Continual treatment with complete emollient therapy (combinations of cream, ointment, bath oil and emollient soap substitute) will help provide maximal effect. Many patients underestimate the quantity needed and frequency of application to achieve maximal effect. Emollients should be prescribed in large quantities, with the recommended quantities used in generalised eczema being 600 g/week for an adult and 250 g/week for a child.

Intensive use of emollients will reduce the need for topical steroids. It should be emphasised to all patients that the quantity and frequency of use of emollients should be far greater than that of other therapies they may be given. A general rule of thumb is that emollient use should exceed steroid use by 10:1 in terms of quantities used for most patients.

No specific information about aqueous cream was included in these guidelines.

Scottish Intercollegiate Guidelines Network (SIGN): Management of atopic eczema in primary care. March 2011 *SIGN publication no. 125.; http://www.sign.ac.uk*
Patients with atopic eczema should have ongoing treatment with emollients. To optimise adherence to emollient therapy, creams, lotions, ointments, or a combination can be used, depending on patient choice. Prescriptions should be reviewed regularly. Patients and parents/carers of children should be educated about regularly applying emollients onto dry skin and eczematous areas even when eczema is under control.
No specific information about aqueous cream was included in these guidelines.

NHS Choices: Treatment of atopic eczema
http://www.nhs.uk/Conditions/Eczema-(atopic)/Pages/Treatment.aspx
You may need to try a few different emollients to find one that suits you. You may also be prescribed different emollients for different uses, such as: an ointment for very dry skin, a cream or lotion for less dry skin, an emollient to use on your face and hands, a different emollient to use on your body, an emollient to use instead of soap, an emollient to add to bath water or use in the shower. The most common reason for emollients not working is that they are used for inflamed skin without the help of an anti-inflammatory treatment, such as topical corticosteroids.

British National Formulary for Children 2011-2012
Emollients hydrate the skin, soften the skin, act as barrier to water and external irritants, and are indicated for all dry or scaling disorders. Their effects are short-lived and they should be applied frequently even after improvement occurs. They are useful in dry and eczematous disorders, and to a lesser extent in psoriasis; they should be applied in the direction of hair growth immediately after washing or bathing to maximise the effect of skin hydration. The choice of an appropriate emollient will depend on the severity of the condition, the child's (or carer's) preference, and the site of application. Ointments may exacerbate acne and folliculitis. Some ingredients rarely cause sensitisation and this should be suspected if an eczematous reaction occurs. The use of aqueous cream as a leave-on emollient may increase the risk of skin reactions, particularly in eczema.

Preparations such as aqueous cream and emulsifying ointment can be used as soap substitutes; the preparation is rubbed on the skin before rinsing off completely.

3.2 Literature review of emollients and aqueous cream use in eczema

Hoare et al. (2000): Systemic review of treatments for atopic eczema.
Health Technology Assessment 2000; Vol.4:No.37
This project was carried out by the NHS Research & Development Health Technology Assessment Programme to review the available evidence on the treatment of atopic eczema and to identify future research needs. On the use of emollients the paper concludes that there is little clinically useful data from randomised controlled trials (RCTs) on the use of emollients in atopic eczema. In addition to measuring efficacy of emollients in treating mild atopic eczema lesions or the dry skin associated with atopic eczema, it is essential that future RCTs on emollients measure long-term tolerability, patient preferences and cosmetic acceptability as these are probably key determinants for successful long-term use.
Emollients have become consecrated through usage and are firmly implanted in the treatment regimens of most European healthcare practitioners.

Gloor et al (2003): O/W Emulsions compromise the stratum corneum barrier and improve drug penetration.
Pharmazie 58: 709–715 (2003)
Water-in-oil emulsions improve the stratum corneum barrier, while oil-in-water emulsions tend to compromise it. Therefore the aim of this study was to explore the effects of oil in water emulsions on the stratum corneum barrier. Aqueous cream, clioquinol cream base (that is, without clioquinol), non-ionic hydrophilic cream without glycerol, hydrophilic skin emulsion base without glycerol, and base cream were tested versus untreated controls in 29 healthy volunteers (without eczema) for 7 days. Outcome measures included transepidermal water loss, skin redness (measured using chromametry a*-value) and erythrocyte circulation in the subpapillary vessels (measured using laser Doppler). Barrier compromise was subsequently explored by performing the hydrocortisone blanching test using hydrocortisone cream 0.5%. (outcome measure: a*-value) in 15 subjects and the sodium lauryl sulfate (SLS) irritation test (outcome measures: TEWL, a*-value, laser Doppler) in 14 subjects.

Pre-treatment with all of the test emulsions produced increases in transepidermal water loss (statistically significant for all test emulsions), skin redness (statistically significant for aqueous cream and base cream), and erythrocyte circulation in the subpapillary vessels (statistically significant for all emulsions except base cream).

Hydrocortisone penetration was statistically significantly increased with all test emulsions versus untreated controls. SLS irritation was mostly statistically significantly increased versus untreated controls when analysing the study endpoint-baseline difference. The authors concluded that oil/water emulsions may compromise the stratum corneum barrier and improve drug penetration. The paper also highlights that effects of oil/water emulsions demonstrated in the study may have adverse effects in patients with atopic dermatitis.

Cork et al (2003): An audit of adverse drug reactions to AQ in children with atopic eczema.
The Pharmaceutical Journal, Vol271, p747-745, 29th Nov 2003
This paper reports the results of an audit comparing the percentage of episodes of exposure to AQ associated with immediate cutaneous reactions with the percentage of episodes of exposure to all other emollients associated with these reactions. The notes of 100 children aged 1 to 16 years with atopic eczema attending a paediatric dermatology clinic at Sheffield Children's Hospital were assessed. Of the 100 children audited, 71 had used aqueous cream and of these 40 – 56% had developed an immediate cutaneous reaction (defined as one or more of burning, stinging, itching and redness, developing within 20 minutes of application). 18% (111 out of 622) of episodes of exposure to all other emollients were associated with an immediate cutaneous reaction. Details of the other emollients used are not given. The difference was statistically significant ($p<0.001$). The authors concluded that the key to successful emollient therapy is education and tailoring the treatment to the individual child. They also suggested that aqueous cream should only be used as a soap substitute and not as a "leave-on" emollient.

Guy et al (2010): Effect of aqueous cream BP on human stratum corneum *In Vivo*
Br J Dermatol 2010; 163:954-8
The aim of this study was to characterise and assess skin barrier function of healthy skin after application of aqueous cream and to study the physical effects of the formulation on the stratum corneum. The left and right volar forearms of six human volunteers without eczema were each separated into treated and control sides. The treated sides of each forearm received twice-daily applications of aqueous cream BP four weeks, at the end of which time concomitant tape-stripping and transepidermal water loss measurements were made. The untreated sides of the forearms were not exposed to any products containing sodium lauryl sulfate (SLS) during the study period.

Decreases in stratum corneum thickness, increases in transepidermal water loss from baseline and a faster rate of increase in transepidermal water loss during tape stripping were observed in skin treated with aqueous cream. The mean decrease in stratum corneum thickness was 1.1µm (18%; $p = 0.0016$) and the average increase in baseline transepidermal water loss was 2.5 g.m-2.h-1 (32%; $p < 0.0001$). Reduced stratum corneum thickness and increased transepidermal water loss, as well as a faster rate of increase in transepidermal water loss during tape stripping, were observed in 16 out of 27 treated skin sites.

The authors concluded that the application of aqueous cream, containing ~1% SLS, has been shown to reduce the stratum corneum thickness of healthy skin and increase its permeability to water loss.

Danby et al (2011): The effect of aqueous cream BP on the skin barrier in volunteers with a previous history of atopic dermatitis
Br J Dermatol, 2011 Aug;165(2):329-34
The aim of this study was to investigate the effect of aqueous cream on stratum corneum integrity and skin barrier function in volunteers with a predisposition to a defective skin barrier. 13 volunteers with a previous history of atopic dermatitis (no symptoms for 6 months) applied aqueous cream twice daily to the volar side of one forearm for 4 weeks. The other forearm was left untreated as a control. Permeability barrier function and stratum corneum integrity were determined before and after treatment by measuring transepidermal water loss in conjunction with tape-stripping. For comparison 13 volunteers with current atopic dermatitis were recruited for assessment, without treatment, of stratum corneum integrity and skin barrier function at unaffected sites.

Topical application of aqueous cream resulted in significant elevation of baseline transepidermal water loss and a concomitant decrease in stratum corneum integrity in volunteers with a previous history of atopic dermatitis. In volunteers with current atopic dermatitis but no treatment, stratum corneum integrity was better, and transepidermal water loss was less at unaffected sites, compared to volunteers with a history of dermatitis who had been treated with aqueous cream. The study suggests that application of aqueous cream negatively affects the skin barrier towards the damaged state associated with onset of flares of the disease.

Mohammed et al (2011): Influence of aqueous cream BP on corneocyte size, maturity, skin protease activity, protein content and transepidermal water loss.
British Association of Dermatologists Jun 2011, 164, pp1304-1310
The aim of this study was to investigate changes in corneocyte size, corneocyte maturity, selected protease activities, protein content and transepidermal water loss in normal skin without eczema after a 28-day application of aqueous cream. The left and right mid volar forearms of six healthy female volunteers without eczema were selected as the study sites. Aqueous cream was applied twice-daily to the selected sites for 28 days. At the end of this period, the site was tape-stripped and corneocyte maturity, corneocyte size and protease activity of the desquamatory kallikrein proteases, KLK5 and KLK7, and the inflammatory proteases tryptase and plasmin were measured. Protein content and transepidermal water loss measurements were also recorded.

Corneocyte maturity and size decreased with increasing number of tape strips, and were significantly lower in treated sites compared with untreated sites. Protease activity and transepidermal water loss values were higher ($p < 0.05$) for the treated sites compared with untreated sites. The amount of protein removed from deeper layers of treated sites was significantly lower than from untreated sites.

The authors concluded that treatment with aqueous cream is associated with increased desquamatory and inflammatory protease activity. Changes in corneocyte maturity and size are also indicative of accelerated skin turnover induced by chronic application of this emollient.

M.J. Cork, S. Danby: Aqueous cream damages the skin barrier.
British Association of Dermatologists 2011, 164, pp1178-1182
This paper is a commentary on Mohammed et al. 2011 - see above.
The authors conclude that the evidence from the above listed three studies (Guy 2010, Mohammed 2011, Danby 2011a) suggests that aqueous cream BP, used as a leave-on emollient, is an important negative environmental factor contributing to skin barrier

damage and the exacerbation of atopic dermatitis. This paper highlights that using emollients containing sodium lauryl sulfate (SLS), such as aqueous cream may exacerbate rather than reduce skin barrier damage.

3.3 The formulation of aqueous cream

Aqueous cream is a light, paraffin-based oil-in-water emulsion used as a topical, external medicine, emollient moisturiser and general-purpose substitute for toiletries such as soap, shower gel, shaving cream and lip salve. It has a high water content and is therefore cosmetically light and non-greasy in feel, which are desirable characteristics amongst users of emollients where long-term use is an essential part of treatment compliance. SLS is not directly added to AQ formulations but its presence is in emulsifying wax, which is an important component of the cream in order to stiffen it, and reduce its otherwise 'sloppy' consistency.

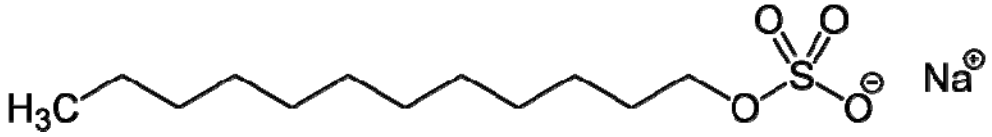
Emulsifying wax also improves the oil-water phase mixing due its detergent properties, and is used to produce oil-in-water emulsions that are stable over a wide pH range.

As well as SLS, the some of the other ingredients used in aqueous cream formulations are known to cause skin irritation (Zondlo et al. 1997; Rowe et al. 2011). These include the preservatives parabens and chlorocresol and cetostearyl alcohol, the latter being a component of emulsifying wax.

An audit (n=100) of children aged 1-16 years attending a dermatology clinic showed that 56% of exposures to aqueous cream in this population produced cutaneous reactions upon application (Cork et al. 2003). The study considered that the adverse skin reactions could be due to the chlorocresol and phenoxyethanol preservatives contained in the cream, but suggested that the most likely cause of the reactions was the presence of SLS in the formulation. However although SLS, parabens and chlorocresol all have possible adverse effects on the skin, no definitive controlled studies using aqueous cream have been carried to determine if any particular excipient is responsible for the skin reactions observed.

It is important to note that despite the differences in preservatives used in aqueous cream products, no studies have been performed to look at the whether the adverse skin reactions observed with aqueous cream result from a particular brand.

Figure 1. Structure of sodium lauryl sulfate



Sodium lauryl sulfate (SLS) is a mixture of sodium alkyl sulfates – mainly sodium dodecyl sulfate (SDS): see figure 1. Its main topical uses are as an ionic surfactant, detergent, emulsifying agent, skin penetrant (Rowe et al. 2011). It is a ubiquitous agent present in a huge range of domestic and commercial products, in particular, tablet coatings, capsules, creams, suppositories, pessaries, liquid soaps, cosmetics, washing detergents. It is also used commonly in toothpaste products, although it has been associated with the formulation of aphthous ulcers (Chahine et al. 1997).

All aqueous cream formulations contain 0.9% w/w SLS. This is considerably lower than liquid hand soap preparations which generally have between 10 – 15% w/w SLS.

SLS has some bacteriostatic action against gram positive which is useful in topical preparations. It is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract, and stomach (Rowe et al. 2011). Repeated, prolonged exposure to dilute solutions may cause drying and cracking of the skin; contact dermatitis may develop (Wigger-Alberti et al. 2000).

Sodium lauryl sulfate is GRAS (Generally Recognized as Safe) listed but should not be used in intravenous preparations for humans. The probable human lethal oral dose is 0.5–5.0 g/kg body-weight.

Emulsifying wax, the aqueous cream component containing SLS is used primarily in topical pharmaceutical formulations and is generally regarded as a non-toxic and non-irritant material (Rowe et al. 2011).

4. DISCUSSION

Unlike many other emollients, aqueous cream contains SLS. At just 0.9% w/w, the levels of SLS contained in aqueous cream suggest its presence is for stabilising the oil-in-water emulsion rather than as a detergent added specifically for its cleansing qualities. SLS appears as a detergent in most liquid- or gel-based soap products due to its foaming properties. There are several ingredients contained in aqueous cream that may cause particular irritation to vulnerable and already damaged skin (SLS, preservatives, and cetosteryl alcohol). SLS is a known skin irritant and as a surfactant it could remove protective oils from skin. In this respect, its inclusion in an emollient, whose purpose is to create an oil barrier, seems to be an anomaly but its presence at low levels may not be a problem to all patients.

In sensitive individuals it appears that it is the presence of SLS rather than a particular level that provokes skin reactions. In addition, despite the potential irritant effects reported in the literature, in clinical practice aqueous cream used both as an emollient and a wash-off soap substitute has been useful in a substantial proportion of patients with atopic eczema. Alternative products may or may not contain SLS.

5. CONCLUSIONS AND ADVICE

Aqueous cream is a light, non-greasy emollient and soap substitute which is popular with some patients suffering from dry skin conditions. It is also used as a low-cost hand cleanser and moisturiser by individuals in a variety of occupations, particularly where frequent hand washing is required, and has been useful as an emollient and a soap substitute in a substantial proportion of patients with atopic eczema.

Aqueous cream products contain sodium lauryl sulfate (SLS) and other ingredients likely to irritate damaged skin. Despite documented skin reactions discussed previously, aqueous cream remains a popular product with eczema patients and patients with other chronic skin conditions. If eczema sufferers switch to other soap substitute containing higher concentrations of SLS and other irritant agents, they may be more likely to cause adverse skin reactions than aqueous cream, which has the value of adding a hydrophobic paraffin barrier to the skin. However there is evidence that suggests longer contact with the skin as a leave-on emollient may cause skin irritation.

On the basis of the review, aqueous cream labelling and information leaflet will be updated with a warning on the potential of local skin reactions, and SLS will be listed as an ingredient.

Advice for healthcare professionals:

- Some patients with eczematous conditions, particularly children, may develop adverse skin reactions if aqueous cream is used as a leave-on emollient, often within 20 minutes of application. These reactions are not generally serious. However, patients and their carers should be warned of this risk during an eczema treatment consultation.

- If a patient reports skin irritation (burning, stinging, itching or redness) after the use of aqueous cream, they should discontinue treatment, and an alternative emollient that does not contain sodium lauryl sulfate should be tried.

- A patient article on potential skin reactions with aqueous cream is available here to download and print [link to patient article when published].

- Aqueous cream labelling and information leaflet will be updated with the following warning on the potential of local skin reactions: ‘Contains sodium lauryl sulfate which may cause local skin reactions (eg, stinging and contact dermatitis)’. Sodium lauryl sulfate will also be listed as an ingredient.

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7. GLOSSARY

Allergen
A substance that causes an allergic reaction, such as sneezing, itching, or skin reactions

Aqueous cream
Aqueous cream is used as an emollient (moisturiser) and a 'wash-off' soap substitute to relieve the symptoms of dry skin conditions such as **atopic eczema**

Atopic
An inherited tendency to develop hypersensitivity conditions such as hay fever, asthma and **eczema**

British Pharmacopoeia
An official British reference book containing directions for the preparation of certain medicines, to ensure that the same prescription written by different doctors and filled by different pharmacists will contain exactly same main ingredients in the same proportions.

Calcineurin inhibitors
An anti-inflammatory prescription medicine which can be used to treat eczema when other medicines are unsuccessful

Chlorocresol
A preservative found in several medicinal and cosmetic products, including **aqueous cream**

Corticosteroids
A group of substances naturally produced in the body which affect various processes in the body, including inflammation and the immune response. Corticosteroids can also be manufactured in a laboratory – these are used as medicines to treat a range of conditions. Corticosteroids such as hydrocortisone are applied to the skin to treat skin disorders such as atopic eczema

Cutaneous
Relating to the skin

Dermatitis
Inflammation of the skin

Dermatology
A branch of medicine that deals with diseases of the skin

Eczema
A noncontagious inflammatory disorder of the skin, characterised by redness, itching, dry skin, and the outbreak of lesions that may become encrusted and scaly

Emollient
A moisturising treatment applied directly to the skin

Emulsifiers
A substance that prevents the liquids in an emulsion from separating (an emulsion is a mixture of two liquids, such as oil and water, that will separate if an emulsifier is not added). **Aqueous cream** is an example of an emulsion product.

Emulsifying wax
An **emulsifier** usually used in cosmetic products

Extensor surfaces
The part of the skin opposite a joint (such as a knee or elbow)

Flexures
A bend or fold in the skin

Folliculitis
Inflammation or infection of one or more hair follicles (openings in the skin that enclose hair).

Hydrophobic
Repelling water, or incapable of dissolving in water

Hyperkeratois
Thickening of the outermost layer of the skin

Immunoglobulin E
A substance produced in the body that is responsible for allergic reactions

Inflammation
Redness, swelling, pain, tenderness, heat, and disturbed function of an area of the body, especially as a reaction of tissues to injury

Nipastat
A commercial preservative mixture containing **parabens** added to several medicinal and cosmetic products, including some versions of **aqueous cream**

Paediatric
Related to the medical care of children

Parabens
A group of preservatives used in several medicinal and cosmetic products, including **aqueous cream**

Phenoxyethanol
A preservative added to several medicinal and cosmetic products, including **aqueous cream**

Phototherapy
The treatment of a disorder, especially of the skin, by exposure to light,

Preservative
A chemical added to food, cosmetics or medicines to prevent decay, spoilage or microbial contamination

Pruritic symptoms
Itching sensation of the skin

Psoriasis
A non-contagious inflammatory skin disease characterised by recurring reddish patches covered with silvery scales

Salicylic acid
A chemical used in making aspirin, as a preservative, and in the external treatment of skin conditions

Sodium lauryl sulphate (SLS)
A detergent chemical added to cosmetic products that is useful for removing grease. SLS is also a component of emulsifying wax (one of the listed ingredients of aqueous cream) which helps to maintain the consistency of **aqueous cream**

Stratum corneum
The outermost layer of the skin

Topical medicine
A medicine applied to body surfaces such as the skin to treat a variety of disorders such as eczema. Topical medicines are available in several forms including creams, foams, gels, lotions and ointments

Urea
A compound occurring in urine and other body fluids as a product of protein breakdown. It is also an ingredient in certain moisturisers to soften thick, rough, or dry skin caused by skin conditions such as eczema