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A Double-blind Comparison of Two Creams Containing Urea as the Active Ingredient

Assessment of efficacy and side-effects by non-invasive techniques and a clinical scoring scheme

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From a group of 72 healthy individuals, 47 with evidence of dry skin according to measurements by non-invasive techniques were enrolled for a 3-week study with double-blind and randomized treatment of one forearm, using either 3% urea cream (HTH lotion 'light'^{R}) or 10% urea cream (HTH lotion 'Original'^{R}). The contralateral forearm served as an untreated control. Two volunteers had to be excluded because measurements of skin surface lipids gave evidence of vehicle components on the skin surface at the time of final evaluations. Evaluations took place not less than 12 h after the last application. According to questionnaire replies, the two creams were equally effective. This was confirmed by "blind" evaluation of the skin hydration state by a dermatologist, measurements of electrical capacitance and conductance indicating epidermal and skin surface hydration, and by D-Squame^{R} tape assessments including optical transmission of tapes with stratum corneum and scales from adhering skin, as well as visual scoring of the tapes. The methods showed a high degree of correlation, i.a. a definite relation between increase in electrical hydration parameters, reduced scaling according to the D-Squame^{R} tape evaluations, and clinical improvement of dryness.

In skin treated with 10% urea cream the transepidermal water loss (TEWL) decreased, indicating an improved water barrier function. Skin colour measurement according to the CIE colour system showed that skin treated with the 3% urea cream turned in the direction of yellow, and there was generally a tendency for the brightness to decrease. Thus, the 3% urea cream gave the skin a more golden colour. There was no change in redness with any of the creams.

Neither data from the questionnaire, the clinical examination, nor results of TEWL and colour measurements indicated any local irritant effect of urea causing water barrier damage or inflammation.

In conclusion, the 3% and 10% urea creams were both found efficient, resulting in improvement of hydration and reduction of scaling. Both were non-toxic. However, specific differences did appear, viz. the 3% urea cream turned the skin colour golden, while the 10% urea cream improved the skin's water barrier function. ***Key words: Urea, lactic acid, moisturizer, efficacy, side effects, hydration, dryness, scaling, colour, capacitance, conductance, transepidermal water loss.***

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The classical publications of Blank and Middleton in the 1950s and 1960s initiated an era of increased understanding of the significance of water for skin functions in various dermatological and cosmetological conditions (1,2). Moisturizers became important requisites in dermatological therapy. Soon, attempts were made to improve the effect of moisturizers by adding active substances. In medicine, urea was used for many years for a variety of conditions, including wound healing. As long ago as 1943, Rattner had used urea in hand creams as a humidity promoting additive and evaluated its efficacy and toxicity in a large material (3). Swanbeck, who studied urea treatment of ichthyosis, became the originator of the HTH^{R} urea-lactic acid cream, which is used extensively for a variety of keratotic conditions, including atopic dermatitis (4,5). Both urea and lactic acid play a part in the waterretaining capacity of both normal and diseased skin. In preparations, lactic acid stabilizes urea and prevents crystallization. In modern dermatology too, urea creams are useful as supplements to corticosteroid and dithranol medication, enhancing penetration and action. The many effects of urea on human skin were recently reviewed extensively (6,7,8,9).

The purpose of the present study was to evaluate the efficacy and toxicity of reformulated HTH^{R} cream, i.e. a 10% urea cream with a composition close to the original cream intended for dermatological treatment, and a new 3% urea cream intended more for cosmetological use. The study was performed by applying a number of recent non-invasive techniques for objective characterization of skin hydration and scaling, as well as clinical evaluations, in a double-blind and randomized design using untreated controls.

MATERIALS AND METHODS

A preselection group of 72 healthy volunteers was studied consecutively by measuring electrical capacitance and the optical transmission of D-Squame^{R} tape stripped from flexor-side forearm skin to diagnose dry skin (concerning methodologies, vide infra.) The preselection studies were carried out in December, i.e. in the cold and dry season. Dry skin was defined as either a capacitance (average of three recordings) less than 104 a.u. or a D-Squame^{R} tape transmission (average of two tapes) of 66 lux or less (transmission of unused tape was 84 lux).

Volunteers with signs of dermatological disorder or a history of atopic dermatitis were excluded. Of the 72 volunteers, 57 met these criteria. For a variety of practical reasons only 47 were eventually able to join the study, which was carried out in late January and early February. Two volunteers were later excluded from the study when recordings gave evidence of vehicle left on the skin surface on the day of the final recordings. Thus, of 47 volunteers, 45 (33 females, 12 males) completed the study.

The study was performed in "double-blind" fashion. After randomization, volunteers were treated with either 3% urea cream (HTH lotion 'light'^{R}) or 10% urea cream (HTH lotion 'Original'^{R}, 1989 reformulated version). The flexor side of one forearm was treated with

two applications of test lotion daily for a 3-week period, with the contralateral side as untreated control. Test lotions were supplied in coded and preweighed containers, which were replaced halfway through the study, and containers weighed again to determine the average quantity of lotion used by each volunteer. The dose of lotion was left entirely to users' own preference in order to create a realistic situation. The last application took place the night before the final recordings, i.e. at least 12 h before measuring. Volunteers were allowed normal washing, including normal use of soaps, during the 3-week treatment period. Neither exaggerated washing nor use of special detergents such as hand cleaners on the forearm skin was allowed, nor was the use of other lotions on the forearms. No restrictions were imposed with respect to habits and normal activities, including physical activity and sport.

All volunteers worked in the same newly built office block, and all had office duties. Thus, their environmental conditions during the study and the treatment were comparable.

22 volunteers (mean age 32.9 years, range 23–49 years; 17 females and 5 males) received treatment with 3% urea cream and 23 volunteers (mean age 38.6 years, range 21–59 years; 16 females and 7 males) treatment with 10% urea cream. A questionnaire at the time of preselection examinations had revealed that 15 volunteers felt that they were constantly troubled by dry skin, 15 had periodic complaints, while 15 had no complaints. There was no difference between the two treatment groups. Of the 12 males, 8 (67%) felt themselves to be free from problems with dry skin, while only 7 of the 33 females (21%) were free from trouble with dry skin, in their own view.

HTH lotion 'light'[R] contains 3% urea, 1.5% lactic acid, 1.5% betaine, plus propylene glycol, mineral oil, polyethylene glycol-5 stearyl stearate, ethylhexyl ethylhexonate, steareth-21, cetearyl alcohol, self-emulsifying glyceryl stearate, tromethamine, fragrance and water. The lipid content is 14%, and pH 3.5.

The HTH lotion 'original'[R] (1989 reformulated version) contains 10% urea, 5% lactic acid, 5% betaine, plus propylene glycol, cetearyl alcohol, ethylhexyl ethylhexanoate, tromethamine, self-emulsifying glyceryl stearate, diethanolamine-cetyl phosphate, demethicon, fragrance and water. The lipid content is 6%, and pH 3.5.

During the study, a mean of 6.531 g (SD 3.688 g) test cream was used per half-treatment container. On average, 0.311 g of test cream was used per day per application, i.e. 0.021 g per cm^2.

The calculated average cream film thickness of one application was 2.8 μm, cream adherent to the treating finger not subtracted and with no correction for non-compliance.

Evaluations after the 3-week treatment period

Volunteers filled out a *questionnaire* regarding their assessment of the effects of the lotions, i.e. change in dryness of the skin, characterization of treatment effects, stinging or skin irritation.

Volunteers had to relax with the forearms uncovered for about 15 min before evaluations and recordings. They were asked when the last application of a test lotion had taken place, and if they had followed the instructions.

"Blind" *clinical evaluation* of the hydration state of flexorside forearm skin, one side compared with the contralateral side, was performed by the author. An assessment was made as to whether any significant side difference in humidity characteristics existed and if so, which side was the drier or more humid. A detailed evaluation was not intended. The skin was inspected in daytime by the light from the window. It was noted whether the surface looked scurvy, white and pale, or smooth and deep in colour. It was deemed by palpation (using both the flexor and the extensor side of the observer's fingers) whether surface friction had increased indicating improved hydration. This assessment was more definite when performed in the centripetal direction, under slight or moderate pressure. Occasionally a distinct and sharp sound was elicited from the surface of dry skin. It was also noted whether signs of skin irritation, i.e. redness, papules or inflammation, had appeared.

Skin colour was measured with the Minolta Chroma Meter CR200[R] (Osaka, Japan) (10) in compliance with the Commission International de l'Eclairage (CIE) system, according to which the registration of colour is adjusted to the non-linear colour sensitivity of the human eye. A colour is expressed in a threedimensional coordinate system with an a* axis (green/red), a b* axis (blue/yellow) and an L axis (brightness). The skin surface is illuminated by a Xenon flash light, and remitted light registered and analysed by a photoreceiver. The effective aperture of the apparatus is 8 mm. Colorimetry is sensitive and accurate for the characterization of redness of skin irritation, including solar erythema. In inflamed skin a positive change on the a* axis is observed, i.e. toward red. We measured three separate spots on each forearm, each spot with three illuminations of the colorimeter flash. Thus, values on each side represented the average of nine recordings.

Electrical, capacitance indicating hydration of the outer epidermis was measured with a Corneometer CM-420[R] (Schwarzhaupt GmbH, Cologne, FRG) (11,12). The probe consists of a circular brass grid 16 mm in diameter, which constitutes one electrode, while the skin represents the other. The probe with its electrode is coated with a 0.02 mm thick plastic film. Application of the probe to the skin is performed with a standard pressure of 35 g. Recording time is 3 s. The capacitance, with the skin as the system's only variable, is expressed digitally in arbitrary units (a.u.). Each value was the average of three recordings.

Electrical conductance, indicating hydration of the skin surface was measured with a Skicon-100[R] high frequency hydrometer, developed by Tagami (11,12). The probe consists of two concentrically arranged electrodes with diameters of 1 and 4 mm. The probe is applied to the skin surface with a standard pressure of 30 g. Recording time is 3 s. Conductance is registered and expressed digitally as reciprocal impedance ($1/\mu\Omega$). Each value is the average of three recordings. The Skicon-100[R] measures hydration more superficially than the Corneometer CM-420[R], and the two apparatuses are considered complementary (11,12).

Transepidermal water loss (TEWL), indicating the skin's water barrier function, was measured with a Servo Med EP1[R] evaporimeter (Servo Med AB, Kinna, Sweden) (13,14). The cylindrical probe chamber is 12 mm in diameter. Two pairs of sensors for registration of humidity and temperature are mounted in the probe cylinder. The equipment registers the water vapour gradient in the humid boundary layer of air next to the skin. The TEWL is calculated automatically, and expressed digitally in g/m^2h. No protection shield was used. Values were obtained after 30–40 s by means of the 10 s filter. Measurements were carried out in a closed box 40×50×100 cm in accordance with the guidelines of the standardization group of the European Contact Dermatitis Society (14), in order to avoid the influence of air convection. The probe was held with an insulating glove. The ambient air temperature was 20–22°C, and humidity, 25–42%. Each value was the average of three recordings.

Scaling and epidermal desquamation were assessed with the DSquame[R] tape (CuDerm, Dallas, USA) method developed by Miller to harvest scales and superficial stratum corneum components (15). The tape consists of a 22 mm crystal-clear foil coated with a special adhesive substance. The tape was applied at a standard pressure (800 g) for 5 s, and removed carefully at an angle of 45°. Two tapes were stripped from each forearm. Tapes were mounted on microscopy object slides, placed in a medical viewer and *assessed visually with respect to degree of scaling*, one forearm in comparison with the opposite forearm. Scaling was scored as nil (no scales), 1 (slight scaling), 2 (moderate scaling) or 3 (heavy scaling). A slight but definite difference, i.e. a similar background scaling but a difference in minor flakes scattered over the tape, was awarded 0.5 point extra. The *optical transmission* through the tapes was measured and expressed in lux according to a recently described method (15). With decreasing stratum corneum material adhering to the tape and increasing moisturizer effect, transmission decreases. Specimens were coded, and evaluations were made independently – with the exception that visual evaluation was performed on the basis of right/left comparison.

The presence of *cream vehicle on the skin surface was excluded* by Sebumeter[R] (Schwarzhaupt, Cologne, FRG) measurements. This is a photometric device for the determination of skin surface lipids. Two volunteers with evidence of cream vehicle remaining on the skin had

Table I. *Volunteers' evaluation of effects of urea-containing creams after 3-weeks' treatment, according to questionnaire*

	3% Urea cream (n=23)	10% Urea cream (n=24)
Improvement of dryness		
Significant improvement	9	7
Some improvement	14	16
No improvement	0	0[x]
Stinging		
Immediate	0	2
Delayed	0	1
Irritant dermatitis	0	0
Skin felt pleasant	15	13
Skin felt greasy	1	5
Skin felt soft an supple	17	11
A cream film was felt	1	2
Skin felt sticky	1	5
Skin felt rough	0	1
Skin felt flexible	15	11
Skin felt taut	0	1

[x]One missing, felt skin was optimal before treatment. [y] One with immediate stinging, questioned if it was irritation.

to be excluded from the study, one with 9 μg/cm² and another with 18 μg/cm². On untreated skin, no value over 6 μg/cm² was recorded.

Statistical calculations were carried out by the paired t-test (treated side versus untreated side) and the two-sample t-test, when independent observations were studied. Correlations were analysed with the parametric correlation coefficient (r). The limit of significance was defined at $p<0.05$, unless otherwise specified.

RESULTS

Results of volunteers' evaluations of the two urea creams according to the questionnaire at the end of the 3-week treatment period are reported in Table I. The efficacy, i.e. amelioration of dry skin, was the same in the two treatment groups. There was an overall tendency for the 10% urea cream to leave a stickier cream film on the skin surface, while the 3% cream made the skin softer and more pliable, i.e. the 3% cream was deemed cosmetically more acceptable. Stinging was reported in 3 cases, all treated with the 10% urea cream. No case of skin irritation was reported.

A review of the results of the statistical evaluations of the different objective assessments is presented in Table II.

"Blind" clinical evaluation by a dermatologist showed that 3% and 10% urea creams were equally and highly effective (see Figs. 1A, 2A). In contrast to volunteers' evaluations, the dermatologist found it very characteristic that the skin surface friction increased on the side, that turned out to be the treated side. The dermatologist's evaluation revealed no case of skin irritation.

Colour measurements according to the CIE colour system showed no differences with respect to skin brightness (Figs. 1B, 2B). There was a tendency for the 3% urea cream in particular to reduce the L value, i.e. turn the skin slightly darker. On the a* axis, expressing redness, there was no change, and no particular tendency (Figs. 1C, 2C). Thus, there was no evidence of inflammatory skin reaction or irritation. On the b* axis there was a significant change in the direction of yellow for the whole material and especially in the group treated with 3% urea cream (Figs. 1D, 2D). This may reflect an alteration of the horny layer and the keratin rather than an increase in bilirubin.

The electrical capacitance increased highly significantly in all groups, with no difference between the two active treatments (Figs. 1E, 2E).

Electrical conductance showed increases similar to those for capacitance (Figs. 1F, 2F). Thus, both creams increased the hydration of the skin surface and the hydration more deeply in the horny layer.

TEWL did not change in the whole group, nor in the group treated with the 3% cream, though in the group treated with the 10% urea cream, TEWL decreased significantly (Figs. 1G, 2G). Thus, the water barrier function of the skin was improved rather than impaired, as a result of skin irritation from the test cream.

Optical transmission through the D-Squame[R] tapes increased in all groups, showing no difference between the 3% and 10% urea creams (Figs. 1H, 2H). Fewer scales were harvested from treated skin, a per definition biological indicator of improvement in skin dryness. In all groups, "blind" visual assessment of the tapes showed, in accordance with the increase in transmission, reduced scaling scores, i.e. fewer scales harvested with the tapes as a result of treatments (Figs. 1I, 2I). Both treatments were equally effective.

Table II. *Urea cream treatment of forearm skin with contralateral untreated control; results of statistical analysis*
Trends are given within parentheses.

	Colour			Hydration			D-Squame[R] tape		Clinically
	Colour L (a.u.)	Colour a* (a.u.)	Colour b* (a.u.)	Capacitance (a.u.)	Conductance (1/μΩ)	TEWL (g/m²h)	Transmission lux	Visual evaluation, scale score	Hydration state of skin, clinical evaluation, score
3% Urea cream	n.s. (–)	n.s.	↑ $p<0.05$	↑ $p<0.01$	↑ $p<0.01$	n.s. (+)	↑ $p<0.01$	↓ $p<0.01$	↑ $p<0.01$
10% Urea cream	n.s. (–)	n.s.	n.s. (+)	↑ $p<0.01$	↑ $p<0.01$	↓ $p<0.01$	↑ $p<0.01$	↓ $p<0.01$	↑ $p<0.01$
Total	n.s. (–)	n.s.	↑ $p<0.01$	↑ $p<0.01$	↑ $p<0.01$	n.s. (–)	↑ $p<0.01$	↓ $p<0.01$	↑ $p<0.01$

Table III. *Correlations (coefficients) between parameters, which shoved a significant change in relation to treatment with the two urea-containing creams.*
Calculations were based upon differences between the treated and the untreated side, n = 45.

	Colour	Hydration			D-Squame[R] tape		Clinically
	Colour b*	Capacitance	Conductance	TEWL	Transmission	Visual evaluation	Hydration state of skin, clinical evaluation
Colour b*	–	0.253 p<0.05	0.221	-0.012	0.202	0.118	0.191
Capacitance	0.253	–	0.705 p<0.001	0.007	0.627 p<0.001	0.534 p<0.001	0.370 p<0.05
Conductance	0.221	0.705 p<0.001	–	0.104	0.514 p<0.001	0.476 p<0.001	0.538 p<0.001
TEWL	-0.012	0.007	0.104	–	-0.023	-0.030	0.326 p<0.05
D-Squame[R] tape transmission	0.202	0.627 p<0.001	0.514 p<0.001	-0.023	–	0.826 p<0.001	0.333 p<0.05
D-Squame[R] tape visual evaluation	0.118	0.534 p<0.001	0.476 p<0.001	-0.030	0.826 p<0.001	–	0.302
Hydration state of skin, clinical evaluation	0.191	0.370 p<0.05	0.538 p<0.001	0.326 p<0.05	0.333 p<0.05	0.302 p<0.05	–

There was a general tendency discernible from the distribution of observations for the 10% urea cream to give more scattered results than the 3% urea cream.

The figures show that, generally speaking, the inter-individual variation in observations was greater than the intra-individual variation as represented by right/left comparisons. Thus, the results of treatments and differences between treatments are more clearly evident in Fig. 2.

Correlations between methods are given in Table III, which shows relations between right/left differences obtained with the different methods. Improvements in hydration registered by the two electrical methods showed a high degree of correlation. Transmission measurement of D-Squame[R] tape and "blind" visual scoring of scaling from the tapes also showed a high degree of correlation. Moreover, electrical methods and tape methods were correlated, and they also correlated with the dermatologist's clinical assessment of skin hydration. Thus, both electrical methods, tape assessments of scaling and dermatologist's clinical assessment of skin hydration all agreed that 3% and 10% urea creams improved the skin with respect to dryness characteristics. Both test creams were equally effective, but had minor though principal differences.

DISCUSSION

This study has demonstrated that both 3% and 10% urea creams were effective and non-toxic. The two creams showed different actions with respect to effects on skin's colour and its water barrier. The results, including the answers to the questionnaire, support the view that the 3% urea cream is better for cosmetological uses, while the 10% urea cream may be more appropriate for dermatological treatment where improvement of the water barrier function is desirable.

It is generally known from treatment of atopic dermatitis that urea cream can cause stinging immediately after application, especially if applied to excoriated or fissured skin. In the present study 3 volunteers treated with 10% urea cream reported stinging, though clinical examinations and objective methods gave no evidence of skin irritation with inflammation. In the past, urea was used in ulcer treatment, with no reported special occurrence of toxicity, and in Rattner's patch test study of 500 individuals, no positive reaction to urea was observed (3). Urea is a normal molecule in human tissues, blood and urine and, consequently, non-allergenic and not particularly irritant. Urea penetrates the skin easily (16). In contrast to Rattner, Cramers & Thormann found irritant reactions in 10% of 79 eczema patients patch tested (application time 48 h) with a 10% urea/5% lactic acid cream (17). Patients did not react to the ingredients, and they concluded that hypertony and acidity of the final product might cause irritation and stinging. Thus, stinging may be due to hypertonia and acidity of the creams and rapid penetration of urea into the skin, though urea itself appears not to be toxic. In the present study of urea/lactic acid creams applied in a non-occlusive dressing in a way realistic for normal long-term consumption, we found no evidence of irritation, whether acute or cumulative.

Evaluations and documentation of the effects of urea by non-invasive techniques were performed in a number of recent studies mainly dealing with skin capacitance or conductance (7,18). Increase in capacitance and conductance need not be due to water, since urea is a strongly dipolar molecule with low molecular weight and some analogy to water. We find it interesting that in the present study, electrical parameters and evaluations of scaling by the tape method and clinically gave consistant results, which confirms that a true and per defini-

tion improvement of dry skin had taken place as a result of the treatment.

The study showed that 10% urea cream improves the water barrier of the skin of healthy individuals, who met liberal criteria of dry skin. This is in accordance with the study of Grice et al., who showed in patients with ichthyosis that a 10% urea cream increased the waterretaining capacity of the stratum corneum and reduced the TEWL significantly (19). In a study of 50% urea solution applied for a week the nitrazine yellow method indicated no damage to the water barrier (20). On the other hand, urea has an accelerant or enhancing effect comparable to dimethyl sulphoxide (DMSO), and it enhances penetration and the effects of corticosteroids and dithranol (21). Thus, the effects of urea on the skin's water barrier are difficult to understand. Urea improves and stabilizes the barrier for diffusional water loss, and at the same time it promotes the diffusion of water-soluble substances into the skin, like an invisible occlusion.

In the present study the majority of the initially studied group were included by using rather liberal but objective criteria of dry skin, as a logical basis for measurement and comparison. However, the proportion was consistent with the feeling of dryness of the skin and common use of moisturizers in the general population. General use is obviously determined by a number of subjective and irrational factors. For example, in the present study very few volunteers reported that the skin felt more taut and rough, which was a feature of major importance for the dermatologist's clinical evaluation the of hydration state. Consumers cannot distinguish skin surface friction from skin elasticity, and naturally expect the skin to be "soft" following moisturizer treatment. Women use moisturizers far more frequently than men do. It is clear that the volunteers we studied included cases with, in the dermatological sense, normal skin relative to season of the year and ambient conditions.

It is known that urea penetration and effect is closely dependent on the vehicle and the type of emulsion (9,22,23). Little is known about the influence of urea on the vehicle. With a 10% urea cream containing 80% water (evaporates almost exclusively within 15 min after cream application onto the skin) and 5% lactic acid, the emulsion lipid is only a very small fraction. Thus, in a study of the effects of urea cream, comparison with a vehicle cream without urea is unlikely to be relevant, since the vehicle probably undergoes a marked alteration on removal of urea. Nevertheless, "blind" and objective studies have demonstrated that vehicle plus urea is more efficient than vehicle alone for improving skin hydration (19,24,25). In the present study the test creams also contained lactic acid, which may enhance efficacy.

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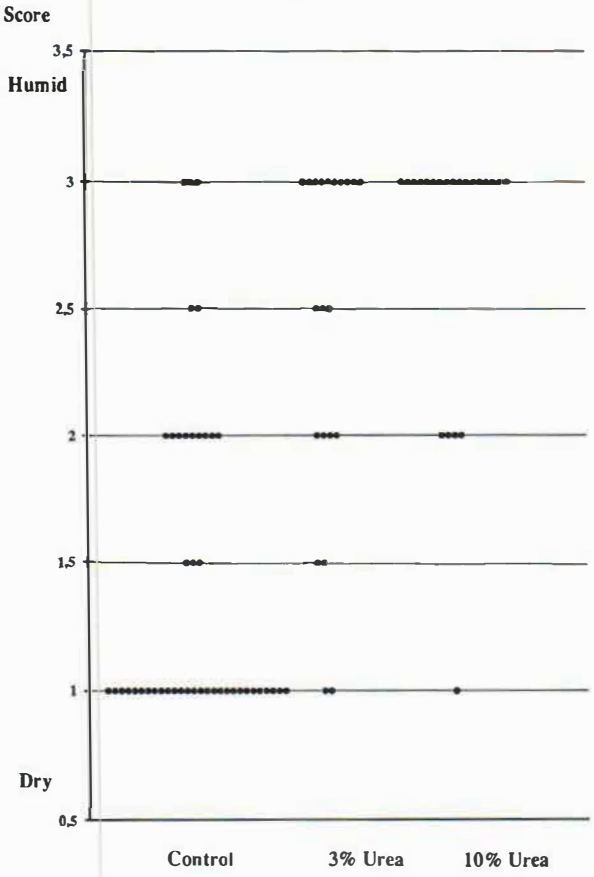
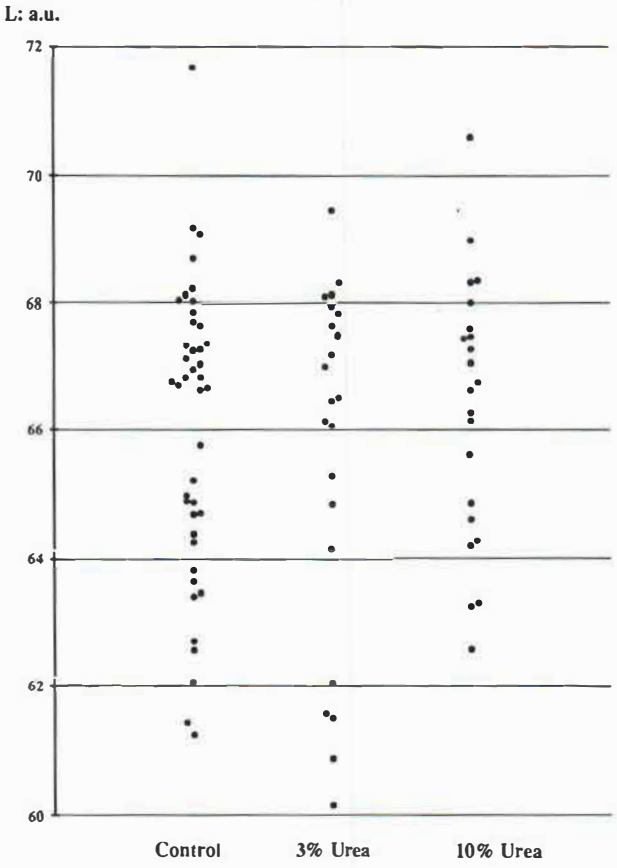
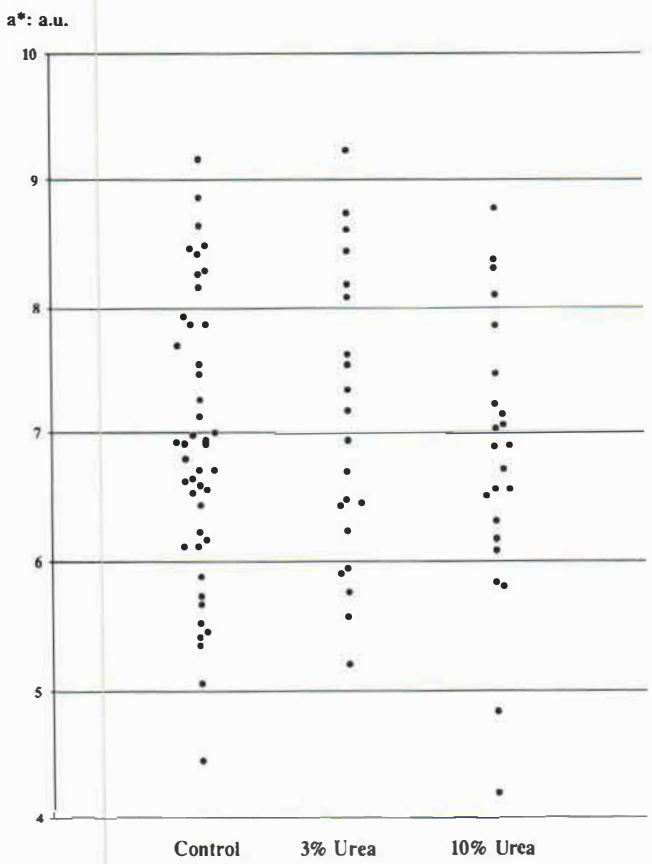
1 A: Clinical evaluation of skin hydration



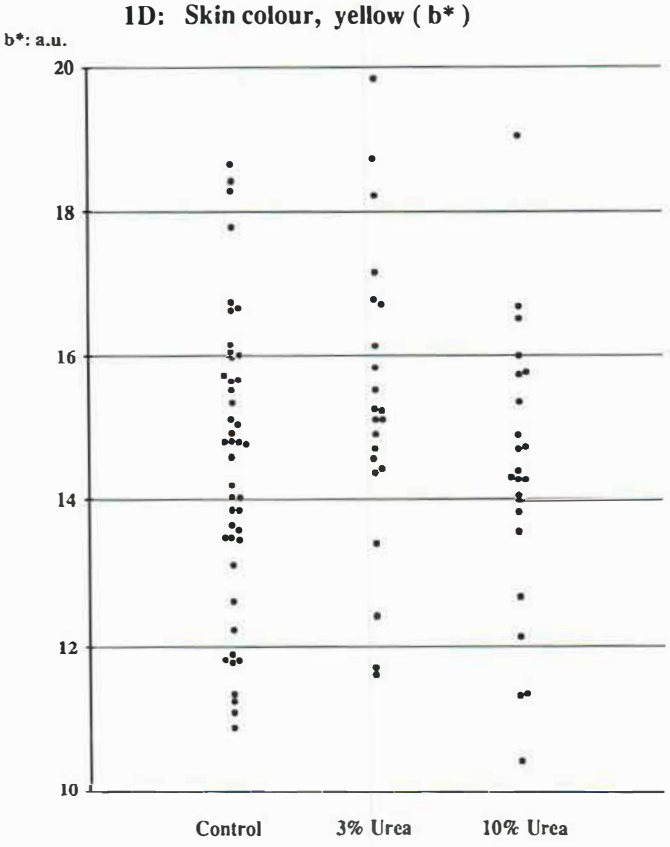
1 B: Skin colour, brightness (L)



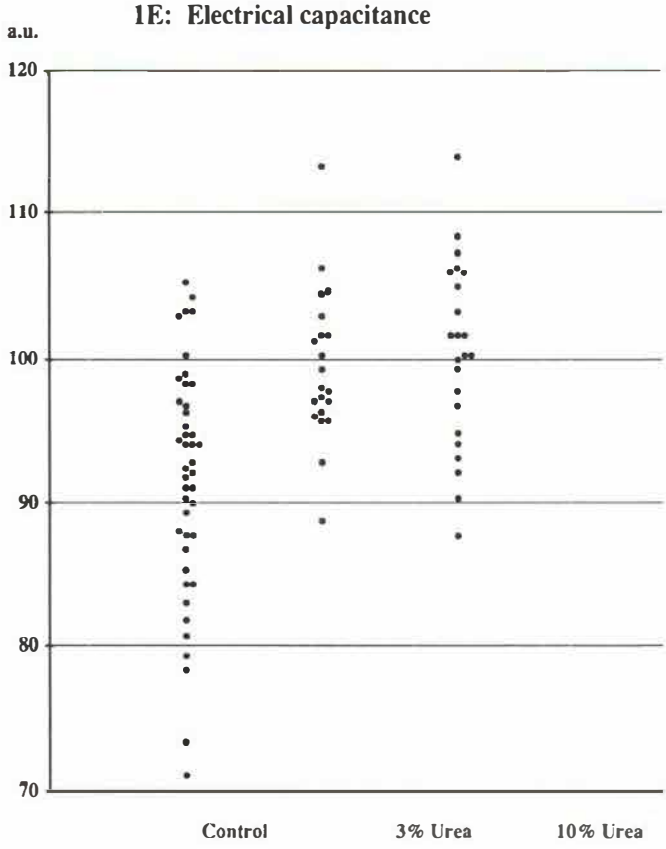
1C: Skin colour, red (a*)



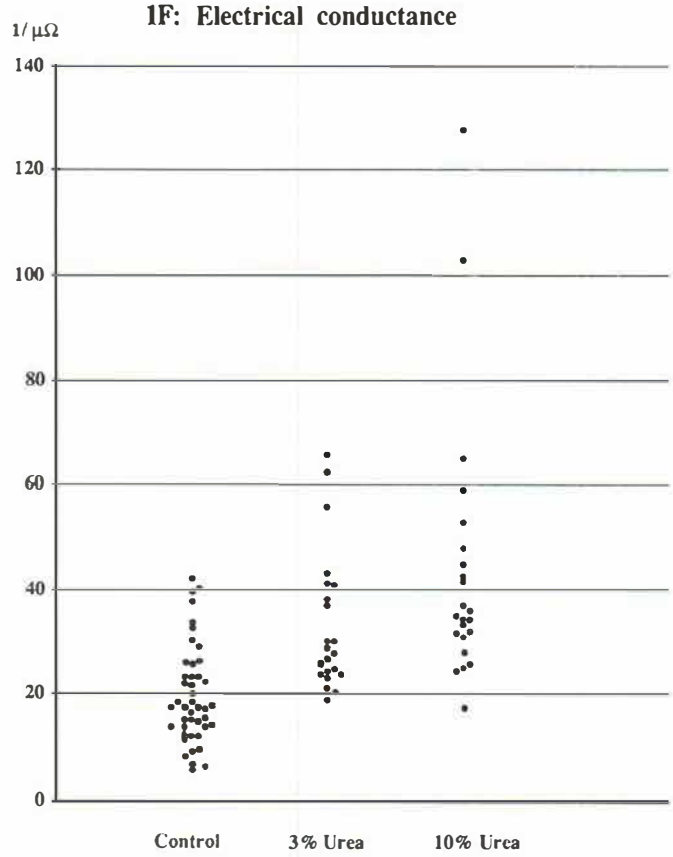
1D: Skin colour, yellow (b*)



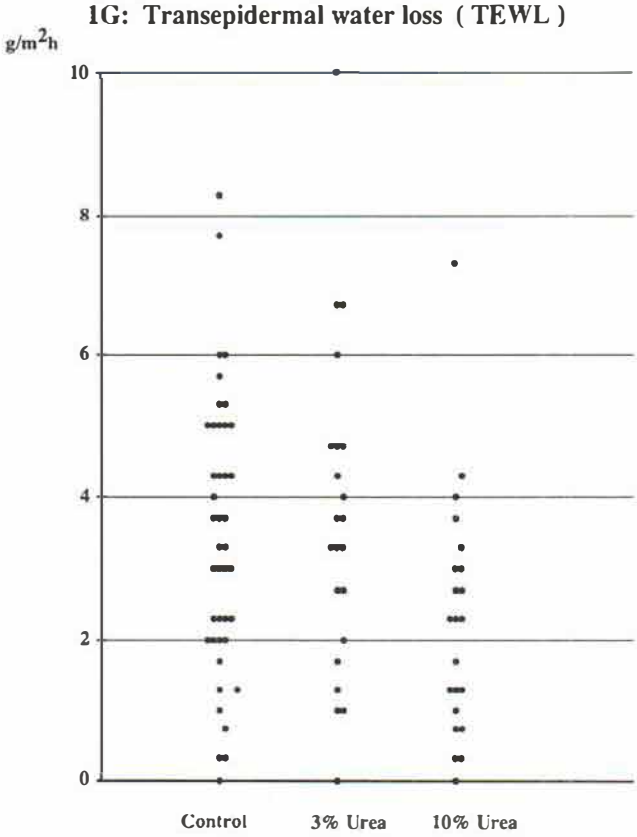
1E: Electrical capacitance



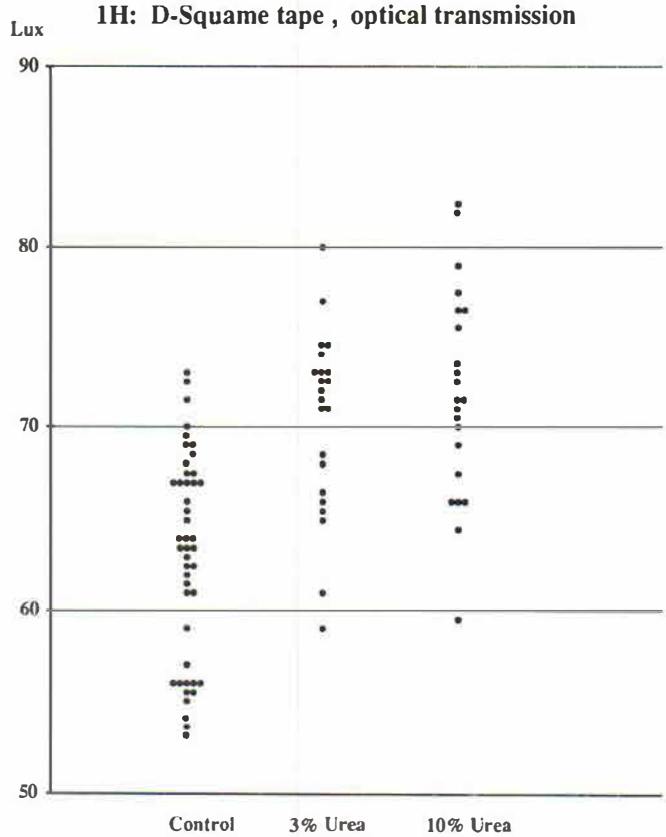
1F: Electrical conductance



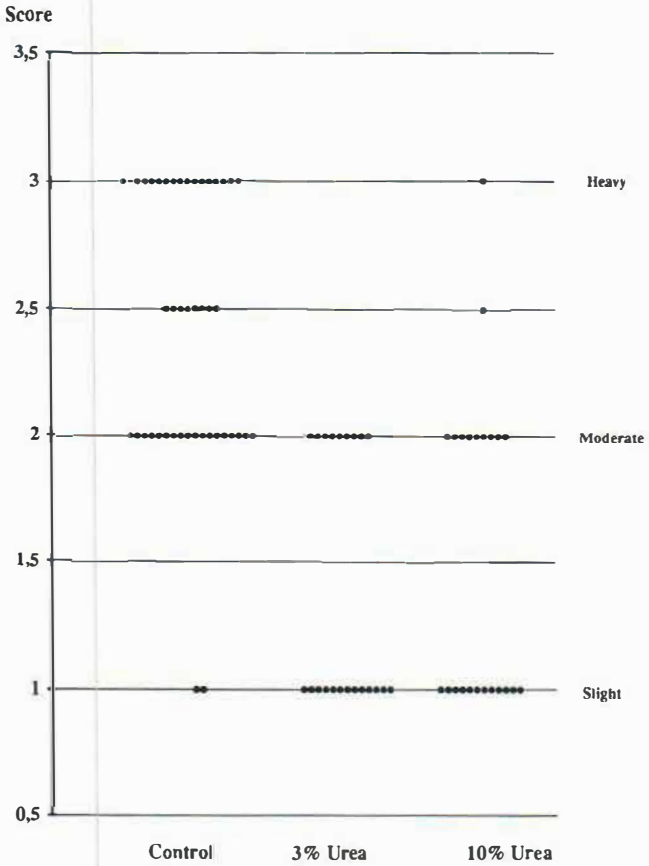
1G: Transepidermal water loss (TEWL)



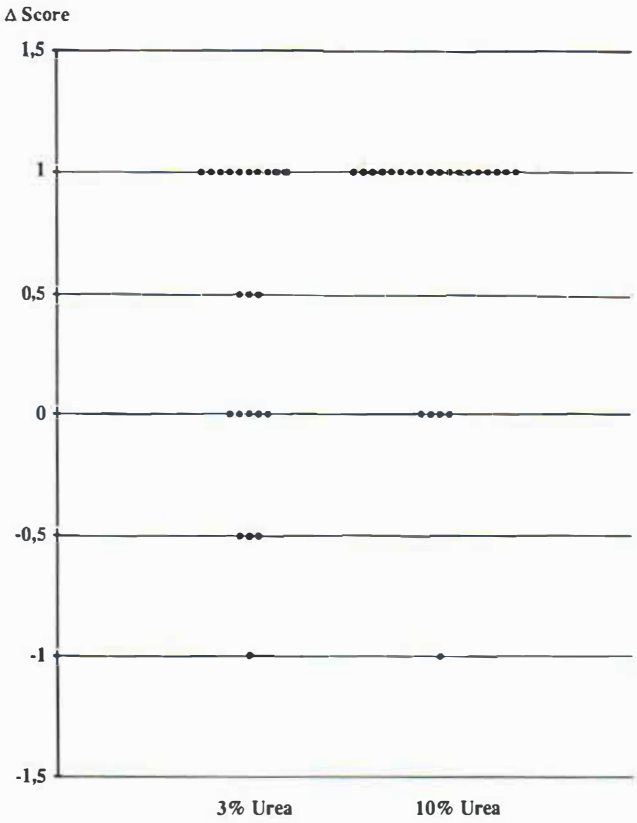
1H: D-Squame tape , optical transmission



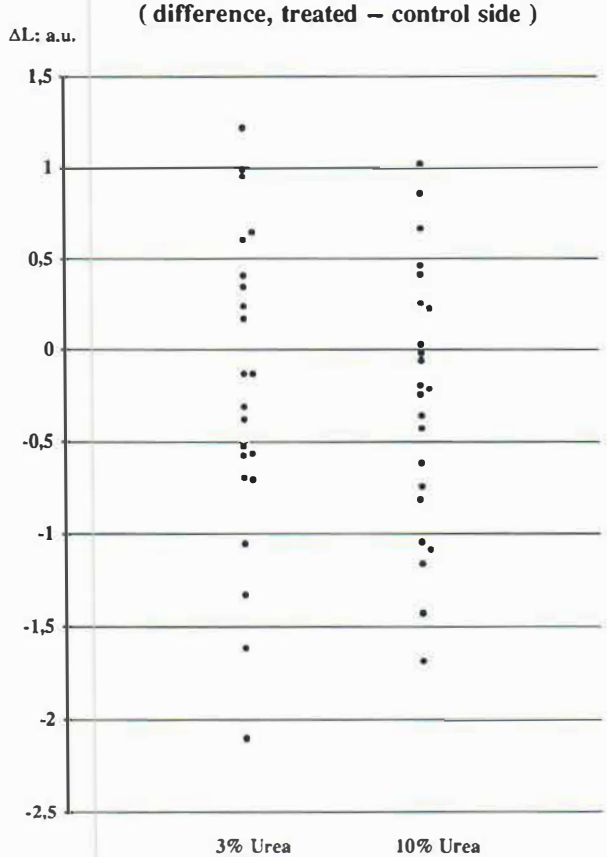
1 I : D-squame tape, visual evaluation of scaling



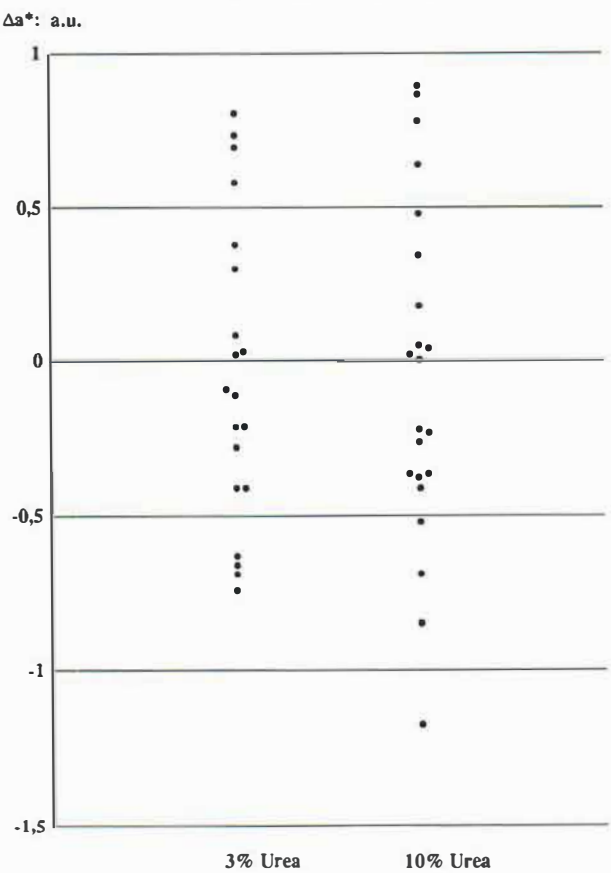
2 A: Clinical evaluation of skin hydration (difference, treated – control side)



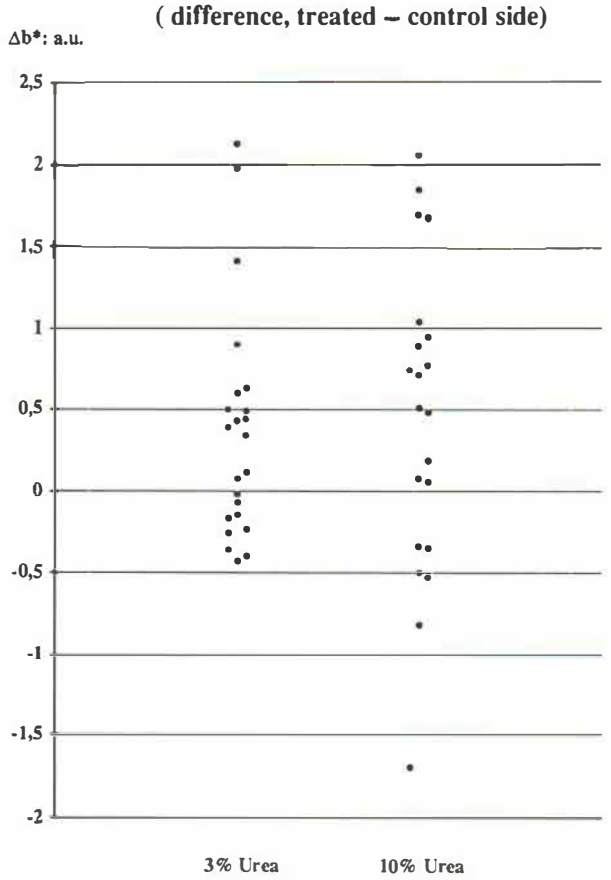
2 B: Skin colour, brightness (L) (difference, treated – control side)



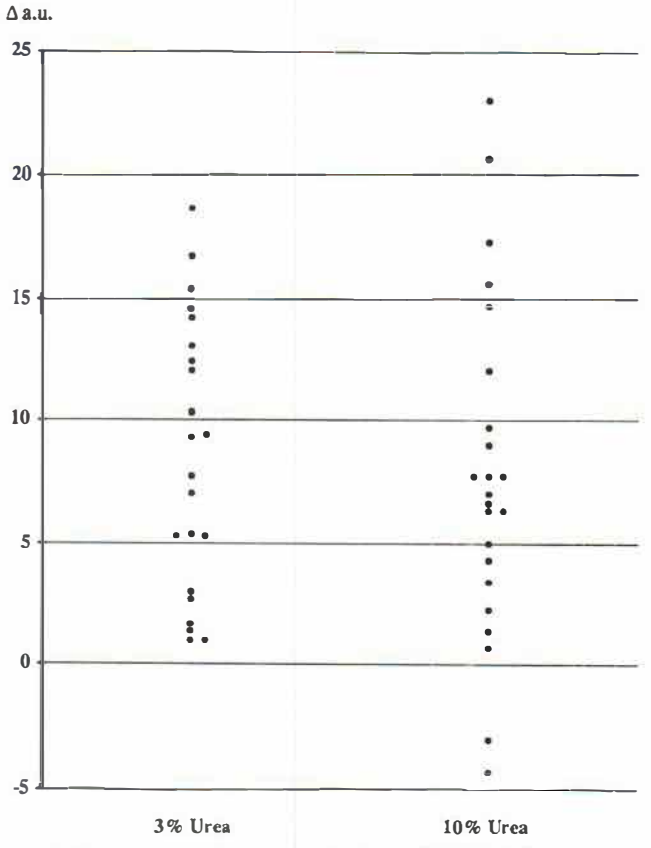
2 C: Skin colour, red (a*)



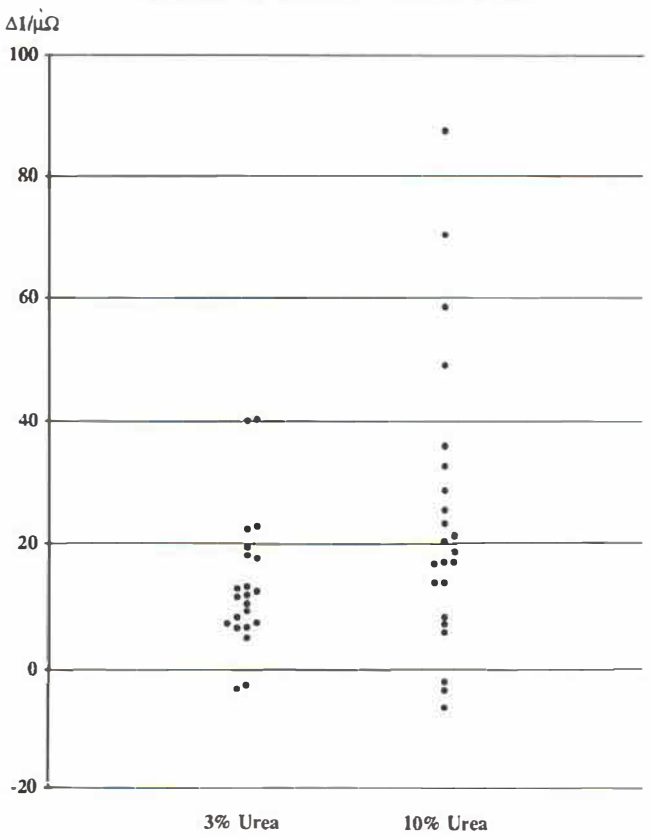
2 D : Skin colour, yellow (b*)
(difference, treated – control side)



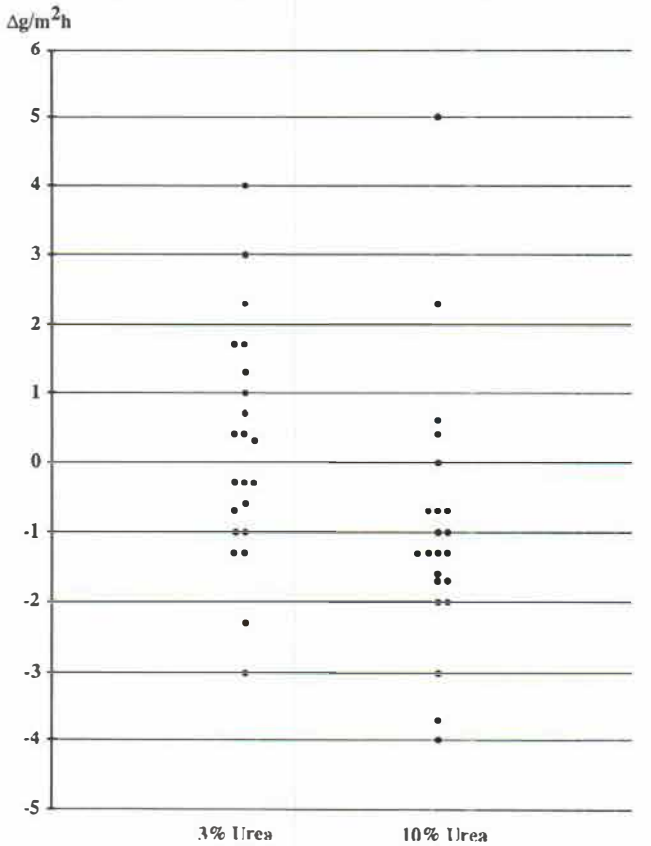
2 E : Electrical capacitance
(difference, treated– control side)



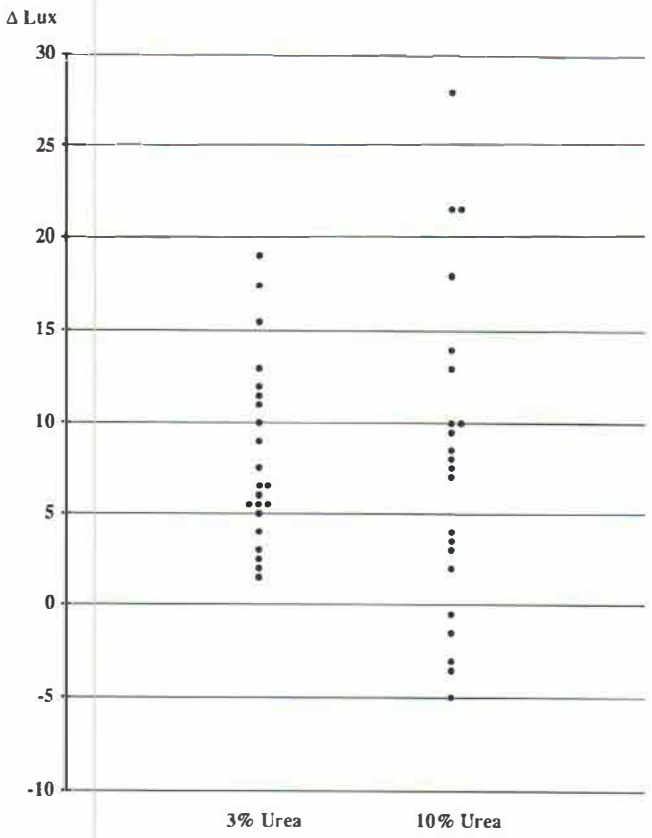
2 F: Electrical conductance
(difference, treated – control side)



2 G: Transepidermal water loss (TEWL)
(difference, treated– control side)



2 H: D-Squame tape, optical transmission (difference, treated – control side)



2 I: D-Squame tape, Visual evaluation of scaling (difference, treated– control side)