ABSTRACT

The development of a computational model is described that allows time-varying erythema and acclimatization to be determined following repeated exposure to solar ultraviolet (UV) radiation. Good agreement was observed between experimental data and model predictions. Results are presented that illustrate how daily, adventitious sun exposure over the course of a year can result in occasional erythema generally in the late spring/early summer, while at the same time showing how the photoadaptive response of the skin changes throughout the year at different latitudes and for different sun-reactive skin types. The model is predicated on three physiological responses; the erythematous response as a function of increasing UV dose, the time courses of erythema and adaptation in response to a single UV exposure. Mathematical models complement observational data and the outputs from the model may help in planning future experimental studies, as well as providing insights into mechanistic responses.

INTRODUCTION

Experimental studies on the erythematous response of skin to ultraviolet (UV) radiation almost always involve a single exposure given over a short time period of typically a few minutes. Yet in life we are exposed to solar UV over much more extended periods, which can be for several hours over the course of a day, as well as on a daily basis throughout the year.

Given that the erythematous response can take up to a few days to resolve depending on the magnitude of exposure and that repeated exposure gives rise to a photoadaptive response, there have been surprisingly few experimental studies where repeated irradiation is involved. This study describes the development of a computer model to simulate repeated exposure and presents results to illustrate how daily, adventitious (i.e. unplanned incidental) sun exposure over the course of a year can result in occasional erythema while at the same time showing how the photoadaptive response of the skin changes throughout the year. These results may help inform a better understanding of where the balance lies between minimizing sun exposure in order to reduce the likelihood of adverse effects or recommending a moderate degree of sun exposure to improve photoadaptation and so limit excessive exposure to the viable epidermis.

MATERIALS AND METHODS

The model is predicated on three physiological responses: (1) the erythematous response as a function of increasing UV dose, (2) the time course of erythema and (3) adaptation in response to a single UV exposure.

Dose response. When skin is irradiated with increasing exposure doses of UV radiation, little or no response is seen at low doses until the minimal erythema dose (MED) is reached when just perceptible erythema is apparent. With increasing doses, erythema increases with the rate of increase falling at higher doses such that even at high doses, redness no longer increases due to maximal vasodilation having been reached. Experience from a number of experimental studies on UV erythema dose response indicates that for sources where the erythematous component lies predominantly in the UVB region, such as sunlight, the MED becomes apparent at about 15% of maximal redness with about 6–10 MEDs resulting in erythema that approaches maximal redness (1-5).

Experimental data on erythema measured as a function of incident dose of UV radiation, little or no response is seen at low doses until the minimal erythema dose (MED) is reached when just perceptible erythema is apparent. With increasing doses, erythema increases with the rate of increase falling at higher doses such that even at high doses, redness no longer increases due to maximal vasodilation having been reached. Experience from a number of experimental studies on UV erythema dose response indicates that for sources where the erythematous component lies predominantly in the UVB region, such as sunlight, the MED becomes apparent at about 15% of maximal redness with about 6–10 MEDs resulting in erythema that approaches maximal redness (1-5). Experimental data on erythema measured as a function of incident dose showed that the form of the relationship could be described by a sigmoid function where the independent variable is the logarithm of UV dose (4,5).

The degree of erythema, relative to maximal erythema, following an exposure to M multiples of an individual’s MED is illustrated by the curve in Fig. 1 and can be expressed as:

$$R(t) = \left(1 + \alpha \cdot M^{-\beta}\right)^{-1}$$  \hspace{1cm} (1)

The function in Eq. (1) asymptotes as M approaches both zero and infinity. Consequently, we fit the curve at intermediate points and assume that 1 MED and 8 MED result in 15% and 90% of maximal redness, respectively. This results in values for \(\alpha\) and \(\beta\) of \(\alpha = [1/0.15 - 1]\) and \(\beta = \log \{([1/0.15 - 1]/[1/0.9 - 1]) / \log (8)\}.

Time course. The time course of UV-induced erythema following a single exposure shows a rapid rise peaking at about 8–12 h after irradiation, with a slow disappearance, the time taken for redness to disappear depending on the exposure dose and maximal erythema (6,7).

We chose to describe this time profile by a function in \(\ln(t)\) such that the erythema relative to the maximum redness achieved for the given exposure dose, \(R(t)\), at time \(t\) following exposure can be expressed as:

$$R(t) = \exp \left\{-\frac{(\ln(t) - \mu)^2}{\theta}\right\}$$  \hspace{1cm} (2)

The coefficient \(\mu\) is the natural logarithm of the time at which erythema peaks, which we take to be 10-h, \(\theta\) is expressed as \([\ln(\frac{1}{T_{1/2}}) - \mu]/\ln(2)\), where \(T_{1/2}\) is the time at which erythema falls to 50% of the peak value. From the examination of experimental data (6,7), as well as the data presented from a number of experimental studies on UV erythema dose response, the following equation was used to illustrate how daily, adventitious sun exposure over the course of a year can result in occasional erythema while at the same time showing how the photoadaptive response of the skin changes throughout the year. These results may help inform a better understanding of where the balance lies between minimizing sun exposure in order to reduce the likelihood of adverse effects or recommending a moderate degree of sun exposure to improve photoadaptation and so limit excessive exposure to the viable epidermis.
as MEDs observed at 8 and 24 h after exposure (8), we deduce $T_{1/2}$ to be 40 h. The normalized time course given by Eq. (2) is shown in Fig. 2.

Photoadaptation. Exposure of skin to UV radiation promotes an acute inflammatory response clinically characterized by erythema. Alongside this acute response, a number of changes occur that are adaptive, in the sense that they result in a diminished future response to equivalent doses of UV radiation (9). This response, described as photoadaptation, is not fully understood, but is viewed as comprising at least two processes: melanogenesis and epidermal hyperplasia.

Epidermal hyperplasia in the ears of mice is evident at about 2 days after exposure, reaches a peak in around a week and, in the absence of further stimulation, returns to normal after about 2 months (10). Following a single exposure to UVB radiation, delayed tanning in humans follows a similar time course becoming evident after 1–2 days, peaking around 1 week, and may persist from weeks to months (11,12).

In response to a single exposure to fluorescent UVB lamps that result in moderate erythema (13), UV-induced adaptation followed a similar pattern with protection reaching a peak about 10 days after the initial exposure and resolving completely within two months. The resulting adaptation was presumably a combination of hyperplasia and tanning. In white skin, both hyperplasia and tanning contribute to the development of photoadaptation with hyperplasia generally being the dominant process (14).

Consequently, we chose to model the increase in epidermal absorbance, $\Delta a(t, X)$, incorporating both hyperplasia and tanning, at time $t$ days after irradiation following a single exposure of $X$ SED as a function given by:

$$\Delta a(t, X) = K f(ST) X \exp\left\{ -\frac{(\ln(t) - \mu_a)^2}{\theta_a} \right\}$$  \hspace{1cm} (3)

$K$ is related to the extinction coefficient of the epidermis and $f(ST)$ is a factor that accounts for skin type; both these factors are derived in the Appendix 1.

We assume that photoadaptation peaks at 10 days following a single exposure, and from the time taken for this to return to preirradiation levels (10-13), we take the time for adaptation to fall to 50% of its peak value to be 25 days. This results in values for $\mu_a$ and $\theta_a$ of 2.30 and 1.21, respectively. That the action spectra for melanogenesis (8) and UV-induced hyperplasia (15) are similar to that for erythema support the expression of UV exposure ($X$) in Eq. 3 in an erythemally weighted unit (SED).

At the $i^{th}$ irradiation time, $t_i$, the increased absorbance $\Delta a(i)$ resulting from repeated exposures is expressed as:

$$\Delta a(i) = \sum_{j=1}^{i-1} \Delta a(t_i - t_j, X_j)$$  \hspace{1cm} (4)

The endogenous protection factor, $PF_{e}$, at this time is then simply expressed as:

$$PF_e = 10^{\Delta a(i)}$$  \hspace{1cm} (5)

RESULTS

Comparison of modeled erythema with experimental data after repeated irradiation

In an experimental study (16), 16 volunteers (eight of skin type II and eight of skin type III) were exposed to solar simulating radiation (SSR) on previously unexposed buttock skin. Duplicate sites were exposed daily (Mon-Fri) for two consecutive weeks (days 1–12) with 0.5 and 0.75 of each individual’s MED. Erythema, corrected for basal erythema on unirradiated skin, was measured on the exposure sites using a reflectance instrument on each occasion during the study and on days 18 and 19.

For comparison, the model described in the Appendix 1 was run with equal exposures of 0.75 and 0.5 MEDs, given on days 0 to 4 and 7 to 11. In order to make a direct comparison between measured and modeled time courses, the mean reflectance measurement taken 24 h after the first exposure of 0.75 MED was normalized to the modeled relative erythema calculated 24 h after the same exposure. A similar normalization was carried out for the 0.5 MED exposures.

The comparison between modeled and measured erythema shown in Fig. 3 appears at first sight not to be particularly close, but note that the ordinate only extends to 0.4 of maximum redness and both modeled and experimental curves indicate no more than mild pinkness. A further point of note is that the increase in erythema indices measured on the 0.5 MED site (16) was around 20–40 but the indices on an adjacent nonirradiated site that the authors used to correct for basal erythema, although not given, would typically be between 100 to 200 units in white skin (1), indicating that systematic errors in the increase in erythema index could be significant.

The model indicated that erythema becomes progressively more pronounced with five daily suberythemal exposures, in keeping with results from an observational study showing that the frequency of erythema in a cohort of subjects increased in a similar fashion (17), but showed little, if any, increase for exposures thereafter.
In a second study (18), the effects of 11 consecutive daily suberythemal exposures of SSR on buttock skin of six healthy volunteers (sun-sensitive skin types I/II) were assessed. A standard dose was given on each exposure that represented about 0.6 MED, and erythema was measured daily. The time course observed on unprotected skin is compared with the model calculation in Fig. 4, where excellent agreement is found.

What both the model and experimental studies illustrate is that daily suberythemal exposure can lead to moderate erythema after a week or so, although redness begins to plateau by around 10 days.

**Sun exposure throughout the course of a day**

In this simulation, we assumed an exposure over the course of a summer day beginning at three hours before solar noon and finishing seven hours later such that by late afternoon, the cumulative exposure was 10 SED, equivalent to 3.6 MED in type II skin (19). The exposure dose and erythema were calculated every 30 min over this 7-h period.

The resulting erythema calculated up to 100-h after the initial exposure is compared in Fig. 5, with that expected from a single “instantaneous” exposure of 10 SED.

With continuous exposure throughout the day, erythema would not be visible around lunchtime, would peak later that evening and eventually disappear by about 4-5 days. On the contrary, with a single exposure of 10 SED, erythema starts to appear by about 1.5-h, peaks 10-h later and has faded after about 3 days.

**Daily adventitious sun exposure throughout the course of a year at different latitudes**

Daily ambient erythemal UV radiation shows a summer-to-winter ratio of about 30:1 or higher in northern Europe, falling to about 6:1 in southern Europe, with day-to-day perturbations superimposed on this annual cyclic pattern as a result of cloud cover. However, the UV exposure of an individual will exhibit much greater fluctuations than ambient variation because of differences in time spent outdoors, behavior and proximity to shade on different days throughout the year (20).

We consider exposure at three locations across Europe: Oulu (65°N, 25°E), Luxembourg (50°N, 6°E) and Nicosia (35°N, 33°E). Typical daily ambient erythemal UV were estimated for these locations using data from an atlas of erythemal-weighted UV climatology over Europe (21) and are illustrated in Fig. 6.

The results obtained from a number of personal dosimetry studies indicate broadly that, excluding vacations to sunny places, adults who work outdoors receive about 10% of the total ambient available on a horizontal plane, while indoor workers and children generally receive around 2–5% of ambient during workdays with higher exposure on leisure days, normally the weekend (22). We assume, therefore, that on any one day the personal exposure on commonly exposed sites, such as the face, neck and backs of hands, is equal to the ambient on that day multiplied by a random number between 0 and 8%.

Daily personal exposures were used as the input to the model and the variation in expected erythema and epidermal photoprotection calculated throughout the year for a person of skin type
II at Oulu, Luxembourg and Nicosia are shown in Figs. 7, 8 and 9, respectively.

We see from Fig. 8 that occasional erythema may result around latitudes of 50°N on some days in late spring/early summer as a consequence of a particularly sunny day and/or more time than usual spent outside. This outcome concurs with results from an experimental study that found that skin is most susceptible to erythema in the spring (23). On the contrary, erythema from adventitious exposure appears less likely in mid- and late summer even though both ambient and personal exposure are generally greater than earlier in the year. The reason for this is that by mid-to-late summer the intrinsic photoprotection due to acclimatization is about twice as high as it is in late spring/early summer. When the model was run for a subject of skin type IV, erythema due to adventitious exposure at latitudes of 50°N is much less likely, whereas for an individual with skin type I, there may well be several episodes of mild erythema mainly in the late spring/early summer.

At northerly latitudes around 65°N, occasional erythema is still predicted to result from adventitious exposure but is most likely in midsummer (Fig. 7). On the contrary, in southern Europe around 35°N, occasional erythema is most likely to occur in late winter to early spring (Fig. 9).

As the year progresses at these locations in the northern hemisphere, epidermal hyperplasia resolves and any tan fades such that by midwinter, there is little or no additional photoprotection. While these findings are based on model predictions, they do mirror common experience where people report getting “caught out” by late spring/early summer sunshine but find they are much more tolerant to sun-exposure by mid-to-late summer (24,25).

We see in Figs. 7-9 protection factors peaking at around 3–4 at northerly temperate latitudes, rising to around 9–10 for more southerly latitudes. While these values are greater than the seasonal variation in MED established on the backs of volunteers reported in cohort studies (26,27), de Gruijl argues (25) that common experience supports the view that chronically exposed skin gradually adapts to increased levels of ambient UV radiation to a far greater extent than seen in studies on normally sun-protected sites such as the back.

The scenario described here is due solely to adventitious exposure since clearly recreational activities, such as sunbathing, that may result in high-dose exposure over several hours can lead to moderate or marked erythema, which we consider in the following section.

Recreational sun exposure and preconditioning exposure before vacation

In order to examine the impact of recreational, as well as adventitious, sun exposure on normally sun-exposed sites such as the face and neck, we consider someone with skin type II living at a latitude of 50°N who receives typically around 5% of ambient from their day-to-day exposure but increasing to 20% of ambient

![Figure 6. Typical diurnal ambient erythemal UV at Nicosia (red curve), Luxembourg (green curve) and Oulu (blue curve).](image)

![Figure 7. Erythema (red curve) and epidermal photoprotection (black curve) predicted throughout the year for a person of skin type II following exemplary daily adventitious sun exposure at Oulu, Finland (65°N).](image)
for a 2-week holiday in midsummer to reflect more time outdoors combined with less time in shade. The vacation equates to a daily exposure averaging 7.5 SED, which over the 2-week period results in about 100 SED.

The red curve in Fig. 10 illustrates the calculated erythemal response on normally sun-exposed sites. We see occasional episodes of mild erythema in spring and early summer but in the 2-week holiday period, indicated by the vertical broken lines, there may well be moderate erythema on these sites, assuming no mitigating protection strategies such as sunscreen or hats.

On vacation, especially sun-seeking holidays, it would be normal practice to expose parts of the body, such as the trunk, that would generally be sun-protected for the remainder of the year. The expected erythema on these sites, assuming equal exposure on all body sites, is indicated by the blue curve in Fig. 10. Here, we might expect to see episodes of moderate-to-severe sunburn (assuming no sun protection) during the holiday period as these sites have not had the same opportunity as, for example, the face for adaptation. Even when the holiday ends, redness may be apparent for a week or so.
There is often debate, particularly by protagonists of cosmetic tanning, that a course of sunbed sessions before going on vacation may help in preconditioning the skin to harsh sun exposure. We model this by assuming 14 daily sessions with a sunbed that has a spectral emission similar to sunlight, that is, UVB comprising about 5% of the UV emission, that begins 24 days before the holiday begins. Each session is the equivalent of 0.5 MED in skin type II, that is, 1.4 SED. The 10-day gap between the sunbed sessions finishing and the holiday beginning is to allow maximum benefit from the hyperplasia and tanning that may develop.

The predicted erythemal response from this approach is shown by the green curve in Fig. 10, where a feature of note is that while sunburn is still expected to occur on holiday, it is not as severe as that without preconditioning.

Let us suppose that the area under the erythema curve integrated over the year is a measure of DNA damage. We estimate that the integrated area for erythema on the back is about one-half of that on the face. That the face and neck receive higher annual “damage” than normally sun-protected body sites are in keeping with a much greater density of keratinocyte cancers on the head and neck (28). While we make no claim for integrated erythema being a defensible measure of biological harm, we use it simply to illustrate that a feature of mathematical models is that they quickly answer **what if?** questions that may stimulate insight into mechanistic processes.

Unlike keratinocyte cancers, which predominate on sites of highest insolation, melanoma occurs relatively more frequently on the trunk. This distribution lends support to the intermittent exposure hypothesis, especially since melanoma is associated with episodes of sunburn (29). So, if we consider only moderate-to-severe erythema, we find that the face barely reaches this degree of sunburn, and that the preconditioned trunk is likely to experience slightly less severe sunburn than the unconditioned trunk, which begs the question: Is a course of sunbed sessions before going on holiday benefit in reducing the risk of melanoma? It should be noted, however, that the cumulative annual exposure from using a sunbed before a holiday exceeds if no sunbed is used by about 15–20%.

**Impact of skin type on photoadaptation**

Daily variation of personal solar UV exposure at latitudes around 50°N is illustrated by the gray curve in Fig. 11. Using this as the time course, the model was used to calculate how photoadaptation during the course of the year varied with skin type. We see from Fig. 11 that the rate of photoadaptation increases as skin type decreases, reaching a peak protection factor in July of 4–5 for skin type I, falling to 3 for skin type IV.

While not directly comparable, it was observed (30, 31) in a cohort of subjects undergoing UVB therapy for psoriasis that the greatest photoadaptive response was seen in subjects with the lowest baseline MEDs, that is, lowest skin types. Repeating the estimates for latitudes around 35°N, we find maximal protection factors of 11–12 for skin type I falling to 6–7 for skin type IV.

**Acclimatization**

There are few studies of acclimatization due to either natural or simulated solar exposure. In one study in which the skin on the back of 25 volunteers was exposed to SSR lamps three times a week for 3 weeks, approximately 4-fold photoadaptation for erythema was achieved (32). In this study, the initial dose was 0.5 MED, the second 1 MED, followed by doses with an increment of 20% MED. On the third day after the final exposure, the MEDs were redetermined. Using this exposure sequence, a calculated protection factor of 3.7 was found, which is in good agreement with the mean value of 4.04 ± 0.46 determined by de Winter et al. (32).

In terms of acclimatization following sun exposure, just a few studies have been conducted (26,27). In one investigation (26), acclimatization was determined on the backs of 21 volunteers of skin types II and III who had deliberately sought 3½ months of Wisconsin (latitude ~ 43°N) summer sun by measuring MEDs on the buttocks (for unexposed skin) and on the midback (for exposed skin) in late summer. A mean protection factor of 2.3 was found.

Modeling a study such as this is fraught with uncertainties since no information was given on frequency or duration of exposure during the 3½ months, behavior, or climatic conditions. We resort to postulating exposure conditions, recognizing the aphorism attributed to Box that “...all models are useful, but some are useless” (33). We make the reasonable assumption that the backs of volunteers were exposed for 2 hours per day on every weekend day over the 3½ months and that the fraction of ambient UV received on the back was 0.3, resulting in a daily exposure to the back of 7.5% of ambient expected in Wisconsin (estimated for a latitude of 43°N (21)) in midsummer. The outcome of this simulation showed that acclimatization resulted in an intrinsic protection factor of 2.2 by mid-August, assuming back exposure began in early May. This degree of adaptation is similar to that of 2.3 observed experimentally and while encouraging, it could simply be due to the forcing function (UV exposure) chosen for the simulation since if we had assumed 4 h of back exposure on each weekend day, rather than 2 h, we would have estimated roughly a 4-fold protection.

**DISCUSSION**

A computational model is described that allows time-varying erythema and acclimatization to be determined following repeated
UV exposure. Reasonable agreement was observed between experimental data and model predictions, notwithstanding the assumptions about dose response and time courses inherent in the model. Clearly, there is always room for improvement in any mathematical model that more closely matches reality and the model described here is not without exception.

The model allows us to explain why the time course of erythema during a summer’s day that results in a cumulative dose of 3.6 MED differs from that expected from a single exposure of 3.6 MED in terms of time when minimal erythema first appears and the time taken to resolve.

Likewise, the model indicates that adventitious exposure to sunlight, principally to the hands, neck and face, on a daily basis throughout the year at midtemperate latitudes can lead to occasional episodes of mild erythema in individuals of skin types I and II, largely in the late spring and early summer, and explains why erythema is less likely as summer progresses. While it is not feasible to reproduce a simulation such as this experimentally due to potential volunteers not agreeing to MED measurements on the face for cosmetic reasons (25), the predictions do concur with common experience (24,25).

A feature of Figs. 7-9 is that while episodes of mild erythema occur earlier in the year as the latitude decreases, the maximum degree of erythema from adventitious exposure is much the same throughout Europe, suggesting that although exposure incident on the skin increases with decreasing latitude, the erythemal-effective UV penetrating into the viable epidermis shows much smaller variation due to the compensatory effect of photoadaptation in sunnier environments. It should be noted, however, that this conclusion is based solely on adventitious exposure and that recreational sun exposure at lower latitudes is likely to result in more episodes of erythema than similar exposure at high latitudes.

Figure 10 compares the impact of holiday exposure on sites of highest insolation (face, neck and hands) with normally sun-protected sites such as the trunk. We see that the trunk is predicted to experience more severe sunburn than the face and that preconditioning the skin by a course of sunbed sessions before the holiday may reduce the degree of severity. Whether or not this is beneficial in reducing the risk of melanoma remains an open question.

From Fig. 11 we see that, in keeping with observations on patients undergoing UVB phototherapy for psoriasis, photoadaptation due to sun exposure is greater for low skin types (I and II) than for people who more readily tolerate sunlight (skin types III and IV). Protection factors over the course of a year peak at 2–3 for skin types III/IV at high latitudes to 10–12 for skin types I/II at lower European latitudes. It might be thought from Eqs. 4 and 5 that protection factors would increase indefinitely for high UV exposures. However, even for the unrealistic example of three SED per day, resulting in an annual personal exposure of over 1000 SED, photoadaptation in skin type I is calculated to plateau at about 6 months with a protection factor of 20 and remain unchanged for the remainder of the year. The reason is that photoadaptation does not continue to increase, as hyperplasia and tanning from earlier exposures start to decrease after about 10 days and so eventually an equilibrium is reached.

When it comes to estimating the intrinsic protection resulting from acclimatization, comparing model simulations with the few experimental data available is problematic since none of the field studies report data on duration and frequency of exposure, behavior or solar UV levels. Nevertheless, the simulations do provide an insight into how acclimatization is developing and receding with increasing, and then diminishing, sun exposure. Also, by choosing the forcing function such that the model predictions are in close agreement with observational data allows us to postulate the nature and degree of sun exposure when details are absent; an example of a situation where the model outcome is technically incorrect but may nevertheless be valuable.

Because of its simplicity and limitations, the notion that a computational model might have credibility will not be shared...
by everyone, especially those who prefer to avoid mathematics (34). Certainly, mathematical models have received high prominence recently as giving insights into how to best manage the SARS-CoV-2 pandemic (35). The beauty of mathematical models is that they can provide both insights into how systems function as well as, in this case, prediction of responses, especially those involving timescales that are impractical to measure such as the variability in erythema and acclimatization experienced in a year of exposure to sunlight.

We accept that experiments on mice are never going to predict exactly how therapeutic agents work in people, but the use of experimental animals is implicitly based on the notion that they may provide insight into human responses. Likewise, mathematical models complement observational data in several ways. The inputs are precise and exactly repeatable, costs are low, timescales are short, and the outputs from the model may help in planning future experimental studies, as well as providing insights into mechanistic responses. This is highlighted by Figs. 7-9 where the similarity of the magnitude of erythemal response due to adventitious sun exposure over latitudes ranging from the subtropical to northerly temperate zones suggests a possible reappraisal of the relationship between UV exposure and skin cancer incidence.

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### APPENDIX 1

It is clear that if UV exposure is repeated at an interval of less than a few days, erythema that may have resulted from preceding exposures will not have had time to resolve before the next UV exposure. Also, a single suberythemal exposure may lead to observable redness after a few days if repeated on a daily basis. Erythema is not linearly additive, that is, successive exposures do not give rise to ever-increasing redness since eventually the blood vessels that result in visible erythema become maximally dilated and increasing the UV dose will not increase the redness. This is reflected in the sigmoid shape of the UV dose-erythemal response curve (Fig. 1).

UV erythema is thought to be initiated by the action of ultraviolet radiation on the epidermis, with subsequent vasodilation seen in the dermis being an indicator of the level of inflammatory mediators, such as eicosanoids and cytokines diffusing from the epidermis (36).

In order to estimate the consequences of repeated irradiation on the development of erythema, a mathematical model was developed that incorporates the time course of erythema following a single UV exposure (Eq. 2) with the dose–response relationship (Eq. 1), taking account of photoadaptation as repeated exposures occur (Eqs. 3, 4 and 5). The input variables are the UV exposures (in SED) at each time interval between successive exposures and the subject’s photoreactive skin type.

At the initial exposure time, the skin is exposed to \( X_0 \) SED that is equivalent to \( M_0 \) MEDs, determined by dividing \( X_0 \) by \( D_{ST} \), the median MED (in SED) for the chosen skin type (19).

Following the seminal work of van der Leun (37), the exposure is given as an impulse resulting over the following hours in the release of a quantity of mediators proportional to the dose \( M_0 \). These mediators diffuse into the dermis resulting in vasodilation, seen as sunburn. At time \( t \) following exposure at time 0, the quantity of mediator substance acting on the dermal blood vessels is given as \( q(0,t) \) leading to the expression:

\[
M_0 \alpha \int_0^\infty q(0,t)dt
\]  

(6)

The expected maximal erythemal response resulting from exposure at time 0, expressed as \( E(0, t_{\text{max}}) \), occurs at time \( t_{\text{max}} \), which we take as the peak of the erythema time course occurring 10-h after irradiation (see above), and is modeled as

\[
\epsilon(0, t_{\text{max}}) = [1 + \alpha(xq(0, t_{\text{max}}))]^{-1}
\]  

(7)

Note that Eq. (7) is numerically equal to \( [1 + \alpha M_0 \beta]^{-1} \) and so \( \epsilon = M_0 / q(0, t_{\text{max}}) \).

At time \( t \) following this exposure, the expected erythema is given by the product of \( E(0, t_{\text{max}}) \) and \( R(t) \), where \( R(t) \) is defined by Eq. 2.

The mediator quantity \( q(0,t) \) present at time \( t \) that would result in this degree of vasodilation is given by:

\[
q(0, t) = 1/\kappa \{\alpha/[1/\epsilon(0, t_{\text{max}}) \cdot R(t)] - 1\}^{1/\beta}
\]  

(8)

If we were to insert this expression for \( q(0,t) \) into the right-hand side of Eq. 7 in place of \( q(0, t_{\text{max}}) \), we get the desired time dependence in erythema \( E(0,t) \), i.e., \( E(0,t)R(t) \), after a single UV exposure.

For the following irradiation time \( t_i \), when an exposure of \( X_i \) SED is given, it follows that:

\[
\epsilon(1, t_{\text{max}}) = [1 + \alpha(xq(1, t_{\text{max}}))]^{-1} = [1 + \alpha M_1 \beta]^{-1}
\]  

(9)

and

\[
q(1, t) = 1/\kappa \{\alpha/[1/\epsilon(1, t_{\text{max}})R(t-t_i)] - 1\}^{1/\beta}
\]  

(10)

At the \( \theta^\text{th} \) irradiation at time \( t_n \), we have:

\[
\epsilon(i, t_{\text{max}}) = [1 + \alpha(xq(i, t_{\text{max}}))]^{-1} = [1 + \alpha M_i \beta]^{-1}
\]  

(11)

and

\[
q(i, t) = 1/\kappa \{\alpha/[1/\epsilon(i, t_{\text{max}})R(t-t_i)] - 1\}^{1/\beta}
\]  

(12)

At each irradiation time, \( t_i \), the equivalent number of MEDs, \( M_i \), is calculated as

\[
M_i = \frac{X_i}{D_{ST} \cdot PF_i}
\]  

(13)

where \( PF_i \) is the protection factor given by Eq. 5.

The process is repeated at each irradiation time such that at the any time \( t \) from the first exposure, the total quantity of mediator, \( Q(t) \), present in the skin is calculated by summing \( q(i,t) \) over the exposure period up to time \( t \) and is expressed as:

\[
Q(t) = 1/\kappa \sum_{i=0}^{t} \{\alpha/[1/\epsilon(i, t_{\text{max}})R(t-t_i)] - 1\}^{1/\beta}
\]  

(14)

Finally, by summing the terms \( q(i,t) \), we arrive at an expression for combining the impact of successive UV exposures while restricting the erythemal response to a maximum and so the expected erythema at time \( t \) follows as:

\[
\left[1 + \alpha(xQ(t))^{-\beta}\right]^{-1}
\]  

(15)

Data on the relationship between skin type and photodadaptation due to sun exposure are lacking. In studies of psoriatic patients undergoing phototherapy for psoriasis with broadband UVB fluorescent lamps (30,31), adaptation was found to increase roughly inversely with MED, with the highest photodaptive response seen in patients with the lowest baseline MEDs. On the other hand, in patients who were treated with narrowband UVB, photodadaptation was found to be more or less independent of skin type (38-40).

Using the erythema action spectrum as a proxy for photodadaptation, we calculate that the peak wavelengths of the effective-ness spectra occur at 298, 308 and 311 nm for broad band UVB lamps, sunlight and narrowband UVB lamps, respectively. Since the peak of the erythemally weighted spectrum of sunlight is closer to that for narrowband than broadband lamps, we conclude that skin type has a weak impact on photodadaptation due to sun exposure.

In order to result in this weak dependence, we arbitrarily chose the weighting factor, \( f(ST) \), to be proportional to the cubed root of the MED for a given skin type and define the factor \( f \)
\( (ST) \) in Eq. 4 as \( \sqrt[3]{D_I / D_{ST}} \) where \( D_I \) and \( D_{ST} \) are the median MEDs for skin type I and the chosen skin type, respectively. So, with median MEDs of 2.5, 2.8, 3.6 and 4.6 SED for skin types I, II, III and IV (19), we have weighting factors \( f(ST) \) of 1.0, 0.96, 0.89 and 0.82, respectively.

The coefficient \( K \) in Eq. 4 is derived from an optimization technique using the SOLVER capability of EXCEL that fits calculated photoprotection after repeated irradiation over a number of days to that observed in a study (16) that exposed volunteers of skin types II and III to SSR. In this study, all exposures were given to previously unexposed buttock skin. Duplicate sites were exposed daily (Mon-Fri) for two consecutive weeks (days 1–12) with 0.5 and 0.75 of each individual’s MED. One week after the final irradiation, the 24 h MED was assessed on one 0.5 MED-treated site and one 0.75 MED-treated site, as well as two adjacent nontreated sites.

The authors defined the protection induced by the irradiation as the MED on the irradiated site divided by the MED on a nontreated site (16). Overall, they found protection factors of 1.5 \pm 0.45 and 2.2 \pm 0.48 with the 0.5 MED and 0.75 MED daily SSR doses, which agree well with the respective model values of 1.65 and 2.12 following optimization that resulted in a numerical value for \( K \) of 0.016. The model was developed and run in EXCEL 2019.