

Acute irritant reactivity to sodium lauryl sulfate in atopics and non-atopics

D. A. BASKETTER, J. MIETTINEN¹ AND A. LAHTI¹

Unilever Environmental Safety Laboratory, Sharnbrook, Bedford, UK and

¹Department of Dermatology, University of Oulu, Oulu, Finland

Predictive testing of chemicals to assess their acute skin irritation potential is an important part of the assessment of their toxicological profile. It is possible, where safety and ethical considerations can be met, to do this work in groups of human volunteers. Previously, the relative responsiveness of atopics and non-atopics has been evaluated. The results showed that atopics (defined broadly by high IgE reactivity) were a little more susceptible to skin irritation, but not significantly so. In the present work, the relative reactivity of a skin atopic group versus a non-atopic group was examined in more detail. Sodium lauryl sulfate (SLS) was applied at a range of concentrations and exposure times, such that a fairly constant degree of skin irritation was produced. At various time points, the irritation response was measured by visual assessment, chromametry, laser Doppler flowmetry and transepidermal water loss. Using all of the methods of assessment, the reactions in atopics were similar to or a little less than those seen in non-atopics. The conclusion is that atopics and non-atopics will give similar results in a predictive human test for acute skin irritation. Furthermore, the pattern of response obtained from short duration exposure should be predictive of that following longer durations of (single) exposure.

Key words: irritant contact dermatitis; acute skin irritation; sodium lauryl sulfate; human volunteers; atopic dermatitis; visual assessment; bioengineering methods. © Munksgaard, 1998.

Accepted for publication 16 December 1997

Individual susceptibility to skin irritation is a complex matter; the human population is highly heterogeneous, but there is also the complication of the many different types of irritant (both in terms of mechanism and of potency) and of skin irritation that they may cause, together with the numerous variables associated with patterns of exposure. Many of the parameters which are involved in this diversity have been examined, some in great detail (see, for example, 1–4). Of particular interest has been the role of atopy in the predisposition to skin irritation. However, what is understood by the term atopy is not always clear. Mucosal atopy, defined as elevated total serum IgE, the presence of specific IgE to one or more common aeroallergens and an appropriate (family) history, does not correlate greatly with an increased susceptibility to skin irritation (5, 6). On the other hand, there is considerable clinical evidence that skin atopy, defined as a past or present history of atopic dermatitis, does correlate with a distinctly enhanced reactivity to irritants (5, 7–9). This predisposition is particularly marked in the occupational setting,

usually reflecting the impact of cumulative insults to the skin (10, 11).

In practice, the increased susceptibility to skin irritation of almost any selected group can be investigated by ethically approved human studies using suitable volunteers. However, the data so produced can be limited in the sense that any differences seen between the test group and a suitably matched control group may only be valid for the irritants used and for the type(s) of exposure involved (12). A similar criticism can be levelled at predictive toxicology tests (whether they use human subjects, animals or in vitro models). Consequently, when human volunteers have been used in a standard protocol to determine the acute skin irritation potential of substances (13), it has been important to demonstrate what impact a number of variables (e.g., sex, ethnic origin, skin type, atopic status, season) might have on the outcome and/or relevance of the data generated (6, 14–17).

In the light of the above considerations, for this present work, we have chosen to evaluate in detail the extent to which varying the duration of a single

acute exposure might have an impact upon the pattern of results observed, particularly when normal subjects were compared with a group known to have a particular susceptibility to irritation, skin atopics. So that the potentially large variable, the degree of irritation induced, should be kept to a minimum, the concentration of the irritant applied was adjusted, i.e., lower concentrations of irritant were used for longer duration exposure. To provide a more critical assessment, the skin reactions have been assessed both visually and by using a range of bioengineering techniques.

Materials and Methods

Test subjects

All volunteers gave fully informed consent for their participation in the study. The atopic group comprised 15 individuals (13 female, 2 male) of mean age 24 years (range 18–32 years) all of whom had a past or present history of atopic skin symptoms (18), involving dry and itchy skin. At the time of the study, none had active eczema at the test site. A reasonably matched group of 15 non-atopics (8 female, 7 male) of mean age 24 years (range 22–32 years) had no past or present history of skin symptoms, allergic rhinitis or asthma.

Irritant application

Sodium lauryl sulfate (SLS) (BDH, Poole, Dorset, UK, >99%) was applied to the skin of the back using 25 mm Plain Hill Top Chambers (Hill Top Companies, PO Box 429501, Cincinnati, Ohio, 45242, USA) dosed with 250 μ l. In this manner, aqueous SLS concentrations of 0.5%, 1.0%, 5.0% and 20% were applied for 24 h, 8 h, 4 h and 2 h respectively. Empty chambers or chambers with only the aqueous vehicle added were used as controls and were applied only for 24 h. Applications were timed such that all the chambers could be removed at the same time. An adjacent completely untreated skin site was used to provide baseline information.

Visual assessment of reactions

This was carried out at 15 min, 24 h, 48 h and 72 h after removal of the test patches. The scale used is given in Table 1.

Chromametry

Skin colour was measured with a Minolta Chromameter (CR-200, Minolta, Osaka, Japan) which uses the standard tristimulus system defined by the Commission Internationale de L'Eclairage

Table 1. Visual grading scale

Score	Description of irritation reaction
0	no visible reaction
1	tobacco paper-like appearance, no erythema
2	slight patchy erythema
3	homogeneous erythema
4	erythema with oedema
5	erythema, oedema and vesicles/bulla

(CIE). The instrument has an interconnected system of light source, filter and photodetector, which simulates the Standard Observer functions and directly computes the chromatic dimensions of the colour. The measurement mode was $L^*a^*b^*$, and the a^* value (red-green axis) was used. The measurements were performed in triplicate for each skin site.

Laser Doppler flowmetry

Blood flow was measured using a laser Doppler flowmeter (LDF) (Periflux[®], PFI, Perimed KB, Stockholm, Sweden) according to the manufacturer's recommendations. The instrument was adjusted to a frequency limit of 12 kHz and a time constant of 0.2 s was used. The device was equipped with a special multifibre probe (Perimed KB) which has 7 fibre triplets in the head, 1 in the middle and 6 forming a circle 8 mm in diameter. Thus the blood flow value recorded is the mean of 7 spots. Blood flow was recorded with a pen recorder for a period of about 30 s and the average flow was estimated from the curve.

Transepidermal water loss

Transepidermal water loss (TEWL) was measured with an Evaporimeter Ep1 (Servo-Med, Stockholm, Sweden). During measurements, the probe was held manually, but an insulated metal laboratory clamp was used to prevent any heating of the probe. The readings were taken 30 s after the application of the probe to the skin, when the level had stabilized.

Statistical analysis

The evaluation of any differences between the reactions of atopic and non-atopics was carried out by comparison of mean values and their 95% confidence limits calculated using the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA).

Results

The extent of the irritation reaction induced by the various doses of SLS was assessed in a number of

Table 2. Visual assessment – mean erythema values

Patch	15 min	24 h	48 h	72 h
none	0/0 ^{a)}	0/0	0/0	0/0
empty	0.13 (0.52)/0.40 (0.83)	0/0	0/0	0/0
H ₂ O	0.87 (1.24)/0.27 (0.70)	0/0	0/0	0/0
0.5%	3.73 (1.39)/3.67 (0.62)	3.93 (0.80)/3.67 (0.82)	3.40 (0.99)/2.67 (1.11)	0.73 (0.70)/2.20 (1.26)
1.0%	3.13 (1.13)/3.40 (0.91)	3.87 (1.21)/4.13 (0.92)	3.33 (1.59)/3.07 (1.22)	2.40 (1.54)/1.98 (1.33)
5.0%	2.73 (1.28)/1.87 (1.25)	3.87 (1.06)/2.80 (1.66)	3.07 (1.53)/1.93 (1.75)	1.80 (1.47)/1.27 (1.49)
20%	2.00 (1.13)/2.20 (1.15)	3.27 (1.39)/3.60 (0.83)	2.67 (1.35)/2.80 (1.21)	1.93 (1.58)/1.60 (1.06)

^{a)}Mean erythema value for non-atopics/atopics with the standard deviation in parentheses.

Table 3. Chromameter measurements

Patch	15 min	24 h	48 h	72 h
none	6.81 (1.75)/5.92 (1.73) ^{a)}	6.74 (1.63)/6.09 (1.85)	6.74 (2.15)/6.15 (1.90)	7.07 (2.03)/6.00 (1.97)
empty	7.49 (1.83)/7.97 (3.17)	7.10 (2.13)/6.46 (1.76)	7.15 (1.85)/6.24 (1.86)	7.08 (1.98)/6.36 (1.86)
H ₂ O	11.53 (3.00)/8.63 (2.75)	9.36 (2.10)/7.82 (1.67)	9.36 (1.80)/7.50 (1.78)	9.35 (1.86)/7.48 (1.89)
0.5%	17.69 (4.24)/13.32 (3.17) ^{b)}	18.11 (4.38)/14.42 (1.75) ^{b)}	16.25 (4.13)/12.53 (2.26)	14.04 (3.26)/11.82 (3.11)
1.0%	14.65 (4.75)/12.64 (3.02)	15.49 (4.11)/13.25 (2.14)	14.46 (4.82)/12.38 (2.40)	13.02 (4.73)/11.11 (2.49)
5.0%	13.37 (4.52)/10.25 (4.69)	13.94 (4.47)/10.58 (3.25)	12.94 (4.13)/9.74 (3.55)	11.07 (3.81)/8.52 (3.06)
20%	11.35 (4.88)/10.84 (4.02)	12.24 (4.28)/12.62 (3.45)	11.15 (4.16)/12.12 (3.59)	10.11 (3.42)/10.44 (3.63)

^{a)}Mean a^* value for non-atopics/atopics with the standard deviation in parentheses.

^{b)}Difference significant at the 95% confidence level.

ways. Visual assessment of erythema was carried out at several time points after treatment; the mean erythema values are summarized in Table 2. As expected, untreated skin and skin sites patched with either empty Hill Top Chambers or with water showed little response. In contrast, SLS at all concentration/exposure time combinations led to a substantial increase in erythema compared to the controls. Although there was a 40-fold difference in the highest and lowest SLS concentrations, the adjustment to the duration of application resulted in similar levels of erythema being generated. This is shown graphically in Fig. 1, in which the data-points for atopic and non-atopics have been combined to provide a general overview. It is evident from Table 2 that the response of atopic and non-atopics was similar, although, in one case, treatment with 5.0% SLS for 4 h, the atopic group appeared generally less reactive.

Table 3 presents the assessment of redness using the Minolta Chromameter. The acute treatments employed in this study produced distinct erythema rather than a scaly dryness pattern of reaction. Consequently, the a^* values do represent a reasonable and objective measure of the degree of erythema present. The readings from untreated skin were similar to those taken from skin treated with an empty Hill Top Chamber; measurements from skin treated with a water filled Hill Top Chamber were somewhat higher. Skin sites which had been exposed to SLS gave higher chromameter readings, with those on the site treated with 0.5% SLS being the highest. However, readings on all the other

SLS-treated skin sites were also higher than those on the untreated sites. Interestingly, the values on atopic skin were in almost every case lower than those on non-atopic skin. This was also true of the control site treated with water only. Nevertheless these differences were not statistically significant, except in 2 instances. Given the number of comparisons between atopic reactivity and non-atopic reactivity being made in this study, 64 in all, these 2 instances are quite likely to have occurred by chance.

Skin blood flow at the treatment sites was evalu-

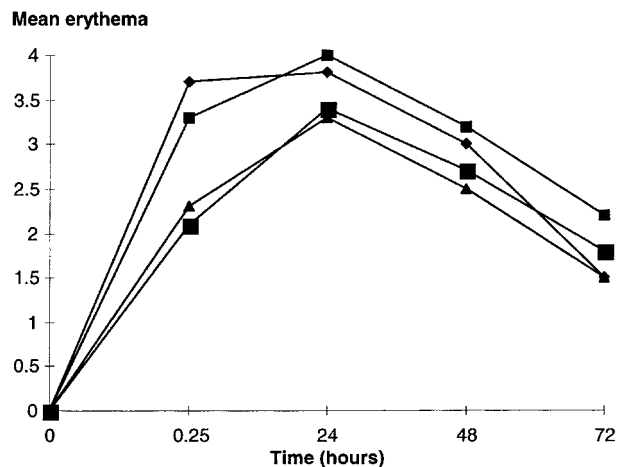


Fig. 1. The combined responses of atopics and non-atopics to the various SLS dosing regimes. Mean erythema values have been plotted against time; ◆=0.5% SLS; ■=1.0% SLS; ▲=5.0% SLS; ■=20% SLS.

Table 4. LDF measurements

Patch	15 min	24 h	48 h	72 h
none	29.2 (5.66)/22.9 (0.42) ^{a)}	25.7 (5.49)/23.1 (5.32)	27.3 (7.73)/26.9 (9.11)	25.9 (6.33)/23.8 (4.59)
empty	31.1 (7.81)/28.7 (11.90)	27.2 (4.89)/27.5 (9.75)	28.8 (7.06)/26.6 (6.79)	29.4 (6.90)/27.2 (7.90)
H ₂ O	42.6 (11.65)/39.4 (15.22)	33.1 (12.64)/33.7 (10.48)	35.2 (10.63)/34.4 (8.98)	36.6 (11.02)/34.1 (5.73)
0.5%	166.0 (62.82)/140.6 (56.57)	158.3 (69.19)/117.4 (39.86)	112.8 (67.63)/94.6 (37.56)	91.2 (71.35)/97.3 (50.40)
1.0%	132.2 (63.72)/115.7 (52.92)	123.1 (76.50)/98.5 (42.23)	110.6 (86.28)/85.1 (49.77)	84.1 (68.28)/66.2 (37.30)
5.0%	71.2 (39.40)/53.2 (46.23)	99.9 (69.29)/68.7 (42.43)	75.1 (55.82)/53.3 (32.70)	59.3 (45.65)/44.9 (25.78)
20%	57.6 (44.19)/66.8 (59.95)	80.7 (54.31)/93.3 (46.63)	55.9 (32.71)/75.7 (62.59)	45.3 (23.51)/62.2 (43.55)

^{a)}Mean value for non-atopics/atopics with the standard deviation in parentheses.

Table 5. TEWL measurements

Patch	15 min	24 h	48 h	72 h
none	8.87 (6.61)/7.47 (2.92) ^{a)}	5.80 (3.23)/6.00 (2.30)	6.00 (3.63)/6.40 (2.56)	5.66 (2.59)/6.67 (2.50)
empty	11.57 (5.18)/14.40 (10.51)	6.07 (3.54)/7.47 (2.23)	7.64 (5.46)/6.80 (2.04)	6.21 (2.94)/6.67 (1.88)
H ₂ O	17.33 (5.18)/23.47 (23.32)	6.87 (4.78)/8.07 (3.17)	8.47 (4.02)/8.40 (2.61)	8.00 (3.96)/9.20 (3.76)
0.5%	63.27 (24.46)/68.47 (32.74)	54.40 (18.62)/63.00 (16.12)	31.33 (12.33)/34.07 (6.79)	28.00 (17.77)/39.60 (16.63)
1.0%	65.63 (34.09)/63.73 (26.62)	58.73 (34.30)/67.80 (36.81)	41.20 (26.52)/39.13 (15.04)	34.33 (31.34)/34.20 (17.10)
5.0%	54.67 (39.47)/53.27 (59.01)	42.07 (30.02)/34.80 (23.44)	29.40 (22.47)/23.53 (14.28)	23.80 (22.63)/17.33 (9.93)
20%	41.47 (44.75)/67.73 (42.11)	31.07 (26.61)/47.40 (24.84)	23.67 (13.98)/35.47 (18.62)	18.93 (9.80)/27.33 (17.35)

^{a)}Mean TEWL values in (g/m²h) for non-atopics/atopics with the standard deviation in parentheses.

ated by LDF. The results are presented in Table 4. As with the previously mentioned measurements, control sites gave similar values to normal skin, although the water treated sites had slightly elevated values; there was essentially no difference in the readings from atopics and non-atopics. More noticeably than with the visual assessment of erythema and the Minolta Chromameter readings, the increase in blood flow was greatest following treatment with lower doses of SLS for the longer durations. This was true even if allowance was made for the difference in the timing of the initiation of exposure. The figures for treatment with 20% SLS for 2 h were only a little elevated compared to the 24 h water treatment values. However, as with the Chromameter readings, the figures for atopics tended to be lower than those for non-atopics.

The final method of assessment was TEWL; the mean values are presented in Table 5. The basal TEWL values for the atopics were similar to those for the non-atopics. This is in contrast to the observations of others (18). As would be expected, occlusion either with an empty chamber or with water led to a transient increase in the TEWL value, but in all cases the readings returned to normal by the 24 h assessment time. Skin sites exposed to SLS displayed marked increases in TEWL. The TEWL readings then decreased with time, but in no case had they returned to normal by 72 h. Interestingly, although the readings for atopics and non-atopics were similar in many cases, it was noticeable that particularly following treatment with 20% SLS for 2 h, the TEWL values for atopics were always higher than for non-atopics.

Discussion

The results of the study presented in this paper indicated a number of points, including that the overall pattern of the response to a given irritant stimulus is fairly constant (Fig. 1). However, the most interesting (and unexpected) observation was that the reactivity of skin atopics was almost identical to that of the matched control group. This was true whether the irritant stimulus was delivered over a short or a long period and was evident whether skin irritation was assessed visually or with objective measures of skin colour, blood flow or transepidermal water loss. As a consequence, it was not possible to demonstrate that the duration of exposure did, or did not, have any impact on the relative degree of irritancy included in skin atopics v non-atopics.

Why was there no difference in the level of irritation reactions to SLS? The answer to this question is not at all clear. Certainly the atopic group were all skin atopics according to standard criteria (19). However, the test work was carried out on healthy back skin – baseline values for all parameters were closely similar in all subjects (Tables 2–5). It has been reported that basal TEWL values may be raised in atopic dermatitis patients, but may be dependent on disease status (reviewed in (18)); these values were essentially the same in our atopic and non-atopic subjects. However, the skin of the back is not one of the most important sites for the expression of atopic eczema. Furthermore, our test work involved single acute application of an irritant, whereas the key to the enhanced reac-

tivity of atopics may actually lie in their increased time taken to recover from an irritant stimulus, thus giving a predisposition to cumulative rather than acute skin irritation (10, 20). Thus it is relevant that Stolz et al. recently reported that they could not find an association between skin hyper-irritability to acute irritant contact and skin atopy, whilst Tupker et al. (22) reported an increased susceptibility to cumulative irritancy in their experiments involving individuals with a past history of atopic dermatitis. Nevertheless, others (5, 8, 23) did find atopic dermatitis patients were more susceptible to acute irritation induced by treatment with SLS.

In conclusion, the results presented indicate that healthy skin atopics do not appear to be more likely than normal subjects to react to an acute irritant stimulus of a given intensity, whether that stimulus is given over a short or over a relatively prolonged period. The implication for predictive testing of acute irritation potential in groups of human subjects is that the information so produced should be broadly applicable rather than specific to the type of population in which it is generated.

References

1. Bjornberg A. *Skin reactions to primary irritants in patients with hand eczema*. (Thesis). Gothenburg, Sweden, Oscar Isacson Tryckeri AB, 1968.
2. Rystedt I. Factors influencing the occurrence of hand eczema in adults with a history of atopic dermatitis in childhood. *Contact Dermatitis* 1985; 12: 247–254.
3. Lammintausta K, Maibach H I. Irritant reactivity in males and females. *Contact Dermatitis* 1987; 17: 276–280.
4. Suter-Widmer J, Elsner P. Age and irritation. In: *The irritant contact dermatitis syndrome* Boca Raton: CRC Press, 1996: 257–261.
5. Nassif A, Chan S C, Storrs F J, Hanifin J M. Abnormal skin irritancy in atopic dermatitis and in atopy without dermatitis. *Archives of Dermatology* 1994; 130: 1402–1407.
6. Basketter D A, Blaikie L, Reynolds F. The impact of atopy on a predictive test of acute skin irritation potential. *Contact Dermatitis* 1996; 35: 33–39.
7. Rystedt I. Atopy, hand eczema and contact dermatitis: summary of recent large scale studies. *Seminars in Dermatology* 1986; 5: 290–300.
8. Agner T. Susceptibility of atopic dermatitis patients to irritant dermatitis caused by sodium lauryl sulphate. *Acta Dermatologica-venereologica* 1990; 71: 296–300.
9. Willis C, Poskitt L. The influence of atopy on susceptibility to irritation. *Allergologie* 1995; 18: 446.
10. Baurle G, Hornstein O P, Diepgen T L. Professionelle handekzeme und atopie. *Dermatosen* 1985; 33: 161–165.
11. Rystedt I. The role of atopy in occupational skin disease. In: Adams R M (ed): *Occupational skin disease*. Philadelphia: Saunders, 1990: 215–222.
12. Hannuksela A, Hannuksela M. Irritant effects of a detergent in wash and chamber tests. *Contact Dermatitis* 1995; 32: 163–166.
13. Basketter D A, Chamberlain M, Griffiths H A, York M. The classification of skin irritants by human patch test. *Food and Chemical Toxicol* 1997; 35: 845–852.
14. Basketter D A, Griffiths H A, Wang X M, Wilhelm K-P and McFadden J. Individual, ethnic and seasonal variability in irritant susceptibility of skin: the implications for a predictive human patch test. *Contact Dermatitis* 1996; 35: 208–213.
15. Griffiths H A, Wilhelm K-P, Robinson M, York M, Basketter D A. Interlaboratory evaluation of a human 4h patch test for the evaluation of skin irritation potential/hazard. *Food and Chemical Toxicol* 1997; 35: 417–425.
16. Robinson M K, Perkins M A, Basketter D A. Application of a 4 hour human patch test method for comparative and investigative assessment of skin irritation. *Contact Dermatitis* 1997: submitted.
17. McFadden J, Wakelin S, Basketter D A. Irritant thresholds in subjects with Type I to Type VI skin. *Contact Dermatitis* 1998; 38: in press.
18. Seidenari S. Skin sensitivity, interindividual factors: atopy. In: *The irritant contact dermatitis syndrome*. Boca Raton: CRC Press, 1996: 267–277.
19. Hanifin J M, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermatol Venereol* 1980; 92: 44–47.
20. Malten K E. Thoughts on irritant contact dermatitis. *Contact Dermatitis* 1981; 7: 238–247.
21. Stolz R, Hinnen U, Elsner P. An evaluation of the relationship between “atopic skin” and skin irritability in metalworker trainees. *Contact Dermatitis* 1997; 36: 281–284.
22. Tupker R A, Pinnagoda J, Coenraads P J, Nater J P. Susceptibility to irritants: role of barrier function, skin dryness and history of atopic dermatitis. *Br J Dermatol* 1990; 123: 199–205.
23. Cowley N C, Farr P M. A dose response study of irritant reactions to sodium lauryl sulphate in patients with seborrhoeic dermatitis and atopic eczema. *Acta Dermatol Venereol* 1992; 72: 432–435.

Address:

D. A. Basketter
Unilever Environmental Safety Laboratory
Colworth House, Sharnbrook
Bedford, MK44 1LQ
UK