

ORIGINAL ARTICLE

# The effect of 222-nm UVC phototesting on healthy volunteer skin: a pilot study

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## Key words:

cyclobutane pyrimidine dimers; human skin; phototesting; volunteer study; UVC; 222-nm non-ionizing radiation

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None.

## ABSTRACT

### Background

Frequent topical antiseptic use to hands is now common in healthcare and other work environments. Inevitably, the use of such antiseptics will present an occupational risk for irritancy and allergic dermatitis. New, less irritant and even non-chemical antimicrobial approaches are under investigation.

### Methods

A Sterilray disinfectant source (222 nm) conventionally used to sterilize equipment and work surfaces was assessed for tolerability in human skin. Using an escalating dosage study methodology, four skin phototype I and II healthy volunteers had their minimal erythema dose (MED) determined. Punch biopsies of irradiated sites were stained for cyclobutane pyrimidine dimers (CPD). The degree of CPD was compared with that in biopsies from unexposed skin and from areas exposed to UVB (280–315 nm) radiation.

### Results

Calibrated spectral measurements revealed emission at a peak wavelength of 222 nm with 97% emission at wavelengths less than 250 nm. At low doses below the threshold bacteriostatic effect, the source was capable of inducing both erythema and CPD formation in human skin. In two individuals, cells in the basal layer were not shielded by the overlying tissue as indicated by the presence of CPD.

### Conclusion

The source showed an erythemogenic or CPD potential at lower doses than those required to reach the reported threshold bacteriostatic effect.

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Skin antiseptics are widely and increasingly used to reduce transfer of viable pathogens. With the advent of antibiotic resistant organisms and in particular *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* (MRSA), frequent topical antiseptic use to hands (as many as 30 times per day) is now quite common in healthcare and other work environments. Inevitably, the use of such antiseptics will, particularly in susceptible subjects, present an occupational irritant and may provoke an allergic dermatitis. The search for new, less irritant and even non-chemical antimicrobial approaches continues.

Ultraviolet C (UVC) 200–280 nm has been used as a germicidal agent to sterilize laboratory and other types of equipment but not for human skin *in situ*. Previously published human data showed that these wavelengths are not only capable of killing organisms or inhibiting their replication but also have limited penetration into the skin (1, 2). Because UVC wavelengths are not part of the solar spectrum on the surface of the earth (they are absorbed by the Earth's atmosphere), scant study has been conducted looking at their clinical effects. It is, however, known that wavelengths at approximately 250 nm can penetrate the viable epidermal layer and are capable of producing skin damage as demonstrated by redness (erythema) and DNA damage (3). It therefore appears that penetration of these wavelengths into the viable epidermal basal layer is possible.

It is also thought that UVC wavelengths shorter than 250 nm penetrate less deeply into the skin, but it is unknown whether they will produce DNA damage if the upper epidermal layers are intact. Until now, UV germicidal action has been limited almost exclusively to a wavelength of 254 nm, emitted by a low pressure mercury lamp. Animal and human studies of single dose UVC (254 nm) irradiation of infected wounds (dose range 2–6 J cm<sup>-2</sup>) have shown effective eradication of microbes with limited damage to host tissue (4, 5). However, these doses are within the range that can induce cyclobutane pyrimidine dimerization [CPD (6–9)] and the carcinogenic effects of repeated cumulative exposure are unknown.

New technical developments in lighting technology have seen the emergence of excimer lamps capable of emitting UV radiation at shorter wavelengths. Work carried out in the 1960s (10) suggested that UV light at 220 nm was approximately 20 times less capable of inducing erythema than UV at 250 nm. This meant that 220 nm would be much safer on skin than 250 nm, but the lighting technology was not available at that time to exploit this very interesting finding. The possibility existed, therefore, that there might be a sterilization window that could be exploited by killing organisms on the surface layer of the skin provided

that no significant damage resulted in the deeper layers of the epidermis.

Our objective was to investigate the effect of exposure of the skin to UV radiation of wavelength 222 nm using a device that is used to sterilize equipment (Sterilray™ Health Environment Innovations, Dover, New Hampshire, USA). We assessed its ability to induce erythema and DNA damage in man by using an escalating dosage regimen with readings for erythema and also assessing biopsy material for CPD. It is known that 300 mJ cm<sup>-2</sup> is capable of destroying common pathogens; however, it was not known if this dose would be comfortably tolerated by human skin. Anecdotal information suggested 500 mJ cm<sup>-2</sup> was used on human hand skin without erythema consequences.

Therefore, with a first-in-man ascending dosage study, we used small areas of upper back volunteer test skin (1.5 cm<sup>2</sup>) and determined the minimal erythema dose (MED; that is the minimum amount of light required to induce a just perceptible redness on the skin) for individuals with susceptible skin phototype. By carefully ascending the dose from a low start level of 5 mJ cm<sup>-2</sup> we would find out whether there is a safe sterilization window that might make the use of UVC at 222 nm a suitable antiseptic treatment option possibly for people with a susceptibility to irritation using current chemical antiseptic treatments.

## METHODS

### Characterization of Sterilray UVC device and device calibration

UV output measurements were carried out in our United Kingdom Accreditation Service accredited UV calibration laboratory. All calibrations are traceable to national standards. The UV emission from the Sterilray device was measured using a double grating spectroradiometer (Bentham Instruments Ltd. Reading, Berkshire, UK) with a cooled (–20°C) photo-multiplier tube in a temperature-controlled laboratory. For day-to-day measurements a semiconductor UV detector was used. The most suitable device that has a good response around 222 nm is the SEL220/W Detector [International Light Technologies, Peabody, Massachusetts, USA], which we calibrated in the UV calibration laboratory. When we placed the IL detector close to the Sterilray, the detector saturated. To overcome this, we added a neutral density filter (QNDS2#29398, International Light), and the IL detector was calibrated with and without this filter.

The uniformity of the irradiance from the Sterilray was determined by taking measurements at 1 cm intervals on the long axis of the lamp. The consistency of the output

was checked by taking repeated measurements over 5 days. Also, output was measured every 10 s for 10 min in order to assess stability of the lamp emission after switch-on.

### Clinical study objectives

The primary objective was to assess the cutaneous erythemogenic potential exposure of UVC wavelengths (222 nm) using the 'Sterilray™' disinfectant wand (Healthy Environment Innovations, Dover, NH, USA). The MED was determined immediately and hourly for 12 h and 24 h post-irradiation using an ascending dose regime. The secondary objective was to assess ultraviolet-induced DNA damage in the skin by visualizing CPD in skin biopsies. The study was conducted in compliance with the regulations, principles and standards of good clinical practice laid down in The UK Medicines for Human Use (Clinical Trials) Regulations 2006 No. 1928. Written informed consent was obtained before any study-specific activity commenced.

### Study design

This was a within-subject dose escalation study ('first in man') conducted in healthy male volunteers in a single centre within the National Photobiology Unit at Ninewells Hospital. Each subject served as his own negative control, with TL-01 (Philips, Eindhoven) narrowband UVB acting as a positive control for erythema and CPDs.

### Study procedure

Four normal male volunteer subjects [age range 22–28 years; skin type 1 (n = 2) and skin type 2 (n = 2)] were tested in this escalating dose study (Table 1). Testing started at the lowest possible practical dose. Subjects 1 and

2 were exposed to escalating doses of UVC (222 nm) up to a maximum of 508 mJ cm<sup>-2</sup>. Subjects 3 and 4 replicated the above testing 1 week after subjects 1 and 2 started. Areas of 1.5 cm<sup>2</sup> on the upper back were used, at a defined distance from the source, with each dose being irradiated separately on a naïve skin test area. Areas not being irradiated were suitably photo-protected. The MED is defined as the minimum dose of irradiation at which just perceptible erythema is observed by visual examination. Skin responses to each dose of UVC (222 nm) were graded visually as previously described (11, 12).

Digital images were taken of skin test sites at each 24-h assessment and in the event of an unforeseen immediate skin reaction. Visual skin assessments of any potential erythema response (MED) were carried out immediately and then hourly for 12 h, and then at 24 h. If there was no erythema and no significant adverse events, we proceeded with further phototesting.

### Biopsies

Skin punch biopsies (4 mm) were taken and fixed within 5 min post-irradiation following:

1% lignocaine local anaesthetic from UVC irradiated sites, positive (TL-01 at 2 × MED dose) and negative controls (normal non-irradiated skin; Table 1). Specimens were randomly labeled as A, B or C. A log was generated linking specimen to subject and skin site. Samples were analysed for CPD within 7 days of being biopsied.

### Immunochemistry

The anti-CPD clone TDM2 monoclonal antibody (2B Scientific, Oxfordshire, UK) was characterized using HaCaT keratinocytes exposed to either 30 mJ cm<sup>-2</sup> UVB, 5 J cm<sup>-2</sup> visible light or sham irradiation (data not shown). The

**Table 1.** Minimal erythema doses (MED) from the UV sources and the doses at the biopsy sites

Dose (mJ cm <sup>-2</sup> )				
Subject	MED	UVC (Sterilray)		TL-01 UVB (positive control)
		Biopsy dose*	MED†	Biopsy dose‡
1	50	101	305	610
2	40	101	183	366
3	50	63	231	462
4	40	63	147	294

\*Dose of Sterilray radiation producing a grade 2 erythema response.

†TL01 MED. An MED below 25 mJ cm<sup>-2</sup> is abnormal.

‡Dose of TL01 radiation equivalent to 2 × MED.

**Table 2.** Histopathological evaluation of biopsies

Subject 1	Control (biopsy A)	UVB exposed (biopsy C)	UVC exposed (biopsy B)
Suprabasal	0	+++	+++
Basal	0	+++	0
Subject 2	Control (biopsy C)	UVB exposed (biopsy A)	UVC exposed (biopsy B)
Suprabasal	0	+++	+ / ++
Basal	0	+++	0
Subject 3	Control (biopsy B)	UVB exposed (biopsy A)	UVC exposed (biopsy C)
Suprabasal	0	+++	++
Basal	0	+++	+
Subject 4	Control (biopsy A)	UVB exposed (biopsy B)	UVC exposed (biopsy C)
Suprabasal	0	+++	++
Basal	0	+++	+

Key to Table 2:

0: No keratinocytes show CPD formation.

+: Small numbers of keratinocytes show CPD formation.

++: Moderate numbers of keratinocytes show CPD formation.

+++: The majority of keratinocytes show CPD formation.

antibody clone is specific to CPD in every dipyrimidine sequence (TT,CC,TC,CT) and is less reactive towards 6–4 photoproducts and Dewar photoproducts. Skin biopsies were collected immediately following exposure to  $2 \times$  MED Sterilray radiation, TL01 radiation or from unirradiated skin and immersion fixed in neutral buffered formalin overnight followed by standard histological processing into paraffin wax.

The immunohistochemical procedure was initially optimized using the formalin-fixed, paraffin-embedded cell blocks prior to staining of the skin biopsies. For immunohistochemistry,  $4 \mu\text{m}$  sections were collected onto charged glass slides (PolySine; VWR International Ltd, Leicestershire, UK) and dried overnight at room temperature before being dewaxed by immersion in HistoSol (National Diagnostics, Hull, UK), rinsed in alcohol and endogenous peroxidase activity blocked in 0.15%  $\text{H}_2\text{O}_2$  in methanol (35 min). After washing, sections were digested with Proteinase K (Dako, Cambridge, UK), washed and immersed in 1N HCl for 30 min at room temperature. Sections were stained with TDM2 (1/2000 overnight at  $4^\circ\text{C}$ ) using the peroxidase-labelled avidin-biotin complex technique (Vector Elite ABC kit for mouse, Vector Labs Ltd., Peterborough, UK) according to the manufacturer's instructions. Antigenic sites were revealed with diaminobenzidine/ $\text{H}_2\text{O}_2$  in the presence of 5 mM imidazole, pH7.0. Sections were counterstained with haematoxylin, dehydrated, cleared and mounted in DPX resin for light microscopy examination. Biopsies were coded and assessed without prior knowledge of treatment by a consultant histopathologist

with expertise in dermatopathology using standard techniques. A simple semi-quantitative scoring system (Table 2) was employed to evaluate the samples. For each sample, dimer formation was assessed firstly in the suprabasal epidermis and then also within the germinal cells of the basal epidermis.

## RESULTS

### Device calibration

UV irradiance at the centre of the lamp was  $4.27 \text{ mW/cm}^2$  and  $6.40 \text{ mW/cm}^2$  at a working distance of 5 cm and 2.5 cm, respectively. The spectral emission shows a narrow peak at 222 nm (Fig. 1a). The Full Width Half Maximum (FWHM), generally referred to as the bandwidth, was 2.45 nm. FWHM is the width of the spectrum at the wavelengths corresponding to 50% of the peak emission. Most of the emission is found within this narrow line spectrum. When the data are plotted on a logarithmic scale (Fig. 1b), there are small emission peaks at 234 nm and 257 nm. Nonetheless, 88% of the UVC is within the 222 nm waveband and 97 % of UVC is emitted at wavelengths shorter than 250 nm.

Beam uniformity on the long axis of the Sterilray was within 5% in the region used for MED testing. Measurements made over a 5-day period showed that the coefficient of variation was only 2%, which signified a stable and predictable output. Measurements made every 10 s for 10 min had a coefficient of variation of 4.4%. Thus, output was shown to be reproducible with little variation over the

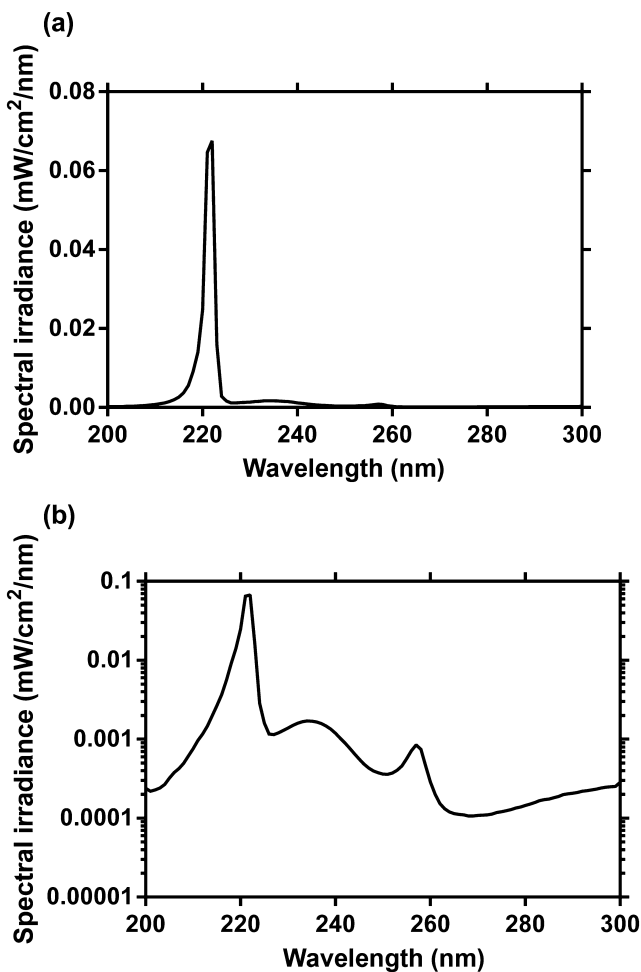


Fig. 1. Spectral emission of the Sterilray device. (a) Linear scale. (b) Logarithmic scale showing peaks at 234 nm and 257 nm.

measurement sites used and for the duration of the erythema investigations.

### Minimal erythema dose (MED)

In the four subjects studied, the primary study objective was to assess the cutaneous erythemogenic potential of exposure to UVC wavelengths (222 nm) using the Sterilray disinfectant wand. With the ascending dose regimen, the MED was determined immediately, hourly for 12 h, and then 24 h post-irradiation. The maximum erythema effect was detected at 12 h. There was no immediate urticarial type reaction. Table 1 shows the MED using the UVC source, in addition to the TL-01 (positive control) source. For UVC the MED values in the four volunteers tested were either  $40 \text{ mJ cm}^{-2}$  or  $50 \text{ mJ cm}^{-2}$  (Table 1). These results are contrary to reported anecdotal observations that suggested that the skin might be able to tolerate as

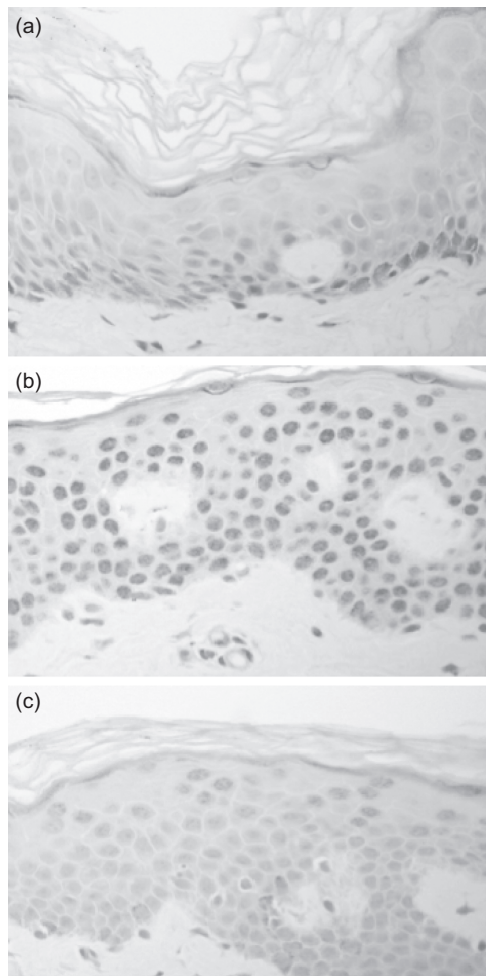
much as  $500 \text{ mJ cm}^{-2}$  without producing erythema. Although testing was conducted on the mid upper back skin, these data nevertheless provide objective evidence that this particular UVC lamp is capable of inducing erythema at low doses. The results for the TL-01 UVB source were within the range that we would expect for photoskin type 1 or type 2 subjects (11).

### Histopathology

The secondary study objective was to assess UV-induced CPD. The assessor did not know the identity of the samples until analysis was completed. The quality of the immunostained preparations was excellent in yielding clear results. Each biopsy was also stained with haematoxylin and eosin and examined for evidence of apoptosis; however, apoptotic keratinocytes (sunburn cells) were exceptionally infrequent even in UVB-irradiated skin, thus the results presented in Table 2 refer only to immunostaining for CPD. For each sample CPD formation was assessed firstly in the suprabasal epidermis and then also within the germinal cells of the basal epidermis.

The pattern and intensity of CPD expression is shown in Figures 2 (subject 1) and 3 (subject 3). In both volunteers, the non-irradiated skin (control) exhibited no dimer formation (Figs 2a and 3a). Skin irradiated with UVB shows pan-epidermal nuclear dimer formation (Figs 2b and 3b). UVB irradiation resulted in strong expression of CPD in both basal and suprabasal epidermis; CPD was also noted within endothelial cells lining dermal capillary blood vessels in the immediate subepidermal zone, and also within the nuclei of dermal connective tissue cells.

There was a different pattern of dimer formation following exposure to UVC (220 nm). Subject 1 (Fig. 2c) showed small to moderate numbers of positively staining keratinocytes within the upper half of the epidermis. The intensity of the staining was less marked than that following UVB exposure. Granular melanin pigment could be discerned within the cytoplasm of the basal layer, but once this was discounted, it was clear that there was no evidence of CPD formation. The pattern of suprabasal dimer formation without evidence of accompanying expression of basal layer CPD was also noted in subject 2 (Table 2). Subject 3 differed, as the epidermis was focally attenuated over the tips of the dermal papillae, and in such thin areas CPD was observed within the nuclei of the basal keratinocytes (Fig. 3c). Again, the intensity of the staining was less marked than that following exposure to UVB. Subject 4 showed the same pattern of focal basal layer staining as observed in subject 3 (Table 2).

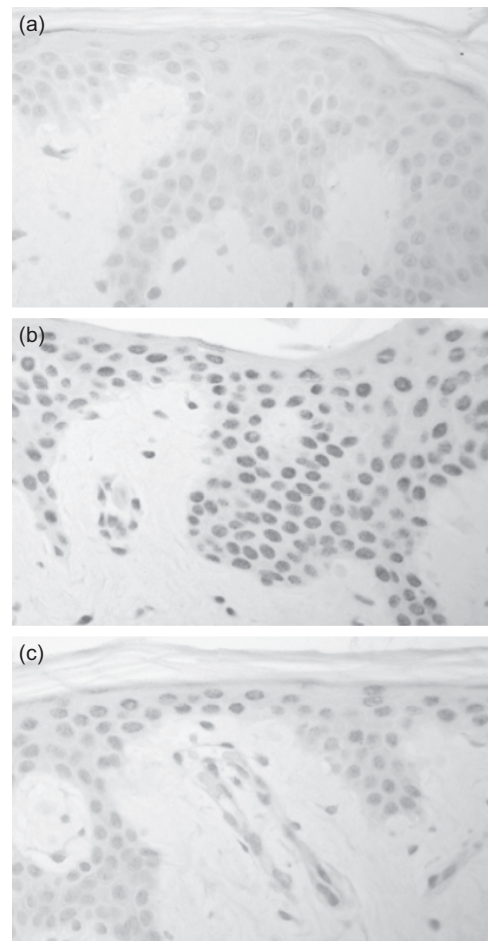


**Fig. 2.** Subject 1. (a) Un-irradiated skin showing basal cell melanin pigmentation; (b) ultraviolet B (UVB) irradiated skin. Cyclobutane pyrimidine dimers (CPDs) occur throughout the epidermis as shown by the intensely brown staining nuclei (examples arrowed). Note focal staining of endothelial cells lining a dermal capillary; (c) UVC irradiated skin. Modest numbers of keratinocytes within the upper dermis show CPD staining. The staining is less intense than that observed with UVB. The granular brown staining in the basal epidermis is cytoplasmic melanin pigment and not CPD staining. Magnification  $\times 400$ .

Thus, in two out of the four subjects UVC (222 nm) exposure resulted in CPD restricted to the suprabasal keratinocytes; however, in the remaining two subjects, CPD was apparent in the basal layer of germinal keratinocytes over the tips of the dermal papillae. These two subjects showed normal variation in epidermal thickness over the dermal papillae.

## DISCUSSION

We have investigated both the erythemogenic and CPD formation potential of the UVC emitting Sterilray device.



**Fig. 3.** Subject 3. (a) Un-irradiated skin. Note the more variable thickness of the epidermis in this subject with some suprapapillary plate thinning; (b) ultraviolet B (UVB) irradiated skin. UVB exposure results in strong cyclobutane pyrimidine dimer (CPD) expression throughout the epidermis. CPDs are again noted in capillary endothelial cells and also in dermal connective tissue cells; (c) ultraviolet C (UVC)-irradiated skin. Modest numbers of keratinocytes within the upper dermis show CPD staining (arrowed). The staining for nuclear dimers is much less intense and less extensive than for UVB; however, there is modest staining of suprabasal cells, and where the epidermis is attenuated over the tips of the dermal papillae some basal layer nuclear staining is also noted. Magnification  $\times 400$ .

The inter-individual results were remarkably consistent. The background purpose was to link the dose of this source capable of producing erythema to the dose known to have a bacteriocidal/static effect. UVC is strongly absorbed by proteins and nucleic acids and causes skin damage (Trevisan *et al.*, 2006). Previous studies in mice have demonstrated antimicrobial effects at doses that did not cause significant damage to the host tissue but did cause detectable CPD [250–260 nm UVC (1)]. Little is known about

the effects of wavelengths < 250 nm. One group (14) have used human skin equivalents to demonstrate MRSA cell killing by a filtered 207 nm radiation source with doses that did not induce detectable CPD. In the present study the photophysics quality control was carefully conducted. Eighty-eight per cent of the UVC was within the 222 nm waveband, but there was a tail of low level emission extending to longer wavelength UVC. Although 97 % of the UVC was emitted at wavelengths shorter than 250 nm, there is the possibility that longer wavelength UVC contributed to the effect.

The histopathology results showed evidence of CPD formation after irradiation with Sterilray UVC. In the case of the UVC irradiated skin, the CPDs tended to be more superficial but were present in the basal layer of the suprapapillary plate region. CPDs are probably responsible for most of the DNA-damage-mediated effects of sunlight. The staining pattern observed correlates with the clinical spectrum of tumours recognized to occur in the setting of actinic damage, which encompasses a range of carcinomas of epidermal and adnexal origin together with tumours from the connective tissue elements such as atypical fibroxanthoma/pleomorphic dermal sarcoma and also angiosarcoma.

The pattern of immunostaining for CPDs differed from UVB, in that the intensity of the staining was less marked and more superficial with no clear evidence of damage to the dermal constituents. The most important question is whether or not there is evidence of CPD within the basal layer keratinocytes. For a treatment or procedure to be safe, then the basal layer should show no evidence of dimer formation.

Two of the four subjects showed no sign of basal layer dimers. However, the remaining two subjects showed a more pronounced pattern of epidermal rete ridges with epithelial thinning over the suprapapillary plates; and where the epidermis was thinned UVC exposure did result in basal CPD formation.

The skin samples for this study were from the back, and it is worth noting that the rete ridge pattern at acral sites

(such as the palm) is likely to be even more pronounced as this binds the epidermis more firmly to the dermis to counteract frictional forces. This suggests that in hand skin, if UVC exposure was employed to reduce micro-surface organisms, then potentially mutagenic damage to the basal layer keratinocytes would occur particularly within the thinned suprapapillary plates. There might be some filtering out of the damaging effects of UVC by the thicker corneal layer on palmar skin but DNA damage might still occur at other less cornified sites such as the dorsal hands and wrists.

These data, when combined, suggest that not only is erythema inducible using the UVC emitting Sterilray, but also that DNA damage in the form of the skin cancer-associated CPDs, has also been induced. These events are occurring at Sterilray dosage levels below the threshold for bacteriostatic/cidal effects suggesting that frequent, several times daily, use of Sterilray irradiation is unlikely to be tolerated as a non-chemical antiseptic for human skin.

## CONCLUSION

This study has investigated the Sterilray disinfectant wand from a skin damage point of view. At low doses below the threshold bacteriostatic effect, the source was capable of inducing both erythema and CPD formation in human skin. In two individuals, cells in the basal layer were not shielded by the overlying tissue. Although most of the UVC emitted by the light source was within the 222 nm waveband, there was a tail of low level emission extending to longer wavelength UVC that could have contributed to the effect.

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