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Review

Improving Photoprotection and Implications for 25(OH)D Formation

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Abstract. *Background/Aim: This review examined the implications of using sunscreen photoprotection on 25(OH)D formation and determined the best photoprotective method to reduce the risk of skin cancer caused by ultraviolet radiation (UVR). Based on previous studies on 25(OH)D formation after use of different amounts of sunscreen and different doses of UVR for approximately one week to different body areas it is possible to estimate the amount of 25(OH)D formed after a week's holiday in Southern and Northern Europe. Conclusion: The best method of photoprotection by sunscreen is two consecutive applications before sun exposure, ensuring the use of sufficient amounts of sunscreen and minimizing the unprotected skin areas. The double application method simultaneously ensures a high photoprotection against erythema from sun exposure. Despite the use of sunscreen, the calculated serum 25(OH)D levels clearly increase to similar levels as those measured after sun vacations.*

The risk of developing skin lesions caused by ultraviolet radiation (UVR) such as actinic keratosis, lentigines, nevi, malignant melanomas, and keratinocyte-derived skin cancers has increased dramatically during the last 50 years. Other UVR-related changes involve damage to elastic and collagen fibres in the skin, resulting in loss of skin elasticity and the development of wrinkles. The increase in sun exposure and subsequent potential risk of skin lesions caused by UVR damage are linked to increasing wealth in the general population, resulting in more frequent travel and holiday making in sunny countries, and exposure of larger skin areas due to less clothes being worn in sunny weather.

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Worldwide effort has been made to reduce UVR exposure through public information campaigns, advising people to avoid direct sunlight (stay in the shade), and to stay out of the midday sun between 11:00 and 15:00 (in some geographic locations between 12:00 and 15:00) and to use appropriate clothing. People deciding to sunbathe are recommended to use sunscreen, which must be applied before exposure to the sun (1). The World Health Organization (WHO) advocates reapplication of sunscreen every second hour, after swimming, and after physical activity (2). These recommendations have proven hard to follow as only about 50% of men and about 80% of women apply sunscreen at the beach in Denmark (3).

Another problem is that people use rather small amounts of sunscreen, in average about 0.5-0.6 mg/cm^2 skin, compared to the 2 mg/cm^2 which is used when the SPF of the sunscreen product is determined (3). To obtain this thickness 30-40 ml of sunscreen should be applied to cover the whole body. Even if this amount is used there is no guarantee that it is evenly distributed and there may still be areas not covered by sunscreen at all.

A rule of thumb has been introduced to make it easier to use an appropriate amount of sunscreen. The advice is: "use a handful" with the intention to increase the applied amount. However, the problem of missed skin areas is not solved by the advice. Based on this we examined if two consecutive applications of sunscreen with a 20-min interval would increase the applied amount and reduce the size of the missed areas (4).

Skin Phototype and UVR Tolerance

People with white skin have different resistance to UVR depending on pigmentation and time of year, as repeated UVR exposure leads to a thicker stratum corneum and increased pigmentation. The sensitivity to UVR is measured in standard erythema dose (SED), and the sensitivity range is 1 SED to about 12 SEDs to provoke erythema in the white-skinned European population. They will reach their minimal erythema dose (MED) when exposed to an average dose of 3-4 SEDs on previously unexposed skin. Skin phototype is most often self-assessed by the Fitzpatrick classification questionnaire in which white-skinned people are divided into four groups according to their tendency to burn, and ability to tan. However, it does not provide a clear picture of how many SEDs are needed to provoke erythema. This information can be obtained by reflectance spectroscopy (Optimize 558, Chromo-Light, Denmark), which predicts the number of SEDs needed to provoke erythema (MED). The relation between SED and MED and Fitzpatrick 's classification is seen in Table I. The range is 1.0 SED to about 8.0 SEDs on previously unexposed, constitutively pigmented skin, and about 2.0-12.0 SED on facultatively (previously exposed) pigmented skin.

UVR Exposure

Erythema-provoking, ambient, solar ultraviolet radiation measured in SED varies during the day, with maximum SED/hour around noon. In Denmark, about 50% of all daily SEDs occurs between 12:00 and 15:00 (18 SEDs in the summer). In the Mediterranean approximately 30 SED occurs during the same time interval. 25% of SED is present before 12:00 and 25% after 15:00. The maximal total daily SED in the two geographic locations are approximately 36 SEDs, and 60 SEDs, respectively (Table II). The average time spent on Danish beaches is around 3.5 h, equal to a received UVR dose of 17 SED (5). UVR doses penetrating into the skin depend on time spent outdoors, geographic location, and photoprotection (Table III). Holiday makers in the Canary Islands were exposed to UVR for approximately 6 h a day, of which 2 h are between 12:00 and 15:00, with >50% of their body surface area exposed. The average total received UVR dose during six days of vacation was 57 SEDs, measured by personal electronic dosimeters worn by each participant (6). This is somewhat lower than what can be obtained when measuring ambient sunlight directly, as seen in Table III.

When to Apply Sunscreen

It is very important to apply sunscreen prior to sunbathing or beach trips. In the middle of the day during summer in the Mediterranean area, as well as in Northern Europe, sunburn may occur after spending less than half an hour outdoors without photoprotection. Nevertheless, during their vacation in the Canary Islands 15% of the participants did not use sunscreen. Around 50% of sunbathers do not apply sunscreen until they have spent 50 min in the sun, predominantly in the mornings, having then already received about 13% (range=0-234%) of their MED before applying sunscreen (7).

A major group does not use sunscreen protection on the beach at all, for several reasons: It is greasy, expensive, because of warnings by the media about systemic absorption, possibly hormone disturbances, suppression of vitamin D formation, and even harmful effect on the blood. Another well-known reason for not using sunscreen is that people wish to tan quickly.

Table I. *SED to minimal erythema dose (MED) on previously unexposed constitutive skin, related to Fitzpatrick's skin type (28-30).*

Fitzpatrick Skin type	I	II	III	IV	V	VI
SED, mean	3	4	5.5	7.5	12	18
Range	1-7	2-8	2-9	2-12	5-21	10-25

Table II. *Total daily ambient UVR dose in SED in the winter, spring, and summer in Denmark and at 3 holiday destinations. An average Dane will suffer erythema after approximately 4 SED. Without protection the risk of sunburn is highest in the winter and the spring where the difference between SED in Denmark and at the holiday destination is most significant.*

Location	January 20th	April 20th	June 20th
Denmark	1.5	22	38
Mallorca	10	36	51
Crete	10	41	56
Canary Islands	20	47	58

SPF Depends on Sunscreen Layer Thickness

Several studies have dealt with this matter. From a physics viewpoint, the relation between SPF and sunscreen layer thickness is exponential which has also been confirmed in several human studies (8). Although it has been contested (9), we have chosen to use the exponential relation in the following. Table IV illustrates the number of SEDs penetrating into the epidermis, depending on sunscreen SPF and applied layer thickness.

Recommendation of Sunscreen Use by WHO

WHO recommend application of sunscreen every second hour, as well as after swimming and outdoor physical activity (2). This approach leads to the use of considerable amounts of sunscreen during the day, with effective photoprotection. However, the protection during the first 2 h in the sun may be rather low as it is to be expected that 20% of the body skin area will be unprotected, and, in average, only about 0.5 mg/cm^2 of sunscreen will have been applied (4). This will likely result in a considerable number of SEDs penetrating into the epidermis, as indicated in Table V. For a white-skinned European, a dose

Table III. *Expected increase in 25(OH)D when exposed at midday daily for 1 h, 3 h, or all day, on 6 successive days in midsummer at different geographic locations. Number of SED penetrating unprotected skin and skin protected by sunscreen (2 mg/cm2) of various SPF are shown. Expected increase in 25(OH)D is calculated based on Figure 1.*

Effective SPF	1 h midday per day				3 h midday per day				Whole day			
	DK		MT		DK		MT		DK		MT	
	SED	25(OH)D	SED	25(OH)D	SED	25(OH)D	SED	25(OH)D	SED	25(OH)D	SED	25(OH)D
No protection	36	29	60	33	108	33	180	33	216	33	360	33
15	2.4	13	4	16	7	19	12	23	15	24	24	27
30	1.2	8	1.8	12	4	17	6	18	7	19	12	23
50	0.6	4	1.2	9	2.4	13	3	14	4	16	7	19

DK: Denmark; MT: Mediterranean area. 25(OH)D is measured in nmol/l.

Table IV. *Shows the relation between sunscreen layer thickness and SED penetration into the epidermis after 3 h of sun exposure (30 SED ambient) in the Mediterranean area, with >50% exposed body surface area. The effective SPF is based on an exponential relation to sunscreen layer thickness. The calculation of expected 25(OH)D after one week is based on Figure 1.*

mg/cm^2	Effective SPF	SED in skin	25(OH)D increase	Effective SPF	SED in skin	25(OH)D increase	Effective SPF	SED in skin	25(OH)D increase
2	15*	2	12	30*	1	8	50*	0.6	5
1	4	7.5	20	5.5	5.5	18	7	4.3	17
0.5	2	15	24	2.3	13	23	2.7	11	22

*SPF labelled on sunscreen container. 25(OH)D is measured in nmol/l.

of more than 3-4 SEDs to the skin will lead to erythema/sunburn, which is the case in several instances, as seen in Table V. However, the repeated applications recommended by WHO may be very difficult to persuade people to perform due to the impracticability of applying sunscreen when in sandy locations, and due to the cost of buying sunscreen. Nevertheless, one study shows that many people on sun holidays apply sunscreen to certain body areas up to 3 times, with an average of 1.7 times per day (7, 10).

Use a Handful of Sunscreen

This recommendation has been popular in many countries. A handful may contain about 35 g of sunscreen, and this amount ought to provide the desired coverage of 2 mg/cm^2 for whole body application. A handful has been chosen from the point-of-view that large people have correspondingly larger hands, which will compensate for natural variations in body size. However, 35 g of sunscreen is a large amount when poured into a hand, and in real life people adhering to this advice use considerably less than 35 g, applying an average amount of less than 1 mg/cm^2, and leaving about 20% of their skin unprotected and with a high risk of sunburn. The estimated number of SED penetrating into the epidermis of the protected skin is seen in Table V. Further, this method prerequisites an instruction in how to apply sunscreens correctly.

Two Consecutive Applications of Sunscreen

To obtain the best possible protection it is important to apply sunscreen before sun exposure. Apart from the instruction to apply sunscreen twice with 20-min intervals, no educational measures are necessary. The amount used is what people prefer. This technique reduces the unprotected skin areas from 20% to 9% and increases the average amount of applied sunscreen to around 2 mg/cm^2, apart from on the back and on the back of legs (4, 11).

Table V illustrates the effectiveness of all three methods in reducing the number of SEDs penetrating into the epidermis. When the number of SEDs exceeds about 4 white-skinned Europeans risk erythema.

Durability of SPF

The need for repeated applications during the day may originate in sunscreen campaign authorities distrusting the waterproof/water-resistant product claim and/or the ability of the sunscreen to keep up its protective effect during daily

Table V. *Number of SED penetrating into the skin during 3 h of sun exposure, in the middle of the day, on 6 days of vacation in summer, as a result of 3 different sunscreen application methods. Erythema (MED) should be expected after 3-4 SED/day. 25(OH)D is measured in nmol/l. Expected increase in 25(OH)D is calculated based on Figure 1.*

Application method	Mediterranean 30 SED/day, 180 SED/week				Denmark 18 SED/day, 108 SED/week			
	SPF 15		SPF50		SPF 15		SPF 50	
	SED**	25(OH)D*	SED**	25(OH)D*	SED**	25(OH)D*	SED**	25(OH)D*
WHO	70	33	60	33	45	30	40	30
Handful	45	32	25	27	27	28	15	24
Apply twice	12	23	3.6	16	7	18	2.1	14

* No correction for unprotected areas; **Estimated number of SED penetrating into the epidermis.

physical activities. However, studies have shown that 45% of SPF is still present 8 h after application, despite sweating, bathing twice, wearing clothes, and being physically active (12) and 70% of SPF is still present 8 h after application when none of these activities have taken place (13). After just one sunscreen application of 2 mg/cm^2 a relevant effective SPF is still present at the end of the day when ambient SED/h is rapidly descending. No relevant SPF is found the next day, and reapplication is needed then. Thus, same-day reapplication may be superfluous if the sunscreen is applied properly prior to sun exposure.

Sunless Tanning Products

The active component in sunless tanning products is dihydroxyacetone, which develops a brown colour on the skin surface when it binds to proteins in the stratum corneum, and this compound absorbs UVR (14). This product can be used by self-application or as a full body spray tan in beauty clinics. It is not classified as a sunscreen but has been shown to provide an effective SPF of 2-4, reducing the risk of erythema accordingly, as well as postponing the development of squamous cell carcinoma (SCC) in UVR exposed mice (15). The protective effect of sunless tanning products diminishes slowly within a week and is well suited as a basic protection before and during sunny vacations (16).

Sunscreen and Vitamin D Formation in the Skin

The formation of vitamin D in the skin is caused by UVB alone and the process is well covered in the literature. Evidently concern has been expressed about vitamin D formation when the skin is covered by sunscreen as all sunscreens absorb UVB to protect the skin from sunburn. However, some UVB will always pass through the sunscreen and enter the epidermis where vitamin D is formed (17) (Tables III-V). In real life, even after intended full-body sunscreen application, major parts of the skin remain unprotected, contributing substantially to the increase in 25(OH)D level.

Most relations between vitamin D and UVR have been examined by measuring serum 25(OH)D and this is also the case in the materials used below, focusing on how 25(OH)D increases during sun holidays with regular use of sunscreen.

Seasonal Variations in Vitamin D Levels

In Southern Europe the daily ambient UVR dose is, theoretically, sufficiently high to maintain the 25(OH)D level during winter (18). However, very small skin areas are exposed, such as face and hands, all or in part, accounting for around 6% of the total body surface area. This may be insufficient to maintain the summer level of 25(OH)D during winter, although the receivable UVR doses may be quite high (Table II). Even though skiers on vacation in Austria only exposed 4% of their skin they still had an increase in 25(OH)D of 8.6 nmol/l, illustrating that enough environmental UVB radiation is present in March due to altitude (850 m-2680 m) and snow reflection (10).

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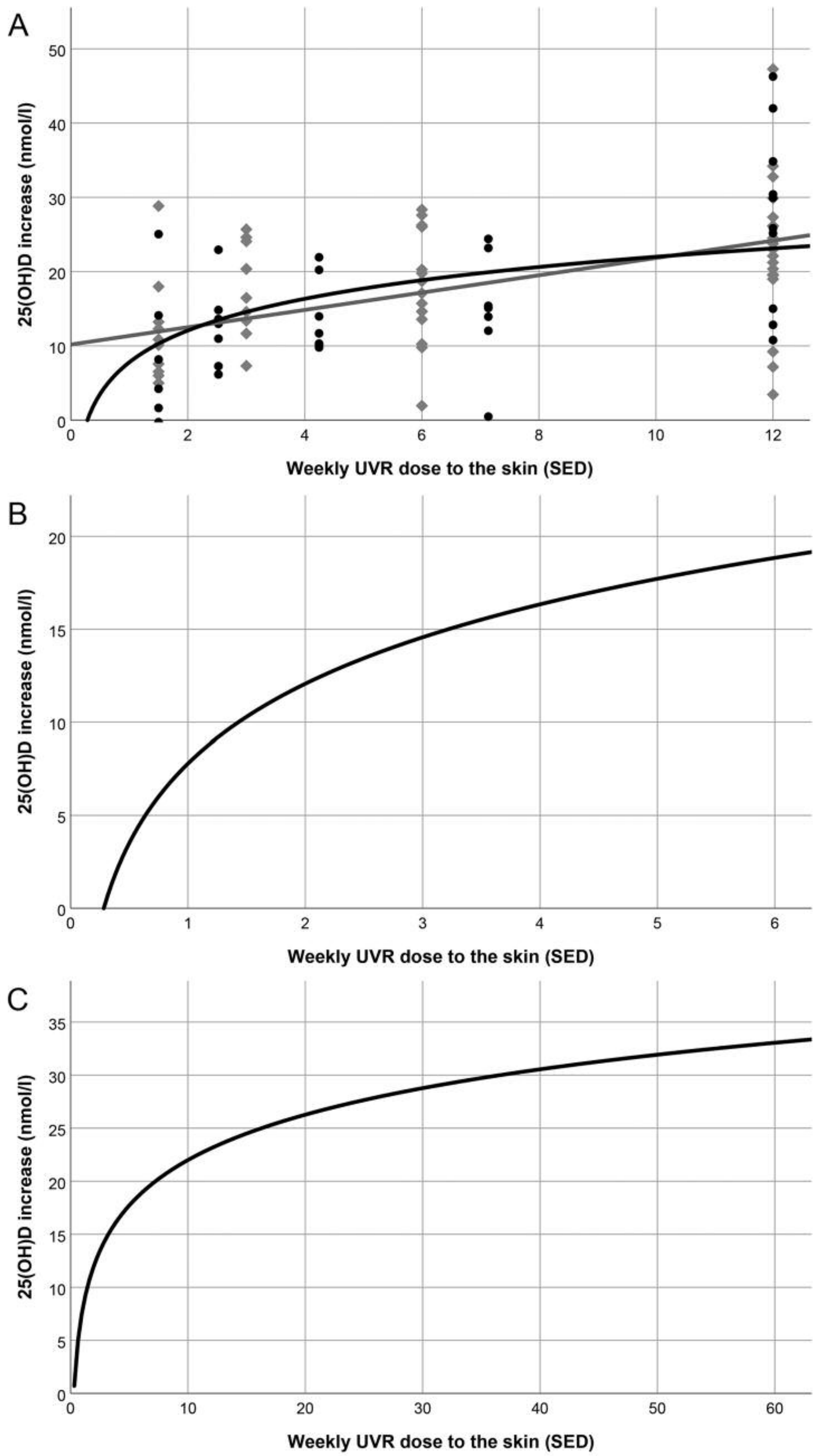
Figure 1. *The relation between weekly UVR dose in SED and the obtained 25(OH)D increase when people have been exposed on 24%/25% of the body surface area by the accumulated doses shown. A linear relation was found for the examined doses (3 SED to 12 SED), but the best fit when including smaller and larger doses is considered logarithmic. The calculations are built on material by Bogh et al. (grey squares) (22), and Faurschou et al. (black bullets) (24). In the latter, the dose is calculated assuming an exponential increase in SED dose the thinner the sunscreen layer is. No significant difference was found between the two materials which is why they are merged (p=0.99). The effect is corrected to a 25(OH)D baseline level of 39 nmol/l. A) The examined weekly dose interval showing a linear relation and a logarithmic relation. B) Suggested relation between SED and 25(OH)D for very small weekly doses. C) Suggested relation between SED and 25(OH)D for very high weekly doses. The relation follows: 25(OH)D weekly increase=7.8+14.2 × log (SED/week).*


A
B
C
25(OH)D increase (nmol/l)
Weekly UVR dose to the skin (SED)

In northern Europe the UVB level in the winter is very low (Table II), resulting in decreasing levels of serum 25(OH)D levels during the winter months. In March, the ambient UVR can keep 25(OH)D levels in steady state. Serum 25(OH)D increases during April and is pronounced in May when temperatures outside allow exposure of larger skin areas (short sleeves) and the environmental UVR increases substantially (19).

Bogh *et al*. (20) have performed a 4-month study in the winter with full-body exposure to 1 SED every week, every second week, and every fourth week and an untreated control group. No sunscreen was used in the trials. From that investigation, the following can be concluded: 0.25 SED/week cannot keep the summer level of 25(OH)D in steady-state for 16 weeks during winter; 0.5 SED/week will increase 25(OH)D levels by 5 nmol/l after 16 weeks, and 1.0 SED/week will increase 25(OH)D levels by 13 nmol/l above summer levels after 16 weeks. In this study, about 0.3 SED/week was needed to keep the summer levels. The corresponding dose found in Figure 1 was 0.28 SED/week indicating robustness of the numbers.

Vacations, Sunscreen and Vitamin D

Several longitudinal studies of sunscreen users and controls have shown similar end-of-summer levels of 25(OH)D in both groups (21), indicating that sufficient amounts of UVB pass the sunscreen barrier to form 25(OH)D, or that sunscreen is used infrequently, and/or unprotected skin areas may also contribute to this result. Generally, it indicates that very small and even irregular exposures to UVB on limited parts of the body may be sufficient to keep 25(OH)D levels increasing (20, 22, 23).

In a short-time exposure study, Faurschou *et al*. (24) examined the relation between sunscreen layer thickness and the formation of 25(OH)D. Four UVR treatments were given in approximately one week on 25% of the body area, in a total of 12 SEDs. Using a SPF 8 (2 mg/cm^2) the UVR dose penetrating the skin was 12/8=1.5 SEDs, resulting in a 25(OH)D increase of 6.4 nmol/l. When 1 mg/cm^2 was used, the effective SPF was $8^{(1.0/2.0)}$=2.83, and 12/2.83=4.24 SEDs pass into the epidermis and 11.5 nmol/l was formed. When 0.5 mg/cm^2 was used the effective SPF was $8^{(0.5/2.0)}$=1.68, and 12/1.68=7.1 SEDs penetrated the sunscreen layer and 25(OH)D levels increased by 12.5 nmol/l. When no sunscreen protection was used, 25(OH)D levels increased by 25.8 nmol/l after 12 SED. These calculations build on the assumption of an exponential relation between 25(OH)D levels and sunscreen layer thickness (11, 24). This material is included in the calculation of Figure 1. Thus, laboratory studies confirm that sunscreens diminish 25(OH)D formation; the thicker the sunscreen layer, the lower the formation (24).

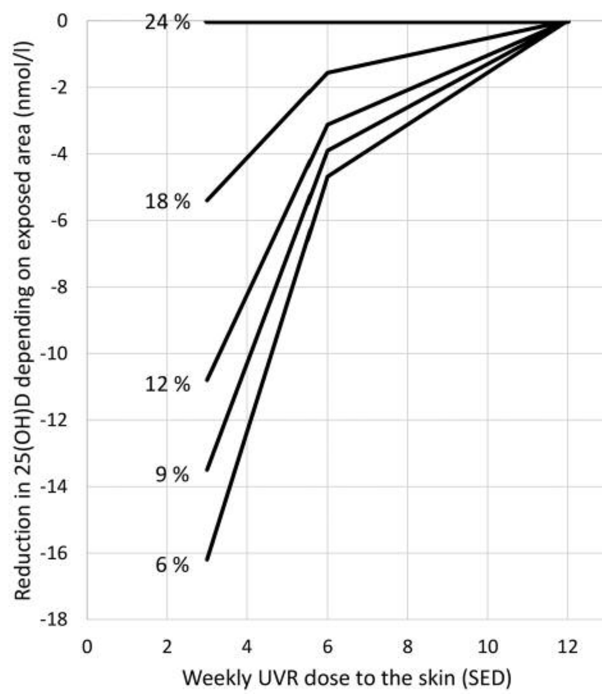


Figure 2. *The reduction in 25(OH)D after one week's exposure to different SED doses on different body surface areas (6%, 9%, 12%, and 18%) relative to that produced by 24% body surface area exposure. The relations are calculated based on material by Bogh et al. (23).*

The increase in 25(OH)D levels after one week with four treatments applied over 24% of the total body surface, administered in weekly doses of 12 SEDs, 6 SEDs, 3 SEDs, and 1.5 SEDs (22), showed a curve not significantly different (p=0.99) from the sunscreen experiment where the 25(OH)D was expected to increase exponentially with decreasing thickness of sunscreen layer and confirm this relation (Figure 1) (24). Data from both materials are considered in the calculation of Figure 1 and used for the estimations of 25(OH)D in Tables III, IV, and V.

Small Area Exposure

Bogh *et al*. (23) performed a study where in approximately one week four UVR exposures were given to different skin areas on 6% to 24% of the total body surface. The effect on 25(OH)D was compared between 6% and the effect on 24% of body area and is shown in Figure 2. Twelve SEDs/week or more gave an equal 25(OH)D effect, independent of exposed skin areas from 6% up to 24% (Figure 2). For each dose, every time the exposed body area increased by 6%, from 6% to 24%, the 25(OH)D level increased linearly. On vacations the exposed areas and the weekly doses will nearly always exceed that which is relevant for the use of the data in Figure 2.

Vitamin D and Uncovered Areas

A single sunscreen application leaves 20% of the body surface area unprotected. After two consecutive applications of sunscreen 9% of the skin is left unprotected. This is important as the unprotected skin areas play a major role in the increase in 25(OH)D. These areas are large enough to ensure a 25(OH)D increase of about 33 nmol/l after one week of summer sun exposure, independent of the sunscreen cover on the rest of the body (Figure 1).

Calculations of 25(OH)D Formation When Using Sunscreen

In the following, the subject of 25(OH)D formation under different photoprotection circumstances is estimated, assuming the whole body is covered by sunscreen with no unprotected areas, and a maximal weekly exposure dose of 60 SEDs, independent of the ambient UVR level. Exceeding 60 SEDs will provoke heavy sunburn in unprotected skin, and this dose is probably rarely exceeded. As UVR intensity does not seem to be of relevance for 25(OH)D formation, only UVR dose is taken into consideration (22). Vitamin D consumption is relevant when considering how to avoid a 25(OH)D decrease over extended periods of time, but not during one week of vacation (20, 25). The discussion of the importance of sunscreen for the formation of 25(OH)D is mainly relevant during vacations where sunscreen is frequently used (Tables III, IV, V).

Based on these assumptions, we calculated the expected 25(OH)D increase and the ambient SED expected to penetrate into the epidermis after approximately one week of UVR exposure. The following factors, crucial to 25(OH) D formation, are taken into consideration:

1. Skin phototype consideration is unnecessary (26).
2. Exposing more than 25% of the body surface area does not significantly increase the level of 25(OH)D.
3. 25(OH)D increases exponentially with decreasing thickness of sunscreen layer.
4. 25(OH)D increases for all doses between 3 SEDs and 12 SEDs for exposed areas of 6% to 24% (Figure 2).
5. Skin areas devoid of sunscreen photoprotection (missed areas) are not considered in Tables III, IV, and V, where the 25(OH)D level is calculated using the data from Figure 1.

As seen in Tables III-V, the estimated increase in 25(OH)D is high, even if unprotected areas are excluded from the calculations. This is mainly due to the very high ambient UVR doses that people may receive on large body areas during sun holidays. Our results are in accordance with measurements on people having spent their holiday in the Mediterranean area (10, 27).

Young *et al*. (27) have shown that repeated high amounts of sunscreen can totally abolish erythema on a one-week sun holiday in Tenerife. The amount of sunscreen (SPF 18) applied to the skin was at least 2 mg/cm2. The individuals were exposed to 43 SEDs in average, and 43:18 ~ 2.4 SEDs may have passed into the skin providing a measured increase in 25(OH)D level of 20 nmol/l. This is even higher than the increase of 13 nmol/l expected from Figure 1B.

During a one-week vacation in Tenerife, Petersen *et al*. (10) found that sun-seekers increased their 25(OH)D levels by 21.5 nmol/l, despite the use of sunscreen.

Both studies have shown a clear increase in 25(OH)D levels despite the use of sunscreens. When evaluating the calculated numbers in Tables III, IV, and V, it is important to keep in mind that UVR exposure under natural circumstances is less consistent than what is obtainable under laboratory conditions, which is also shown by Datta *et al*. (19). Nevertheless, 25(OH)D increases substantially during sun holidays with intensive use of sunscreen (17).

It is important to remember that the presented data build on group averages, although the individual 25(OH)D formation is highly variable, as seen in Figure 1A.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Hans Christian Wulf has contributed with the article text. Peter Alshede Philipsen has contributed with figures, and statistical calculations.

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