Research Note

Computer Modeling Indicates Dramatically Less DNA Damage from Far-UVC Krypton Chloride Lamps (222 nm) than from Sunlight Exposure

Ewan Eadie[1]* (iD), Paul O'Mahoney[2] (iD), Louise Finlayson[3], Isla Rose Mary Barnard[3] (iD), Sally Helen Ibbotson[2] and Kenneth Wood[3] (iD)

[1]NHS Tayside, Photobiology Unit, Ninewells Hospital and Medical School, Dundee, UK
[2]Photobiology Unit, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK
[3]School of Physics and Astronomy, SUPA, University of St Andrews, St Andrews, UK

ABSTRACT

This study aims to investigate, with computer modeling, the DNA damage (assessed by cyclobutane pyrimidine dimer (CPD) formation) from far-ultraviolet C (far-UVC) in comparison with sunlight exposure in both a temperate (Harwell, England) and Mediterranean (Thessaloniki, Greece) climate. The research utilizes the published results from Barnard et al. [Barnard, I.R.M (2020) *Photodermatol. Photoimmunol. Photomed*. 36, 476–477] to determine the relative CPD yield of unfiltered and filtered far-UVC and sunlight exposure. Under current American Conference of Governmental Industrial Hygienists (ACGIH) exposure limits, 10 min of sunlight at an ultraviolet (UV) Index of 4—typical throughout the day in a temperate climate from Spring to Autumn—produces equivalent numbers of CPD as 700 h of unfiltered far-UVC or more than 30 000 h of filtered far-UVC at the basal layer. At the top of the epidermis, these values are reduced to 30 and 300 h, respectively. In terms of DNA damage induction, as assessed by CPD formation, the risk from sunlight exposure greatly exceeds the risk from far-UVC. However, the photochemistry that will occur in the stratum corneum from absorption of the vast majority of the high-energy far-UVC photons is unknown, as are the consequences.

INTRODUCTION

Since the beginning of the COVID-19 pandemic, there has been incredible scientific and commercial endeavor to research and develop technologies to reduce the transmission risk of the SARS-CoV-2 virus. One such technology utilizes ultraviolet-C (UVC) wavelengths between 200 nm and 230 nm (often called "far-UVC") to inactivate viruses in air and on surfaces (1–4). The attraction of this technology is its apparent effectiveness accompanied by a lack of acute skin and eye reactions, even at radiant exposures above the current exposure limits (5, 6). In addition, several studies have now shown that these wavelengths

of UVC appear to induce minimal amounts of deoxyribonucleic acid (DNA) damage in the skin and the damage that is induced is limited to the upper-most non-proliferating skin cells (7, 8). This suggests that long-term exposure to these wavelengths is unlikely to be associated with increased skin cancer risk through induction of cyclobutane pyrimidine dimers (CPD) or 6–4 photoproducts (6–4PP) (8, 9).

However, implementation of this promising new technology could encounter resistance after decades of public health warnings about ultraviolet exposure from the sun (which does not include wavelengths below 290 nm). Importantly, we wished to put potential risks into context and convey the message that exposures to UVC wavelengths below 230 nm and to sunlight are distinctly different.

MATERIALS AND METHODS

To place exposure to wavelengths below 230 nm in context of sunlight exposure, we utilize the results from Barnard et al. (10), who provided two wavelength-dependent graphs of Monte Carlo radiative transfer (MCRT) simulated fluence and relative CPD yield at different locations within the skin—the top of the epidermis, the middle of the epidermis and the basal layer. To determine these values, Barnard et al. combined MCRT with a five-layer skin model, assuming no melanin protection in the epidermis (Fitzpatrick Skin Type I) and a stratum corneum thickness of 15 μm. From their data, it is possible to determine the relative CPD yield per incident irradiance, by dividing the spectra in figure 2 of Barnard et al. by the incident irradiance of the source detailed in figure 1 of the same publication. This provides three action spectra for CPD yield at the three different locations within the skin (Fig. 1), which can be used to determine the relative CPD yield of any ultraviolet source up to 365 nm.

We use these action spectra to compare the relative CPD yield at a given point in each skin layer from:

- A krypton chloride (KrCl) excimer lamp without restriction of wavelengths above 230 nm (Woods et al. 2015) (11).
- A krypton chloride (KrCl) excimer lamp with filtering to restrict emissions above 230 nm (Ushio Care222, Ushio Inc., Tokyo, Japan).
- Sunlight exposure from Harwell, England (51.6o N, −1.3o E) with a UV Index of 4.1. These data are from the 29th of June 2019 captured at 0900 Coordinated Universal Time (UTC).
- Sunlight exposure from Thessaloniki, Greece (40.6o N, 22.9o E) with a UV Index of 8.6 (12).

Two different sunlight exposures were chosen to represent two different scenarios: a moderate UV exposure that is typical of early morning sunshine in a temperate climate from Spring to Autumn and a high UV

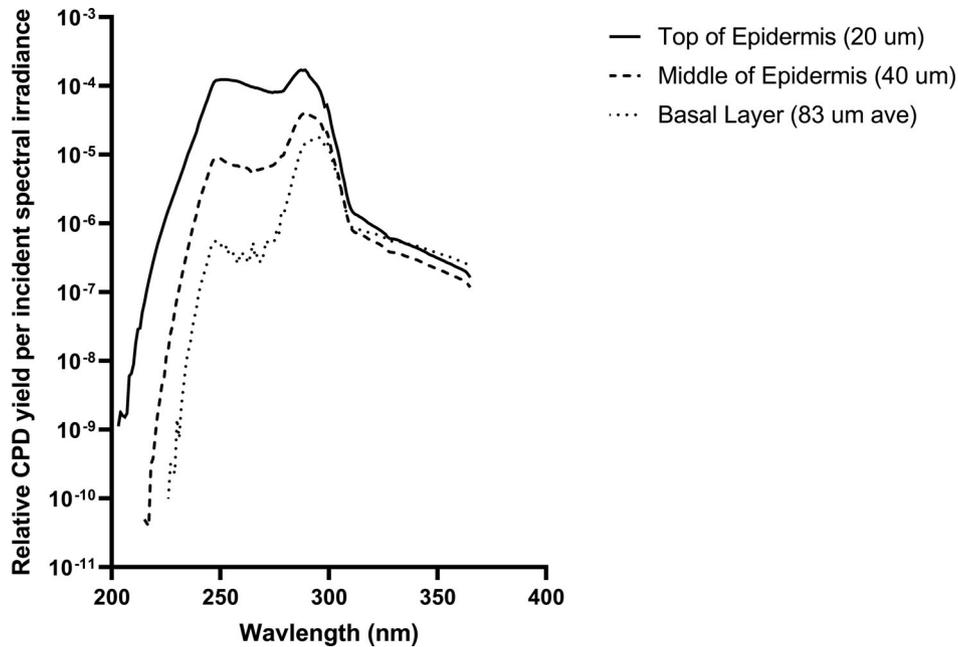*Corresponding author email: ewan.eadie@nhs.scot (Ewan Eadie)

Figure 1. Relative CPD yield at different locations within the skin as a function of the incident spectral irradiance.

exposure in a Mediterranean climate (13). To compare the relative CPD yield between light sources in an appropriate manner, the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLVs) were applied to the artificial UV sources (14). Threshold, or exposure, limits are often legally binding and aim to place a maximum threshold value on exposure to artificial ultraviolet radiation for a specific group of people, such as employees. Exposure limits are not a target and the general radiation safety principle of "As Low As Reasonably Achievable (ALARA)" should still be adhered to. As far as we are aware, there are no exposure limits for natural ultraviolet radiation, although the ALARA principle does apply. According to the International Commission on Non-ionizing Radiation Protection (ICNIRP), the radiant exposure incident on unprotected skin from ultraviolet radiation should be less than 30 Jm^{-2} when spectrally weighted by the relative spectral effectiveness for exposure guidelines (15). This exposure limit applies to an eight-hour period, which means the average spectrally weighted irradiance should be less than 1.04 mWm^{-2}.

RESULTS

The spectral irradiances of the optical radiation sources are shown in Fig. 2. The total irradiance of each source was 2.8 Wm^{-2} Woods et al. (200–400 nm at 40 cm distance), 3.0 Wm^{-2} Ushio Care222 (200–400 nm at 20 cm distance), 35.5 Wm^{-2} Harwell (290–400 nm) and 56.0 Wm^{-2} Thessaloniki (280–400 nm).

By combining Figs. 1 and 2 and integrating the area under the curve, it is possible to obtain the total relative CPD yield at each skin location (Fig. 3).

The spectrally weighted irradiance of the Woods et al. source was 421 mWm^{-2} and the Ushio Care222 was 382 mWm^{-2} at their respective measured distances. To quantify the relative CPD yield of these artificial sources in actual use conditions relative to sunlight exposure, the spectrally weighted irradiance was reduced to equate it to the exposure limit spectrally weighted irradiance (1.04 mWm^{-2}). Given this restriction on irradiance, the exposure time required to reach an equivalent number of CPD to 10 min of sunlight exposure was calculated for each skin location (Table 1). Results were rounded to one significant figure

to reflect a degree of uncertainty which comes from the underlying research upon which the inputs to the computer model are based.

DISCUSSION

The results in Table 1 demonstrate the dramatic difference between the minimal CPD produced by the KrCl lamps when compared with computer-modeled CPD produced by sunlight exposure. This is particularly true in the most critical (in terms of skin cancer risk) basal layer, where the computer modeling estimates that approximately 30 000 h of exposure to the Ushio Care222 at current exposure limits would produce the equivalent number of CPD that would occur from 10 min when the UV Index is 4, typical of morning English sunshine from Spring to Autumn (13). CPD are a type of DNA damage that is specific to UV, and they are more prolific than other markers of DNA damage such as 6-4PP (8).

The numbers reported by our modeling appear large; however, they are supported by several in vivo and in vitro studies. Hickerson et al. showed minimal CPD in vivo from a filtered KrCl source with DNA damage found only immediately below the stratum corneum (7). The radiant exposure in that study was 6000 mJ cm^{-2}, which is 260 times the current TLV. Buonanno et al. also demonstrated, in a skin model, limited DNA damage confined to the upper most layers of the skin only from a filtered KrCl lamp: 0.016% of keratinocytes had CPD at TLV which was 730 times less CPD than exposure to 254nm at TLV (8). In contrast, Shih et al showed prolific CPD throughout the epidermis from simulated sunlight exposure at just 80% of the Minimal Erythema Dose (MED) (16). Similarly, Yamaguchi et al. and Tadokoro et al. demonstrated that 1 MED of UVA and UVB (60% and 40%, respectively) produced fluorescence intensity of CPD around 80% of the fluorescence intensity of nuclei in fair skin, a ratio which did not vary with depth (17, 18). This is in agreement with our results which show CPD depth variation with
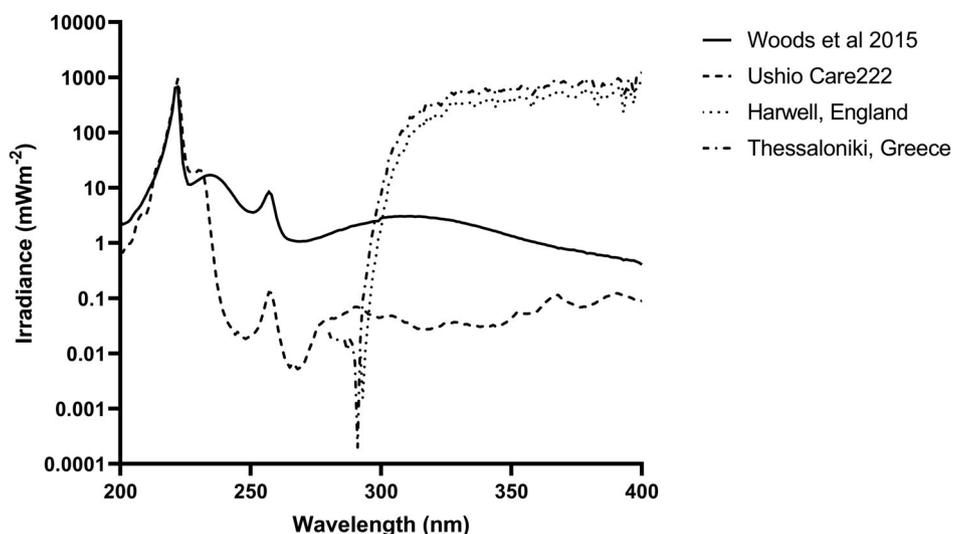
Figure 2. Spectral irradiance (mWm^{-2}) of an unfiltered KrCl lamp (Woods et al. 2015), a filtered KrCl lamp (Ushio Care 222), sunlight in Harwell, England (UV Index 4.1) and sunlight in Thessaloniki, Greece (UV Index 8.6).
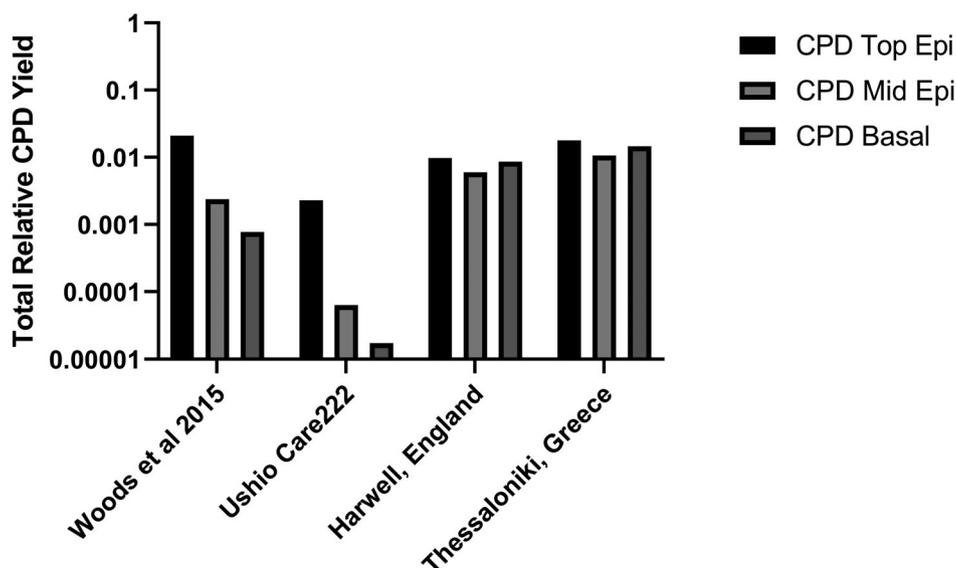

Figure 3. Integrated relative CPD yield for each of the spectra at the different depths in the skin.

Table 1. Time in hours to produce equivalent CPD to 10 min of sunlight exposure in Thessaloniki (UV Index 8.6) and Harwell (UV Index 4.1). Woods et al. (2015) is a KrCl excimer lamp without restriction of wavelengths above 230 nm, Ushio Care222 is a KrCl excimer lamp with filtering to restrict emissions above 230 nm.

	Thessaloniki		Harwell	
	Woods et al. (2015)	Ushio Care222	Woods (et al.) 2015	Ushio Care222
Top Epidermis	60	500	30	300
Mid-Epidermis	300	10 000	200	6000
Basal Layer	1000	50 000	800	30 000

There are large differences between sunlight and KrCl exposure in these computer-modeled results, demonstrating the limited penetration of short wavelength UVC.

the KrCl excimer sources, particularly the filtered source, but little depth variation with sunlight (Fig. 3). Although there is no direct in vitro or in vivo comparison between CPD induced by sunlight exposure and by far-UVC sources, the values from Yamaguchi et al. and Tadokoro et al. are approximately 5000 times higher than Buonanno et al., which are similar proportions to those presented here.

In further support of the computer modeling, Buonanno et al demonstrated that CPDs produced by a filtered KrCl excimer lamp were approximately 10–12% of the CPDs produced by an unfiltered source (8). MCRT simulation indicates that the Ushio Care222 (filtered) would produce 7% of the CPD produced by the source from Woods et al. 2015 (unfiltered). However, further investigation of other damage mechanisms is warranted as there is strong absorption in the stratum corneum of high photon energy at 222 nm and the impact of this is, as yet, unknown.

Furthermore, the CPD from these simulations should not be directly compared to erythema. A just perceptible reddening of the skin, defined as the MED, has previously been demonstrated to happen with an unfiltered KrCl lamp at 40–50 mJ cm^{-2} (approximately twice the current TLV). The MED in Fitzpatrick Skin Type I is approximately equivalent to 2–3 Standard Erythema Dose (SED) which can be achieved in 33–50 min of sunlight exposure when the UV Index is 4 (11). In terms of erythema, not CPD, this would equate 10 minutes of sunlight exposure to between 3 and 5 h of an unfiltered KrCl lamp. The same comparison cannot be performed for the filtered KrCl lamp used in this study as it has, as yet, not been possible to induce erythema—even at very high doses (6).

The computer models described in this study have been extensively published and validated in the investigation of ultraviolet and visible light interaction with the skin (19–21). With any model, there is uncertainty and the main source of uncertainty in these results is the input parameters, which have been obtained from experimental results in the published literature. In reality, there will be large variation in skin layer thicknesses, DNA concentration and melanin distribution between individuals and within body sites in an individual. In particular, the stratum corneum plays a critical role in the quantity of CPD induced by far-UVC due to the very high absorption of short wavelength UVC. The effect of stratum corneum thickness has already been demonstrated in vivo (7). Another source of uncertainty is the skin model, with factors such as voxel size influencing results.

Regardless of uncertainty in the model, published studies all support the conclusions of our computer modeling—CPD induced by far-UVC sources are a fraction of those produced within very short time periods in Spring–Autumn sunlight. Furthermore, the penetration depth of far-UVC is limited to the upper-most superficial skin layers whereas sunlight penetrates to the basal layer producing CPD throughout the skin. These data are reassuring and helpful in terms of explaining potential risk in the context of typical sunlight exposures. However, further human safety studies *in vivo* are indicated to further investigate potential damage mechanisms and the safety of these far-UVC devices.

REFERENCES

1. Buonanno, M., D. Welch, I. Shuryak and D. J. Brenner (2020) Far-UVC light (222 nm) efficiently and safely inactivates airborne human coronaviruses. *Sci. Rep.* **10**, 1–8.
2. Welch, D., M. Buonanno, V. Grilj, I. Shuryak, C. Crickmore, A. W. Bigelow, G. Randers-Pehrson, G. W. Johnson and D. J. Brenner (2018) Far-UVC light: A new tool to control the spread of airborne-mediated microbial diseases. *Sci. Rep.* **8**, 1–7. https://doi.org/10.1038/s41598-018-21058-w
3. Kitagawa, H., T. Nomura, T. Nazmul, O. Keitaro, N. Shigemoto, T. Sakaguchi and H. Ohge (2020) Effectiveness of 222-nm ultraviolet light on disinfecting SARS-CoV-2 surface contamination. *Am. J. Infect. Control* **49**, 299–301.
4. Kitagawa, H., T. Nomura, T. Nazmul, R. Kawano, K. Omori, N. Shigemoto, T. Sakaguchi and H. Ohge (2021) Effect of intermittent irradiation and fluence-response of 222 nm ultraviolet light on SARS-CoV-2 contamination. *Photodiagnosis Photodyn. Ther.* **33**, 102184.
5. Fukui, T., T. Niikura, T. Oda, Y. Kumabe, H. Ohashi, M. Sasaki, T. Igarashi, M. Kunisada, N. Yamano, K. Oe, T. Matsumoto, T. Matsushita, S. Hayashi, C. Nishigori and R. Kuroda (2020) Exploratory clinical trial on the safety and bactericidal effect of 222-nm ultraviolet C irradiation in healthy humans. *PLoS One* **15**, e0235948.
6. Eadie, E., I. M. R. Barnard, S. H. Ibbotson and K. Wood (2021) Extreme exposure to filtered far-UVC: A case study. *Photobiol, Photochem.* **97**, 527–531.
7. Hickerson, R. P., M. J. Conneely, S. K. H. Tsutsumi, K. Wood, D. N. Jackson, S. H. Ibbotson and E. Eadie (2021) Minimal, superficial DNA damage in human skin from filtered far-ultraviolet-C (UV-C). *Br. J. Dermatol.* **184**, 1197–1199.
8. Buonanno, M., D. Welch and D. J. Brenner (2021) Exposure of human skin models to KrCl excimer lamps: The impact of optical filtering†. *Photobiol. Photochem.* **97**, 517–523.
9. Ikehata, H., T. Mori, T. Douki, J. Cadet and M. Yamamoto (2018) Quantitative analysis of UV photolesions suggests that cyclobutane pyrimidine dimers produced in mouse skin by UVB are more mutagenic than those produced by UVC. *Photochem. Photobiol. Sci.* **17**, 404–413.
10. Barnard, I. R. M., E. Eadie and K. Wood (2020) Further evidence that far-UVC for disinfection is unlikely to cause erythema or pre-mutagenic DNA lesions in skin. *Photodermatol. Photoimmunol. Photomed.* **36**, 476–477.
11. Woods, J. A., A. Evans, P. D. Forbes, P. J. Coates, J. Gardner, R. M. Valentine, S. H. Ibbotson, J. Ferguson, C. Fricker and H. Moseley (2015) The effect of 222-nm UVC phototesting on healthy volunteer skin: a pilot study. *Photodermatol. Photoimmunol. Photomed.* **31**, 159–166.
12. Tierney, P., J. Ferguson, S. Ibbotson, R. Dawe, E. Eadie and H. Moseley (2013) Nine out of 10 sunbeds in England emit ultraviolet radiation levels that exceed current safety limits. *Br. J. Dermatol.* **168**, 602–608.
13. McLellan, L. J., P. O'Mahoney, M. Khazova, M. Higlett, S. H. Ibbotson and E. Eadie (2019) Ultraviolet radiation exposure during daylight Photodynamic Therapy. *Photodiagnosis Photodyn Ther.* **27**, 19–23.
14. American Conference of Governmental Industrial Hygienists (2020) *TLVs and BEIs: Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices.* ACGIH Worldwide, Cincinnati, OH.
15. International Commission on Non-Ionizing Radiation Protection (2004) ICNIRP Guidelines on Limits of Exposure to Ultraviolet Radiation of Wavelengths between 180 nm and 400 nm (Incoherent Optical Radiation). *Health Phys.* **87**, 171–186.
16. Shih, B. B., M. D. Farrar, M. S. Cooke, J. Osman, A. K. Langton, R. Kift, A. R. Webb, J. L. Berry, R. E. B. Watson, A. Vail, F. R. de Gruijl and L. E. Rhodes (2018) Fractional sunburn threshold UVR doses generate equivalent vitamin D and DNA damage in skin types I-VI but with epidermal DNA damage gradient correlated to skin darkness. *J. Invest. Dermatol.* **138**, 2244–2252.
17. Yamaguchi, Y., K. Takahashi, B. Z. Zmudzka, A. Kornhauser, S. A. Miller, T. Tadokoro, W. Berens, J. Z. Beer and V. J. Hearing (2006) Human skin responses to UV radiation: pigment in the upper epidermis protects against DNA damage in the lower epidermis and facilitates apoptosis. *FASEB J.* **20**, 1486–1488.
18. Tadokoro, T., N. Kobayashi, B. Z. Zmudzka, S. Ito, K. Wakamatsu, Y. Yamaguchi, K. S. Korossy, S. A. Miller, J. Z. Beer and V. J. Hearing (2003) UV-induced DNA damage and melanin content in human skin differing in racial/ethnic origin. *FASEB J.* **17**, 1177–1179.
19. Barnard, I. R. M., P. Tierney, C. L. Campbell, L. McMillan, R. Valentine, H. Moseley, E. Eadie, C. T. A. Brown and K. Wood (2018) Quantifying direct DNA damage in the basal layer of skin

exposed to UV radiation from sunbeds. *Photochem. Photobio.* **94**, 1017–1025.
20. Campbell, C. L., K. Wood, R. M. Valentine, C. T. A. Brown and H. Moseley (2015) Monte Carlo modeling of daylight activated photo-dynamic therapy. *Phys. Med. Biol.* **61**, 4840–4854.
21. Valentine, R. M., K. Wood, C. T. A. Brown, S. H. Ibbotson and H. Moseley (2012) Monte Carlo simulations for optimal light delivery in photodynamic therapy of non-melanoma skin cancer. *Phys. Med. Biol.* **57**, 6327–6345.