Objective determination of Fitzpatrick skin type

- in relation to minimum erythema dose, minimal melanogenic dose, constitutive and facultative pigmentation after single and multiple UV-exposures to different wavelengths

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I. Henriksen M, Na R, Aagren MS, Wulf HC. Minimal Erythema Dose after multiple UV-exposures depends on pre-exposure skin pigmentation. Photodermatol Photoimmunol Photomed 2004: 20: 163-169.

II. Ravnbak MH and Wulf HC. Pigmentation after single and multiple UV-exposures depending on UV-spectrum. Arch Dermatol Res 2007: 299: 25-32.

III. Ravnbak MH, Philipsen PA, Wiegell SR and Wulf HC. Skin Pigmentation kinetics after UVB exposure. Acta Derm Venereol 2008: 88: 223-228.

IV. Ravnbak MH, Philipsen PA, Wiegell SR and Wulf HC. Skin Pigmentation kinetics after exposure to ultraviolet A. Acta Derm Venereol 2009: 89 (4): 357-363.

ABBREVIATIONS AND DEFINITIONS

BCC: Basal cell carcinoma
bUVA: Broadband UVA
CIE: Commission Internationale de l'Éclairage (the International Commission on illumination)
CMM: Cutaneous malignant melanoma
Constitutive pigmentation: Skin pigmentation in previously un-exposed skin (e.g. nates)
Facultative pigmentation: Skin pigmentation in previously exposed skin
J Joule
MED: Minimal Erythema Dose, the UV dose to elicit just perceptible erythema 24 hours after UV-exposure
MMD: Minimal Melanogenic Dose, the UV dose to elicit just perceptible pigmentation. Evaluated 7 days after a single UV-exposure. When multiple exposures were performed, MMD was evaluated 7 days after the last exposure.
nm: Nanometer = 10-9m
nUVB: Narrowband UVB
PPF: Pigment protection factor, numbers of SED to 1 MED
SED: Standard Erythema Dose, the UV dose that elicits just perceptible erythema in the most sensitive people in a group of very sun-sensitive, but otherwise healthy individuals. One SED is defined as 100 J/m2 (= 10 mJ/cm2) at 298 nm using CIE erythema action spectrum
Skin cancer: SCC (spinocellular carcinoma) and BCC
Solar: Solar Simulator
UVA: Long-wave ultraviolet radiation (321-400 nm)
UVA1: Long-wave UVA (341-400 nm)
UVB: Mid-wave ultraviolet radiation (281-320 nm)
UVC: Short-wave ultraviolet radiation (100-280 nm)
UVR: Ultraviolet radiation (100-400 nm)

BACKGROUND

INTRODUCTION

The Fitzpatrick skin typing system was created in 1975 for predicting skin reactivity in PUVA photochemotherapy (1). Since the Fitzpatrick classification of skin type has been used world wide to estimate the risk of skin cancer (basal cell carcinoma (BCC)(2-5) and cutaneous malignant melanoma (CMM) (5-10).

This self-reported skin type is determined by the use of a questionnaire, where the person grades his/her tendency to burn and ability to tan respectively 24 hours and 7 days after the first un-protected sun-exposure in the early summer. Defined by Fitzpatrick as "an initial sun exposure, ie, to three 3 MED exposures or about 45 to 60 minutes of noon exposure in northern (20º to 45º) latitudes in the early summer, equivalent to 90 mJ/cm2" (defined as 2 hours at noontime in May in Denmark). There are four possible answers for "white"-skinned persons (skin type I, II, III, IV)(table 1). Brown skin is classified as skin type V and black skin as skin type VI (1).

Table 1. Fitzpatrick skin type classification system for self-assessment of sun sensivity

Skin type	Erthema and tanning reactions to first sun exposure in early summer
I	Allways burn, never tan
II	Usually burn, tan less than average (with difficulty)
III	Sometimes mild burn, tan about average
IV	Rarely burn, tan more than average (with ease)
V	(Brown-skinned persons)
VI	(Black-skinned persons)

Classification is based on what a person recalls as his typical reaction to 2 hours* (in Denmark) of unprotected sun exposure first time in the summer. The system has 4 grades for Caucasians and 2 grades for brown- and black-skinned persons (1). *2 hours of sun exposure from noon to 2 pm on the first sunny day in May in 2006 gave 7.7 standard erythema doses (SED). The highest dose in May was 8.1 SED. This was measured on the roof at Bispebjerg Hospital, Copenhagen, by 501 UV-Biometer (Solar Light Co. Inc., Philadelphia, PA, USA).

This skin type concept was based on responses in "white" skin. Later brown skin was divided into 3 groups; skin type IV for light brown, skin type V for brown skin and skin type VI for dark brown/ black skin (11).

Skin type is a historical expression of the recalled individual sun-sensitivity assessed in two ways:

1) the acute effect - erythema

2) the induced pigmentation

These are different effects of UV radiation, which enter into the description of a person's sun-sensitivity. The question of erythema is one way of expressing the sun-sensitivity and the question of pigmentation gives information of the protection capacity of the skin upon UVR. It may be difficult for persons to combine the answers to one skin type in the Fitzpatrick system.

The golden standard for determining the skin's UV sensitivity is a phototest with a Solar Simulator. The skin is exposed to a series of increasing doses of UV with increments of 25-45 % and the resulting erythema reactions are assessed visually 20-24 hour post-exposure (12-15), whereby the minimal erythema dose (MED) can be determined.

Although a number of studies have recorded significant differences in skin reactivity to UVB or Solar Simulated light between groups of different skin types (11, 16-21), other studies have found that skin type is not synonymous to objectively measured UV-dose to elicit erythema (22-34). Rampen et al found that the self-reported tanning ability showed a better correlation with skin complexion characteristics than the self-reported burning tendency (24).

Despite of the disagreement in the litterature on the relation between erythema and skin type and the in some studies reported doubtful erythema parameter, skin type is still a significant risk factor for development of skin cancer. This could indicate that people mainly pay attention to the question of the ability to tan, when they recall their sun sensitivity. Hereby indicating that skin type, with regard to the skin's reaction to UVR, may represent the individual tanning ability or lack of it. It might therefore be the lack of tanning ability that is a risk factor for development of skin cancer. We therefore found it important to include clinically determined tanning ability (MMD) in the description of skin type.

Fitzpatrick's (1) skin type evaluation is easy to use, but has several limitations and has been criticized scientifically (24, 27, 29, 33). A validated objective alternative has been sought to replace the subjective Fitzpatrick skin type in predicting constitutive UV-sensitivity, and so far Pigment proctection factor (PPF) calculated from skin reflectance measurements of the pigmentation (35) is a noteworthy attempt (29). PPF indicates how easily a person will sunburn and how much the pigmentation protects by predicting the number of SED to 1 MED. Until now PPF has only been used for prediction of MED and not the pigmentation response (MMD). Despite the lack of documentation of which reaction skin type represents in scientific terms, self-reported skin type is still used extensively in epidemiological surveys of skin cancer and in other research of sun related skin diseases. The discrepancies between self-reported skin type and objective measurements of UV-sensitivity, the repeatedly reported association between skin type and risk for skin cancer together with the importance of skin type in epidemiological skin cancer research, therefore in our opinion merited further investigation to clarify what skin type actually represents with regard to the skin's reaction to UVR. This was the background for this Ph.d. study.

The approach was to investigate the subjective Fitzpatrick skin type and the measured skin type PPF (pigment protection factor) parallelly in relation to the clinically determined dose to erythema (MED) and/or pigmentation (MMD) on nates/back (constitutive/facultative pigmentation) to determine which one related best after single and multiple UV-exposures to different wavelengths.

Fitzpatrick skin type in the epidemiological context (risk for skin cancer) may stand for burns and ability to tan may represent "cumulative" dose. PPF indicates how easily a person will sunburn and how much the pigmentation protects by predicting the number of SED to MED. In our study PPF or SED to MED is equivalent to burns. PPF may also indirectly represent cumulative dose – the less pigmented skin the more UVR is able to penetrate the epidermis and accumulate.

But obviously cumulative dose is also dependent on the extent of the UV-exposure, which is highly individual and lies beyond the scope of this study.

Most of the knowledge on UV sensitivity in humans is derived from investigations of erythema response after a single UV-exposure (i.e. 16, 21, 26, 28, 29, 30, 32, 34, 36-41), or to a lesser extent pigmentation after a single UV-exposure (i.e., 26, 28, 36-38, 40, 42, 43).

So far only few studies have investigated the erythema and/or pigmentation response following multiple UV-exposures in relation to skin type (i.e. 21, 22, 44, 45), these studies are performed in volunteers with a narrow range of pigmentation e.g. skin type II and III.

Earlier there has been no attempt to objectify skin type determination by measuring both the UV-dose to elicit erythema and the ability to tan and the ability to tan after multiple UV-exposures in volunteers with a broad range of pigmentation. As the response to repeated exposures is more relevant to the "daily-life" situation it may be more closely related to people's assessment of skin type.

First some background information is given on problems concerning the Fitzpatrick skin type evaluation, PPF, ultraviolet radiation, clinical evaluation of erythema, standard erythema dose, photoprotection, skin pigmentation and regional differences in UV-sensitivity.

PROBLEMS CONCERNING THE FITZPATRICK SKIN TYPE EVALUATION

Low reproducibility and limited number of classes are some of the problems associated with the skin type evaluation. Instead of only 4 combinations of tendency to burn and following ability to tan, ideally there should have been 16 possible answers (4 x 4).

Volunteers often mention that none of the 4 combinations of burning tendency and tanning ability meet their personal assessment of sun sensitivity and they have to choose a category fitting only with one of the two sun sensitivity parameters (24, 27). Rampen et al questioned 790 fair-skinned persons separately on burning tendency and tanning ability. Afterwards they combined the answers and found that only 41% were classifiable according to the original skin type scheme, table 1 (24).

Recall errors are frequent, in example only two of three persons were classified in the same class by repeated questioning after some months (29).

Another example is the observation of a shift towards reporting a reduced ability to tan after being diagnosed with CMM compared to reporting before they experienced the CMM (46). Skin cancer cases reported to be more sun sensitive than controls, but did not differ from controls in objectively tested sun sensitivity (5). A controversy thus exists between subjective evaluations of sun sensitivity and objective measurements. It can therefore be speculated whether the often reported differences in self assessed sun sensitivity between skin cancer cases and controls are partly due to recall bias.

The relation between self-assessed skin type and objectively measured sun sensitivity by phototest (MED) is, as mentioned, also doubtful. Several phototest studies found self-assessed skin type unable to classify volunteers reliably according to their MED (23-27, 29-34). Generally, MED tended to increase with increasing skin type, but the range of MEDs within each skin type group was broad and with considerable overlap between different skin types. The range of UV doses to induce just perceptible erythema (29) and erythema with a well demarcated border (31) on the buttocks was almost identical for skin type I, II and III. These data indicate that skin type is unreliable to predict an individuals constitutive UV-sensitivity.

In clinical practice there is consensus that, if Fitzpatrick skin type should be constant throughout life it must be based on sun-sensitivity on nates (constitutive pigmentation), but that is probably not what people consider, when they answer. However, it is not specified in the Fitzpatrick classification, which skin site the sunburning and tanning reaction refers to, nor can information about this be found in the literature (47).

Facultative pigmentation (back) was better correlated to skin type and MED than constitutive pigmentation in a Thai population (skin types III, IV, V)(28). This suggests that it is likely, that people refer to sun sensitivity on the back, when they recall their first sun exposure in early summer. Accordingly, the pigmentation in exposed skin increased slightly from skin type I to IV, but the relation between skin type and pigmentation was poor due to extensive overlapping (26, 48).

For the constitutive pigmentation skin type I and skin type II had nearly similar pigmentation and skin type III and IV had nearly similar pigmentation too (48). Thus, Fitzpatrick skin type could not classify individual volunteers reliably according to their constitutive or facultative skin pigmentation (26, 28, 48).

Moreover to most people it may seem difficult to imagine that it concerns the reaction after only one exposure. Probably their answers reflect repeated exposures such as on a sunny holiday. Therefore we exposed 2 and 4 times per week during 3 weeks in study II so steady-state pigmentation was reached.

Lightly pigmented Scandinavians like the Danes have a low natural photoprotection and could be expected to indicate themselves as sun sensitive. However, in a Danish population sample 41% of the volunteers stated that they were skin type III or IV (48) and thus indicated that they only sometimes or rarely experienced sunburns. This raises the question of which skin reaction is perceived as a sunburn by non-professionals and of self-assessed erythema contra assessment by professionals. To the professional, erythema on the day following sun exposure is a sunburn, but many non-professionals only associate sunburns with painful reactions and erythema without pain or soreness often go unnoticed (24, 47).

Considering the description of “tan less than average”, “tan about average” and “tan more than average” in the skin type categories (table 1), it can be speculated whether skin type will provide consistent results in populations with different tanning abilities such as lightly pigmented Scandinavians versus more pigmented populations in e.g. the South of Europe or in Asian countries. The average tan of a typical Mediterranean person, a Korean or an Inuit is certainly different from the average tan of a typical Scandinavian (41, 47, 49-51).

Another confounding issue is the fact that the Fitzpatrick classification does not quantify the degrees of burning or tanning but rather their frequencies (always burn, never tan etc.). These two variables are not necessarily synonymous (24).

PIGMENT PROTECTION FACTOR (PPF)

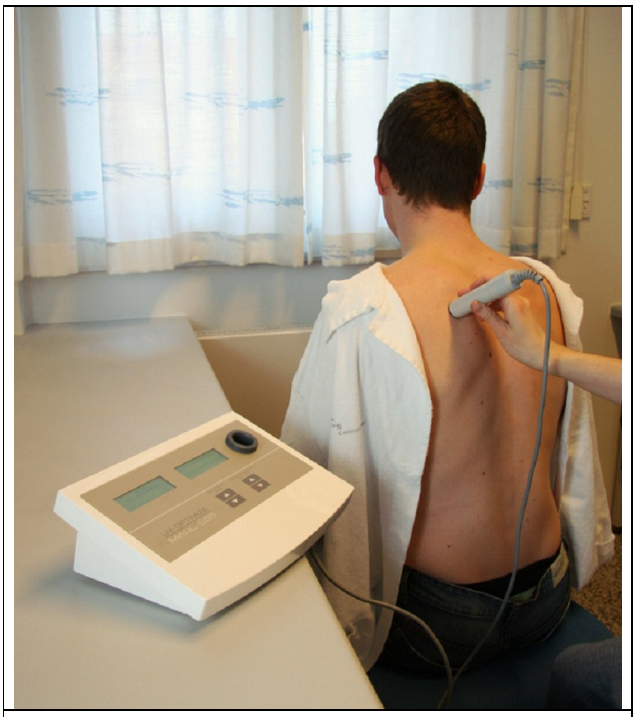

Figure 1
The UV-Optimize.

We used a skin reflectance measurement system, the UV-Optimize (UV-Optimize 555, Matic, Nærum, Denmark)(fig. 1) that in few seconds measures skin erythema and skin pigmentation independently and correlates these measurements to the UV sensitivity determined by a MED test performed with a broad-band UVB-source (Philips TL12)(35). The pigment protection factor (PPF) is calculated to predict the UV dose (SED) to produce 1 MED on nates. Hence, PPF is a value for the photo-protection provided by the nates pigmentation, the constitutive UV-sensitivity.

But PPF can as well be used for facultative pigmentation on the back (52). The PPF is well investigated and predicts the MED well (29, 35, 52, 53). Thus PPF estimates well both the constitutive and the facultative UV sensitivity, when erythema is the endpoint. In the most fair-skinned individuals the PPF is 1 (1 MED is provoked by 1 SED). PPF has been used as a substitute for the subjective Fitzpatrick skin type in an attempt to determine an objective skin type (29, 48) with erythema as endpoint.

ULTRAVIOLET RADIATION AND EXPOSURE

Ultraviolet radiation (UVR) is electromagnetic energy emitted by the sun and some artificial sources. UVR is arbitrarily divided into three bands: UVA (321-400 nm), UVB (281-320 nm) and UVC (100-280 nm). UVA is further subdivided into UVA1 (341-400 nm) and UVA2 (321-340 nm).

The intensity of solar UVR reaching the surface of the earth depends on several factors: solar altitude, latitude, clouds, ozone levels and ground reflection (54). The atmosphere of the earth, and in particular the ozone layer in the stratosphere, is filtering the UVR reaching the surface. UVC is completely absorbed, UVB is partly absorbed while UVA is only minimally affected. The erythemal efficacy of UVR is strongly dependent on wavelengths. The effectiveness of different wavelengths to induce erythema is expressed in the erythema action spectrum (Commision Internationale de l'Eclairage (CIE)).

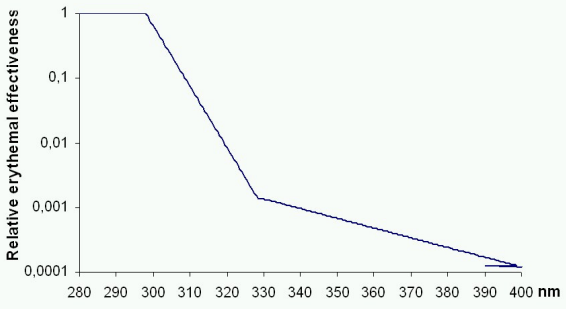

Figure 2
The CIE-erythema action spectrum

The CIE erythema action spectrum (fig. 2) clearly shows that the erythemal efficiency varies hugely through the UV-spectrum. When SED is calculated/measured, the UVR at 400 nm only counts 1/10.000 of the UVR at 300 nm, and UVR at 325 nm only counts about 1/1000 of UVR at 300 nm (55). At noon during summer the spectrum of the sun begins at approximately 294 nm, while it begins at approximately 307 nm during the winter. Thus, the total number of SED in December and January together is lower than SED during one bright summerday (50). Apart from the direct UVR the reflection influences the dose, especially when on the sea or in the snow (56). 50 % of the daily UVR dose is received between noon and 3 pm (57) hence the advice to stay out of the sun this time of the day.

Human exposure to UVR is mainly due to recreational or occupational exposure to natural sunlight, but exposure to artificial UVR such as industrial UVR sources, phototherapy and tanning beds also plays a role.

ULTRAVIOLET RADIATION AND THE SKIN

Although UVR has some beneficial effects to humans such as stimulation of vitamin D synthesis, most evidence indicates that UV is predominantly toxic to human skin and health (58). The adverse acute effects of UV exposure are sunburns (erythema), keratitis, skin diseases and immunosuppression while long term effects are premature skin ageing, pre-malignant and malignant skin lesions and possibly also cataract, (58, 59). Both UVA and UVB are classified as probably carcinogenic (group 2A) to humans (60).

Depending on the optical properties of the skin, a minor amount of the UVR is reflected from the surface of the stratum corneum (about 5%) or scattered in the epidermis (about 10%)(61). The remaining UVR is absorbed in melanin and other molecules and can cause structural cell damage (61).

The depth of the penetration into the skin of the UVR is wavelength dependent. UVA penetrates deeper than UVB, which only minimally passes the epidermis. The biological effects of UVR are therefore wavelength dependent. Therefore we chose to use different UV-sources with different wavelengths in the UVB and the UVA spectrum.

In fair-skinned persons with skin type II and III multiple exposures with sub-erythemogenic UVA-doses induce pigmentation, whereas exposure to sub-erythemogenic UVB doses does not induce pigmentation (45). In skin types II and III UVA proved to be more melanogenic than erythemogenic, as evidenced by MMD/MED < 1.0, whereas the opposite was true for UVB (44). Due to this relation we chose not to investigate MED after UVA exposure, as this would have required very long time of exposure in the most darkskinned volunteers.

CLINICAL ASSESSMENT OF ERYTHEMA

In all the studies erythema was classified clinically on a 5 point visual scale by the same observer approximately 24 hours after irradiation on a 5 point visual scale:

0	no erythema
(+)	just perceptible erythema in all or most of the area without a clear demarcation
+	erythema with a well demarcated border
++	bright red erythema with palpable induration of the reaction
+++	bright red erythema with edema raised above the adjacent non-irradiated skin.

STANDARD ERYTHEMA DOSE

There has been some confusion about the term minimal erythema dose (MED). MED has been used in two different ways; as the minimal ultraviolet energy necessary to elicit erythema of the skin and as a measure of the erythema potential of a UV source such as the sun or a UV treatment lamp (62). Fitzpatrick used the latter, when he defined skin type as the response to 3 MEDs (1). Therefore it was proposed on the 12th International Congress on Photobiology in 1996 that the erythema activity of a UV source should be measured in standard erythema dose (SED) (62, 63) and that was accepted by the CIE (64).

It has been proposed that one SED should be defined as the UV dose that elicits just perceptible erythema in the most sensitive persons in a group of very sun-sensitive but otherwise healthy individuals (10 mJ/cm2 at 298 nm using the CIE action spectrum) (65). In Denmark, one SED is equivalent to the dose received by approximately 10 minutes of sun exposure at noon on a clear and sunny day in July. In our studies UV doses were expressed in SED.

PHOTOPROTECTION

The epidermis protects the individual against a range of harmful environmental agents. For protection purposes it may be divided into an outer horny layer, the stratum corneum, and the viable epidermis where we find the keratinocytes and the melanocytes.

Absorption and scattering of UVR in keratin and other components in the stratum corneum reduce the amount of UV reaching the viable cells in the basal layer of epidermis (61, 66, 67) and accordingly the thickness of stratum corneum is important for photoprotection (66, 68).

Acclimatization or protective adaptation implies tolerance to solar radiation or a significant increase in the MED (69). Invariably it has been assumed that such protection is a result of increases in epidermal melanin. However, there are many other reasons for increased tolerance such as changes in the distribution of epidermal melanin pigmentation and increased UVB attenuation by thickening of the stratum corneum. The latter changes result from increased proliferation of keratinocytes in UV-irradiated skin (43, 70). The UV-induced increasing proliferation of keratinocytes (thickening of the stratum corneum) is wavelength dependent. UVB exposure provokes proliferative response in keratinocytes resulting in photoprotection by thickening of stratum corneum. UVA does not thicken stratum corneum. Bech-Thomsen and Wulf calculated how much of the achieved photo-protection that was caused by skin pigmentation and how much was caused mainly by increased epidermal thickness. In test sites exposed to UVA-sources with a low output of UVB, 63-95% of the increased photoprotection could be explained by increased pigmentation. In test sites exposed to UVB-sources, 6-11 % of the increased photoprotection could be explained by melanogenesis (53).

The skin pigmentation and the stratum corneum are the two major natural protection factors against UV-damage. Apart from Albinos and humans with vitiligo, the skin pigmentation is generally regarded as the most important photoprotection factor in Caucasians with normal skin (15, 71).

Epidermal UVR transmission was quantified in black skin (skin type VI) and Caucasian skin (skin types I, II and III). On average five times as much UVR reaches the upper dermis of Caucasians as reaches that of blacks (71). However, samples were taken from previously sun-exposed sites (abdominal skin) and we know that stratum corneum can modulate the UV sensitivity considerably in exposed skin (53).

For the same UV-dose the significance of stratum corneum in photoprotection may be greater in fair-skinned individuals than in pigmented individuals, and especially in albino or vitiliginous skin where the stratum corneum may represent the only source of protection and thereby become the determining factor for the UV sensitivity (72).

SKIN PIGMENTATION

The melanocytes synthesize melanin by stepwise oxidation of tyrosine and incorporate it into organelles (melanosomes)(73). In the keratinocytes the melanosomes of black-skinned persons are singly dispersed, whereas they are aggregated in groups in fair-skinned persons and Orientals. The superior photo-protection of black epidermis is due not only to increased melanin content, but also to the distribution of the melanosomes, which appears to be important with regard to skin colour and photoprotection (47, 71, 74). The larger and more melanized melanosomes of black-skinned persons adsorb and scatter more energy, thus providing a higher photoprotection (75). Apart from the amount of melanin, the skin colour is also influenced by other pigments such as hemoglobine and carotene. Normally, the carotene content of the skin is minimal and the main chromophores to be considered for measurements of skin colour are melanin and hemoglobin (35, 76).

Much of the work to date on natural photoprotection is based on constitutive pigmentation. Black albinos have a much greater risk of non-melanoma skin cancer than the normal population (77). Thus, evidently constitutively pigmented skin is more resistant to acute and chronic damage (sunburn and skin cancer) of repeated sun exposure than fair skin (71). This photoprotective role of melanin is well documented (i.e. 37, 61, 70, 71, 75, 78). However, globally the prevalence of malignant melanoma in albinism remains relatively rare and the increase in fair-skinned Caucasians is not replicated in Negroid albinos, despite the fact that by the age of ten solar elastosis is a universal occurrence in albinos living in the tropics (79).

A close correlation is also reported between UV-sensitivity and degree of constitutive pigmentation tested by a single UV-exposure and skin pigmentation is the most important factor for MED (i.e. 26, 38, 52, 80, 81). Others do not find this correlation (16). The UV-Optimize reflectance system offers measurements of the constitutive UV-sensitivity on a scale with 240 steps, where pigmentation protection factor (PPF) is based on the range of 1-25 SED to give 1 MED from the most white-skinned to the most black-skinned persons (25 SED represents a theoretical value of no reflection at all)(35). In skin type I-III/IV a range of approximately 1-10 SED (90 steps) covers the constitutive UV-sensitivity (35). In our group of volunteers, skin types I-V, the max. PPF-value was 19, yet the first 180 steps cover the range of UV sensitivity found.

The extent of the protection offered by the constitutive pigmentation is variable depending on the biological end point chosen. In terms of MED, the protection reaches a maximum value of 10-15 for very black individuals, whereas for Hispanics, Kuwaitis or dark Mediterraneans it reaches a value of 2.5 (70). However in terms of skin cancer the protection is substantial: a factor of 5-10 for Hispanics and a factor of 500-1000 for dark blacks, with “an average light-skinned white subject” stated as the reference for these ratios for MED and skin cancer (70).

There are two different tanning reactions: Immediate pigment darkening (IPD) and delayed tanning (74). IPD is a temporary darkening observed immediately after exposure to UVA or visible light and is due to a re-distribution within the keratinocytes of pre-existing melanin (82). IPD fades within minutes or hours and is mainly seen in darker skin types (19). The biological role of IPD remains poorly understood. Delayed tanning is due to an increased neo-synthesis of melanin induced by UVB and UVA (74, 82). IPD has no practical significance in this study, as pigmentation and erythema never was evaluated less than approximately 24 hours after UV-exposure.

It has been suggested that the pheomelanin/ eumelanin ratio of the skin might be a use-ful indicator of skin cancer risk (83). Pheomelanin is less photo-protective than eumelanin, and by UV exposure generates free radicals with a carcino-genic potential. Eumelanin in cultured human melanocytes, but not always pheomelanin, consistently correlates with the visual phenotype and lighter melanocytes tend to be more pheomelanic in composition than darker melanocytes (84), suggesting that the pheomelanin/ eumelanin ratio differs within different skin types.

REGIONAL DIFFERENCES IN UVR SENSITIVITY

There are many variables to consider when studying the effect of UVR on the skin. It can therefore often be difficult to com-

pare directly the results of studies from different centers. For instance, regional differences in UVR sensitivity must be considered as the UVR sensitivity varies between body sites on the same person. Recently striking differences in erythemal sensitivity (MED) of up to 5-fold at different body sites to the same challenge dose was reported in a UK-population. Site variation was just as important as between-person variation. The chest and the upper back appeared to be most susceptible and the legs the least sensitive to UVB (85). In addition, the skin on the back is more sensitive to UVR than the buttock skin (52, 86).

The reasons for these body site variations are not completely understood but may be due to within-person variations in stratum corneum/epidermis thickness and site-specific variation in pigmentation (87) and may also be due to variations in blood flow (86).

PURPOSE

With the great significance of the Fitzpatrick skin type as a risk factor for skin cancer kept in mind, together with the reported problems connected to this self reported skin type and the lack of knowledge of what Fitzpatrick skin type actually represents with regard to the skin's objective reaction to sunlight, the overall aim of the performed studies was thus:

To clarify what the subjective Fitzpatrick skin type actually represents with regard to the skin's reaction to UVR.

METHODS TO REACH THE AIM

The approach was to investigate the subjective Fitzpatrick skin type and the measured skin type PPF (pigment protection factor) parallelly in relation to the clinically determined dose to erythema (MED) and/or pigmentation (MMD) to find which one related best after single and multiple UV-exposures to different wavelengths. Moreover, to determine which UV-source should be used for objective skin type determination.

Finally, based on these parameters we tried to predict the Fitzpatrick skin type by multinominal logistic regression analyses to evaluate the significance of the different parameters for the subjective skin type classification and thereby enlighten what Fitzpatrick skin type represents. Likewise we tried to predict PPF based on Fitzpatrick skin type, SED to MED and/or SED to MMD.

Volunteers with a wide variation in constitutive pigmentation were selected (skin types I-V). In the 3 performed studies erythema response and tanning ability were evaluated clinically and tanning also instrumentally by skin reflectance after single and multiple UV-exposures and related to Fitzpatrick skin type and PPF (the measured skin type) to determine which of the two skin type concepts was best related to clinically determined UV-sensitivity (MED and MMD). By UV-Optimize measurements PPF was calculated before the first UV-exposure on nates/back (constitutive versus facultative pigmentation) and therefore represented the photoprotection provided by the pre-exposure pigmentation of the skin in the test areas.

We investigated if the relation between SED to MMD and skin type/PPF was dependent on wavelength to determine which UV-source should be used for objective skin type determination.

In two of the studies 5 consecutive UV-exposures were performed (Papers I, II).

Pigmentation did not reach steady-state level after 5 UV-exposures, therefore to come closer to a "daily life" situation study II was performed. In this study pigmentation reached steady-state level after a total of 6 or 12 UV-exposures (2 or 4 consecutive exposures per week during 3 weeks). Besides SED to MMD also the absolute increase in pigmentation was determined as an expression of tanning ability and related to Fitzpatrick skin type/PPF, wavelength and number of UV-exposures.

MATERIAL AND METHODS

STUDY DESIGN

Three studies were performed (Table 2). Study I is described in details in papers I, II, and study II is described in papers III, IV. Twelve volunteers (7 Scandinavians and 5 Indians) participated in both project I and II. Study III is described below.

Study III (skin type I)

Volunteers

Study III took place outside the summer with the same conditions as in papers II, III, IV. Ten fair-skinned healthy volunteers of ethnic Danish origin, 5 females and 5 males, aged between 20 and 59 years (mean age 30 years) were recruited. All volunteers had self-assessed skin type I. The definition of skin type I ("always burn, never tan" after the first sun exposure in early summer) makes the MMD determination after a single exposure a challenge in this group. Nonetheless it is important to investigate objective reactions to single and multiple UV-exposures in this group in particular according to their increased risk profile regard-

Table 2**. Overview of the three studies on 84 persons: Data is given on volunteers, UV-sources and anatomical location of UV-exposures**

Study	Number of volunteers and UV-exposures (back)		UV-sources		Nationality	Skin types Mean age (range) Female/male
	Single exposure	Multiple exposures	Single expoure nates	Single/multiple exposures back		
I	**62**	**49-52** **5 exp.***	**Solar**	**nUVB** **Solar** **bUVA** **UVA1**	Scandinavians Hispanics Asians: Koreans, Chinese, Vietnamese Indians/Pakistani	**II-V** **25 years (19-44)** **Single exp.: 34** **F/28M**
II	**24**	**24** **6 and 12 exp.**	**Solar**	**nUVB** **Solar** **bUVA** **UVA1**	Scandinavians Indians/Pakistani	**II-V** **25 years (20-33)** **15 F/9 M**
III	**10**	**10** **5 exp.***	**Solar**	**nUVB** **Solar** **bUVA** **UVA1**	Scandinavians	**I** **30 years (20-59)** **5 F/5 M**

*** In study I and II erythema after multiple exposures was evaluated after 4 UV-exposures (24 h after the fourth exposure) and pigmentation was evaluated 7 days after the fifth UV-exposure.**

ing skin cancer.

In all the studies the dose level at the pretest (MED and/or MMD determination after a single UV-exposure) was guided from reflectance measurements of skin pigmentation and in study III also from experience from study I, where four Scandinavians with skin type II did not develop tanning (only showed persistent erythema) after a single UV-exposure to TL01 and/ or Solar and therefore would have been more correctly classified as skin type I.

Phototest nates

To ascertain that these volunteers were true skin types I, after the first unprotected sun-exposure around noon (2 hours in Denmark) in May they would always burn and never tan (1), they were tested by a single Solar Simulator exposure on nates. Six doses with 25 % increments were used on each buttock (fig. 3). Mean MED for left and right nates was calculated. If a tan occurred 7 days after the exposure, mean MMD for left and right nates was calculated. In an area with just perceptible erythema (MED) 24 hours after the single exposure to the Solar Simulator, skin type I does not develop a tan 7 days after the exposure (table 1), neither did our volunteers. But skin types I may be able to tan after a single UV-exposure, provided that it is preceded by a higher erythema grade than (+).

MED and MMD determination

Single UV-exposure (pretest on the back)

The same UV-sources were used as in study I and II (table 2). The pretest procedure was identical. Except in volunteers where MMD could not be determined (no pigmentation 7 days after the single UV-exposure). In these cases we used the MED value instead and defined that 2 MED equals 1 MMD for Solar Simulator and nUVB; pigmentation is preceded by erythema. A relation found in study I in the mentioned 4 skin type II volunteers for the UV-source where they developed pigmentation provided that it was preceded by a high erythema grade. MED was not determined for the UVA-sources (bUVA and UVA1) in any of the studies as MED determination would require very long exposure time in the most darkskinned volunteers due to the relation MED > MMD in the UVA-spectrum (44). Thus, for the UVA-sources we therefore focused on pigmentation.

Multiple UV-exposures on the back

When the individual MMD was determined in the skin type I volunteers, they were exposed to the four UV-sources in four new areas for 5 consecutive days in 24-hour intervals. MED was determined 24 h after the fifth UV-exposure (only for Solar and nUVB). Seven days after the fifth UV-exposure the minimal pigmentation (MMD) was evaluated clinically.

Dosimetry and UVR sources

Throughout the 5 days of exposure, in study III (skin type I), 6 doses were given with 40 % increments. Six 2 cm $\times$ 2 cm squares, each square representing one UV dose, were arranged as 2 $\times$ 3 openings in an UV impermeable mask (fig. 4).
Maximum dose for bUVA (Cleo) and UVA1 (TL10) was 1 MMD. For Solar and nUVB (TL01) maximum dose was lowered compared to study I and II (Papers II-IV) and was 0.5 MMD to minimize the risk of burns. UV-exposure was interrupted in a specific area at erythema grade +++ or complaints of burning irrespective of the erythema grade.

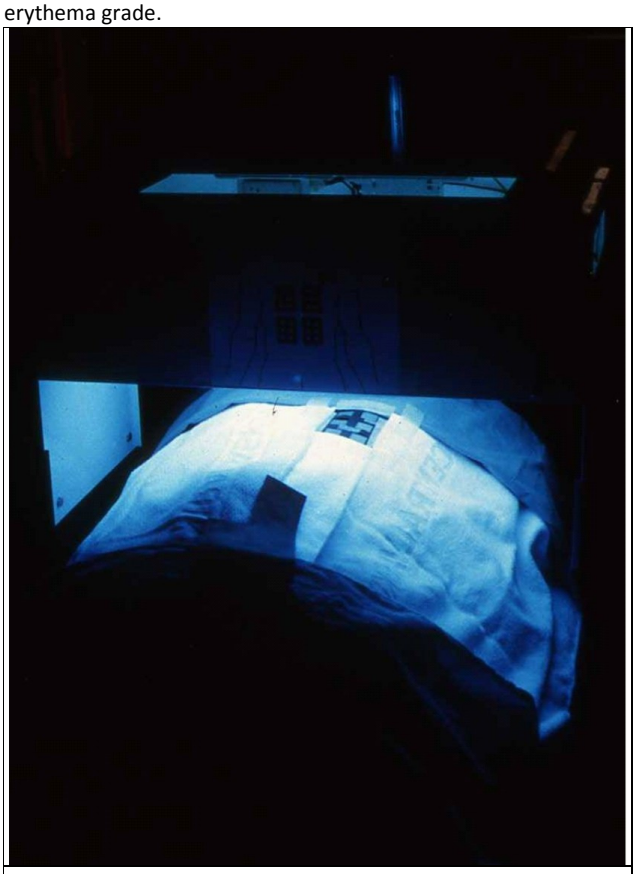

Figure 4
UVA exposure on the back.

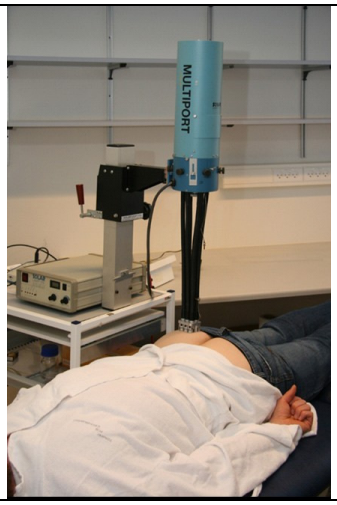

Figure 3
Phototest by Solar Simulator.

Emission spectrum of the UV-sources are shown in fig. 5 and the spectral distribution in percent is shown in table 3.

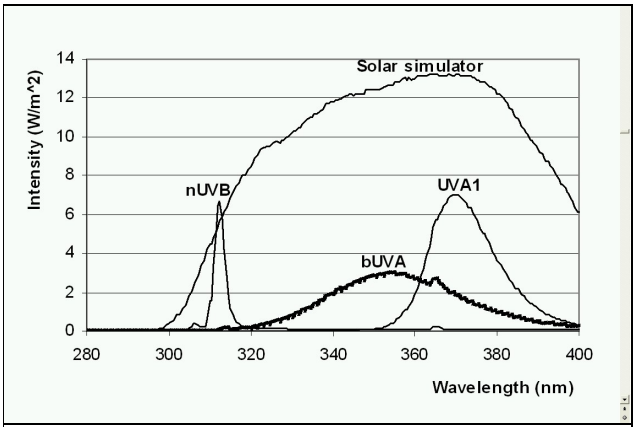

Figure 5
Emission spectrum of the four UV-sources

Table 3. Spectral distribution of the 4 UV-sources.

UV-source	UVB	UVA
nUVB (TL01)	**81 %**	**19 %**
Solar Simulator	**8.7 %**	**91.3 %**
bUVA (Cleo-performance)	**1 %**	**99 %**
UVA1 (TL10)	**0.1 %**	**99.9 %**

Pigmentation evaluation – visual and instrumental

In all three studies, just prior to each UV-exposure, the skin pigmentation in the test areas was evaluated visually as no pigmentation or + for just perceptible pigmentation. At the same time the skin pigmentation was measured by a reflectance meter, which was also used to measure the pre-exposure pigmentation in the test areas just before the first of the consecutive UV-exposures in all three studies (fig. 1). This reflectance meter, the UV-Optimize (UV-Optimize 555, Matic, Nærum, Denmark)(35) gives a value for pigmentation% and PPF. Equations for calculation of redness percent, pigmentation percent and pigment protection factor (PPF) are built into the instrument. For further details please see ref. 47, 88. Measurement of redness% is unreliable in very dark-skinned people (pigmentation% higher than 60%). Therefore erythema was only evaluated visually according to the clinical scale on page 4.

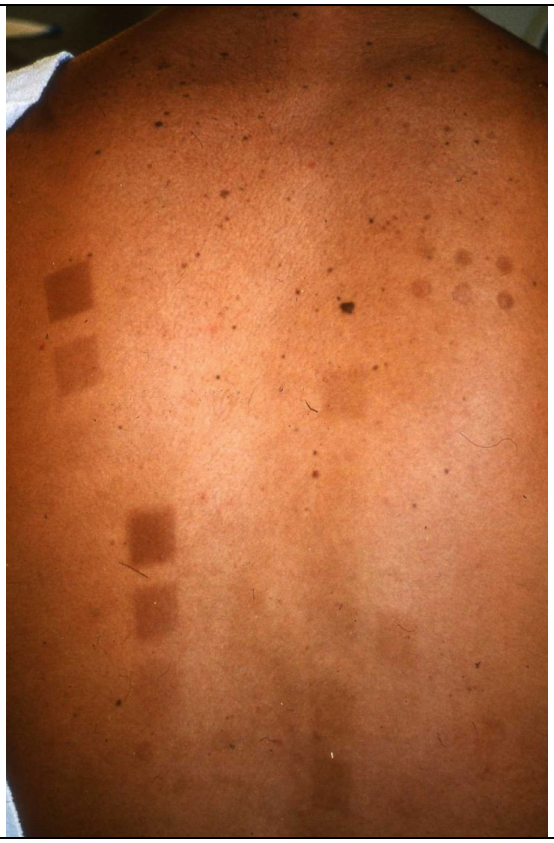

Figure 6
Pigmentation 7 days after the last of 5 UV-exposures in a volunteer with skin type III.

Fig. 6 shows the pigmentation 7 days after the fifth UV-exposure in study I in a volunteer with skin type III. On the left UVA1- and below bUVA-induced pigmentation is shown. To the right spots with Solar-induced pigmentation and just below and more medial nUVB-induced pigmentation is shown. Further below some test areas with remaining pigmentation from the pre-test (single UV-exposure) are visible.

Reproducibility of skin reflectance measurements

The clinical reproducibility of the pigmentation measurements has been found to be within 1% pigment (47). Two-way analysis of variance showed no significant difference in redness or pigmentation between repeated measure-ments at the same spot of arm, shoulder, front and buttock during weeks. The mean of all observations in % (residual standard deviation) was 25.1 (3.6) for redness% and 20.6 (1.5) for pigment% (89). Measurements of pigmentation can not be performed in sites with dense hair growth and should be avoided in sites with mottled pigmentation like freckles, naevi etc. The MED-values include thickness of stratum corneum, which therefore enter into calculation of PPF as a basic value. But obviously increased thickness of stratum corneum after multiple UV-exposures has not been taken into account.

ETHICS

See papers I, II, III, IV.

STATISTICS

When planning study I, a basic knowledge in this area was lacking, which meant that we could not make a sample size calcu-

lation to determine the number of volunteers. In stead we chose a suitable sample size, which was fully sufficient, when we subsequently performed linear and logaritmic regressionanalysis, which gave highly significant differences for erythema- and pigmentation response.

In study II, apart from SED to MMD after multiple UV exposures to different UV-sources, we also wanted to determine the increase in pigmentation (absolute and percent) as an expression of the tanning ability, which is individually variable. We did not know these parameters in advance, neither their variation. Therefore we could not make a sample size calculation, but chose a suitable sample size.

Alternatively, when the variation of the parameter to be investigated is unknown, the sample size can be assessed with relative precision by determining an acceptable size for relative standard error.

Equation: Relative SE = SE {estimated sigma parameter}/σ

$\sigma = 1/\sqrt{2f}$ (NB. σ = sigma).

In example: if a relative SE = 0.1 is desired $\Rightarrow 0.1 = 1/\sqrt{2f} \Rightarrow f \cong 50$, this means $n \cong 50$.

At a relative SE = 0.15 the number of volunteers (n) can be reduced to 22.2. Therefore we decided to include 24 volunteers.

Skin types II-V ranged from approximately 13 – 60 % pigmentation (table 8). We wanted to extend the pigmentation spectrum of the volunteers in the paler end of the spectrum, values below 13 pigmentation%, and therefore we included 10 volunteers with skin type I. We assumed that a number of ten was sufficient, as they were not a group "per se", but contributed to the entire investigations.

We wanted to examine which of the objective parameters were able to predict the subjective Fitzpatrick skin type. Therefore multinominal logistic regression analyses were performed in SPSS in a forward stepwise manner. The effect of the following parameters on prediction of Fitzpatrick skin type was tested.

Single UV-exposure (on the back):

Solar and nUVB: pre-exposure pigmentation, SED to MED and SED to MMD.

Solar, nUVB, bUVA and UVA1: pre-exposure pigmentation and SED to MMD.

Multiple UV-exposures (on the back):

Solar and nUVB: pre-exposure pigmentation, SED to MED after 4 UV-exposures and SED to MMD 1 week after 5 UV-exposures (the daily dose, not the cumulative dose).

Solar, nUVB, bUVA and UVA1: pre-exposure pigmentation and SED to MMD after 5, 6 and 12 UV-exposures.

In logistic regression there is no true R2-value. However, because deviance can be thought of as a measure of how poorly the model fits (i.e. lack of fit between observed and predicted values), an analogy can be made. In SPSS, there are two modified versions. We used Nagelkerke Pseudo-R2. Pseudo-R2 measures are not goodness-of-fit tests, but rather an attempt to measure the strength of association. It should be emphasized that pseudo-R2-values cannot be compared directly with conventional R2-values. Moreover, it is debatable whether Pseudo-R2-values from different studies can be compared. We state our Pseudo-R2-values as r-values.

In an attempt to predict PPF from SED to MED, SED to MMD and Fitzpatrick skin type multiple regression analyses in a forward stepwise manner were performed in SPSS.

MAIN RESULTS AND DISCUSSION

ERYTHEMA

SED to MED in relation to skin type/PPF after a single UV-exposure to Solar and nUVB (Paper I) and the relation to constitutive versus facultative pigmentation

The UV-dose to MED on back versus nates in relation to skin type after a single exposure to Solar simulator was investigated (n = 74, skin types I-V). The correlation coefficient r (Spearman's rank correlation test) showed a stronger correlation between SED to MED on nates compared to back and for PPF compared to Fitzpatrick skin type (table 4). Hence, despite what we expected Fitzpatrick skin type was better related to SED to MED on nates (constitutive pigmentation) compared to the back. When skin type V was excluded from the analysis, the correlation was considerably weakened for Fitzpatrick skin type, whereas PPF showed to be more robust.Table 1

Table 4. Correlation coefficient, r, for SED to MED on nates versus back after a single exposure to Solar simulator and on the back to nUVB against skin type and PPF. (Solar: n= 74, skin type distribution: 10 I, 10 II, 19 III, 19 IV, 16 V). (nUVB: n= 73, skin type distribution: 7 I, 8 II, 21 III, 20 IV, 17 V).

	Solar Simulator				**nUVB**	
	Correlation coefficient r (I-V)		r (only I-IV)		r (I-V)	r (I-IV)
	Nates	Back	Nates	Back	Back	Back
Skin type	0.79	0.63	0.58	0.42	0.59	0.33*
PPF	0.87	0.81	0.75	0.74	0.71	0.55

P<0.0001 except for *p=0.01

SED to MED in relation to skin type/PPF after multiple UV-exposures (Paper I)

Paradoxically the UV-sensitivity of the skin after multiple UV-exposures is only sparsely investigated (21, 22, 44, 45), although the effect of multiple UV-exposures on erythema better reflects sun exposure in daily life and phototherapy of various skin diseases.

The UV-dose (SED) needed to elicit erythema on the back after 1, 2, 3 and 4 consecutive daily UV-exposures to nUVB/ Solar Simulator was therefore investigated in 49 volunteers with a broad spectrum of pigmentation (skin types II-V) and correlated to the pre-exposure skin pigmentation level, skin type and PPF (table 5).

We found a positive and significant exponential relationship between skin pigmentation and UV-dose to elicit a specific erythema grade on the back after 1, 2, 3 and 4 UV-exposures (Paper I).

Table 5. Correlation coefficient, r, for SED to MED on the back after 4 UV-exposures in relation to skin type and PPF.
(Solar: n= 38, skin type distribution: 9 I, 2 II, 9 III, 9 IV, 9 V).
(nUVB: n= 44, skin type distribution: 9 I, 4 II, 14 III, 10 IV, 7 V).

	Solar Simulator		**nUVB**	
	Correlation coefficient r (I-V)	r (only I-IV)	r (I-V)	r (I-IV)
Skin type	0.85	0.85	0.68	0.63
PPF	0.83	0.78	0.62	0.54*

P<0.0001 except for *p=0.0008

With erythema as endpoint, we hereby show that Fitzpatrick skin type, as expected, is better related to multiple UV-exposures than to a single UV-exposure (table 4 and 5). PPF (the measured skin type) correlated almost equally well with SED to MED after single and multiple exposures to Solar, and correlated slightly

better to single exposure to nUVB compared to multiple UV-exposures.

Conversely to a single exposure, the correlation coefficient r (Spearman's rank correlation test) for SED to MED was the same or higher for Fitzpatrick skin type compared to PPF (table 5). This difference was more pronounced when skin type V was excluded.

Discussion

People do not normally expose nates to the sun, and therefore do not know if they will get a sunburn on nates. Furthermore facultative pigmentation (back) was better correlated to skin type than constitutive pigmentation in a Thai population (skin types III, IV, V), as the mean of the measured facultative pigmentation increased with increasing skin type number, although not significant (28). Our assumption was therefore, that it is likely that people do refer to the sun sensitivity on the back, when they recall their first sun exposure in early summer. This was indicated by the study of Leenutaphong, where the correlation between MED and facultative pigmentation was slightly better than for constitutive pigmentation, although generally poor (r = 0.39 versus r = 0.36)(28). On the contrary, our results in skin types I-V showed a better correlation between sun sensitivity on nates and Fitzpatrick skin type (r = 0.79), compared to sun sensitivity on the back (r = 0.63)(table 4).

Generally the pigmentation was higher on the back compared to nates. But in 50 % of the Indians, there was higher pigmentation on nates. Therefore we tried to exclude skin types V to see if the correlation coefficient between SED to MED and Fitzpatrick skin type/ PPF would increase, but instead the correlation was impaired (table 4). Thus, the correlation coefficient increases considerably for Fitzpatrick skin type and also for PPF (although less pronounced), when we include skin type V at single UV-exposure. This indicates that the problem with overlapping of MED-values between skin types may be more pronounced within the fair-skinned skin types (I-IV).

Objectively determined UV-sensitivity (practically always only referring to MED determination), usually performed in a variety of skin types I-IV (e.g. 24, 29, 31), but also in skin types V (28) and VI (32) has been badly correlated to Fitzpatrick skin type. Our studies confirm this, especially when exposed on the back. Therefore it is not advisable to replace the MED test with the Fitzpatrick skin type determination when dose level for phototherapy should be determined (23, 24, 32). Instead our results show that the dose level can be guided safely and easily by a skin reflectance measurement of the pigmentation and calculation of PPF by UV-optimize. Other studies have shown that the PPF-value predicts SED to MED well after a single Solar Simulator exposure in skin types I-IV (back, r = 0.86; nates, r = 0.87 (52), nates, r = 0.7 (29). Our study shows in addition that also in a broader pigmentation spectrum (skin types I-V) and for multiple UV-exposures PPF works well as a predictor for MED.

When comparing the literature, it is important to notice that until about ten years ago it was common practice to use the erythema reaction with sharp borders as the MED value. But just perceptible erythema is now standardized as the MED because this erythema reaction is the most reliable and reproducible estimate of UV sensitivity (14).

Diminutive bikinis as well as the common habit of whole body exposure in sun tanning beds make measurements of constitutive pigmentation more difficult with limited un-exposed skin area available on the buttocks. In addition UV radiation may even pass thin clothing in particular if synthetic (90, 91) leading to increased pigmentation of skin that has not been directly exposed. The MED on the back is highly variable due to seasonal variations in skin pigmentation (92). Measurements of constitutive UV-sensitivity on the buttocks should therefore be made well outside the summer period (29), in our studies 3 months after sun exposure.

Reliability and reproducibility of MED test (phototest)

The MED test even performed under optimal conditions will show considerable variation due to the following aspects. The MED is not an exact dose since the true dose will be between the registered one and the lower preceding dose. It is also known that the visual scoring of erythema may vary between and within observers by more than one step and also depends on skin pigmentation. Inter- and intra-observer agreement is better for fair skinned persons and for low grade erythema (14).

Minor variations can also be caused by the skin temperature at time of the visual erythema assessment (93) or incorrect distance between UV-source and skin surface, and curved skin surfaces like nates. The curved surface on nates makes the available area for phototest limited and makes it a challenge to obtain correct UV-source-skin distance in all the exposed sites.

Repeatability judged by simultaneous testing of the left and the right buttocks with 25% dose increments in 14 fair-skinned persons varied by 2 steps in one person and by 1 step in 6 persons (65).

PIGMENTATION

SED to MMD on back versus nates in relation to skin type/PPF after a single exposure to Solar Simulator

The UV-dose to MMD on back versus nates in relation to skin type after a single exposure to Solar simulator was investigated (total n = 72, skin types I-V). The correlation coefficient r (Spearman's rank correlation test) showed a stronger correlation between skin type and SED to MMD on nates compared to the back (table 6). Hence both the relation between MMD and respectively skin type and PPF relate best to constitutive pigmentation. In addition table 6 shows that PPF is clearly better correlated and therefore preferred compared to Fitzpatrick skin type, when UV-exposure is performed on the back. The correlation of SED to MMD and skin type is fairly low (r = 0.45) for facultative pigmentation (back) and even lower than the equivalent relation for SED to MED (r = 0.63) indicating that SED to MED is better related to skin type after a single UV-exposure to Solar than SED to MMD.

Table 6. Correlation coefficient, r, for SED to MMD on nates versus back after a single exposure to Solar Simulator in relation to skin type versus PPF. (n= 72, skin type distribution: 3 I, 8 II, 21 III, 22 IV, 18 V).

	Correlation coefficient r	
	Nates	**Back**
Skin type	0.73	0.45
PPF	0.75	0.69

P<0.0001 for both nates and back.

SED to MMD in relation to skin type/PPF after a single UV-exposure on the back (Paper II)

We investigated pigmentation response (MMD) after a single UV-exposure on the back to Solar, nUVB, bUVA and UVA1 (n = 77, 76, 84, 82) in relation to skin type/ PPF to determine which of the two parameters related best to pigmentation response (Paper II).

Table 7. Correlation coefficient r and p-values from Spearman´s rank correlation test of the relation between MMD on the back and respectively skin type/PPF for different light sources after one UV-exposure. Skin types I-V. Solar, nUVB, bUVA, UVA1: n = 77, 76, 84, 82.

	Solar		nUVB		bUVA		UVA1	
	r	P	r	p	r	P	r	p
Skin type	0.51	<0.0001	0.55	<0.0001	0.37	<0.0005	-0.21	n.s.
PPF	0.71	<0.0001	0.72	<0.0001	0.33	<0.0023	-0.23	0.03

PPF was clearly more predictive of induction of pigmentation than skin type (table 7) for Solar and nUVB. Conversely, for bUVA there was a slight difference in favour of skin type. Table 6 and 7 show results from the same study, but for nUVB, bUVA and UVA1 exposures were only performed on the back.

For all UV-sources, except for UVA1, there was a significant correlation between SED to MMD and skin type (table 7) and a positive linear relation between SED to MMD and PPF (Paper II). This means that the more pigmented a person is the higher SED dose to tan after a single exposure to Solar, nUVB and bUVA (table 8). For UVA1 the relation between SED to MMD and pre-exposure pigmentation/skin type was constant, thus the dose to 1 MMD was independent of pre-exposure pigmentation and skin type, being approximately 1 SED for all skin types after a single UVA1 exposure (table 8).

Table 8. Average SED for each skin type group to equal 1 MMD for each UV-source after a single UV-exposure (Papers III, IV).

Skin type	Total (n)	Pre-exposure pigm. Mean pigmentation% Range (min.-max.)	SED to 1 MMD			
			Solar	nUVB	bUVA	UVA1
II	5	23.2 (13-32)	5.3	5.2	1.7	0.8
III	6	27.0 (16-38)	7.5	6.6	1.8	0.9
IV	4	31.0 (22-42)	9.6	8.3	2.2	0.9
V	9	46.7 (34-60)	10.5	8.9	2.4	0.9

SED to MMD in relation to skin type/PPF after multiple UV-exposures (Papers II, III, IV)

Single UV-exposure was performed on nates and on the back. Multiple UV-exposures were only performed on the back. Pigmentation response (MMD) in relation to Fitzpatrick skin type/ PPF was investigated in skin types II-V after respectively 5 consecutive UV-exposures in 49-52 persons (Paper II) and after a total of 6 or 12 UV-exposures in 24 persons (Paper III, IV) to determine which of the two parameters related best to pigmentation response (table 9).

In study I (5 UV-exposures) six doses with steps of 100% increments were used and maximum dose was 2 MMD for the UVA-sources and 1 MMD for nUVB and Solar. In study II (6 or 12 exposures) only submelanogenic doses were used (0.8, 0.6, 0.4, 0.2 MMD) to minimize the risk of excessive erythema. Due to this difference in exposure frequency and MMD dose intervals the results from the three studies could not be analyzed together.

The relation between SED to MMD and skin type/ PPF for the four UV-sources is almost the same as after a single UV-exposure. Again PPF was clearly more predictive of induction of pigmentation than Fitzpatrick skin type (table 9) for Solar and nUVB.

The only differences are that the Spearman rank correlation between UV-dose to 1 MMD and skin type after 5 UV-exposures was significant only for nUVB (table 9) and the correlation between UV-dose to 1 MMD and PPF is only significant for nUVB and the Solar Simulator (the most erythemogenic UV-sources)(table 9). In other words SED to MMD is independent of skin type and PPF for both UVA1 and now also bUVA (table 9)(Paper II).

Table 9. Correlation coefficient r and p-values from Spearman´s rank correlation test of the relation between MMD and respectively skin type/PPF for different light sources after 5, 6 or 12 UV-exposure. Skin types II-V. After 5 exposures, n = 49, 49, 52, 52 for respectively Solar, nUVB, bUVA, UVA1. n = 24 for 6 or 12 exposures.

Number of exposures		Solar		nUVB		bUVA		UVA1	
		r	p	r	p	r	p	r	p
5	Skin type	0.17	n.s	0.43	0.002	0.01	n.s.	-0.05	n.s.
	PPF	0.32	0.02	0.50	0.0003	0.22	n.s.	0.01	n.s.
6	Skin type	0.73	<0.0001	0.63	0.001	0.20	n.s.	0.06	n.s.
	PPF	0.81	<0.0001	0.70	0.0001	0.37	n.s.	0.08	n.s.
12	Skin type	0.59	0.003	0.70	0.0001	-0.06	n.s.	-0.15	n.s.
	PPF	0.66	0.0005	0.74	<0.0001	0.02	n.s.	-0.05	n.s.

After 6 and 12 UV-exposures the steady-state pigmentation was reached. By using individualized MMD doses consequently the absolute increase in pigmentation was independent of pre-exposure pigmentation (Papers III, IV), whereby the percent increase in pigmentation was higher the more fair-skinned the person. This proves that the MMD determination after a single UV-exposure was correct and worked for multiple UV-exposures. However, the number of SED to minimal pigmentation was higher the more dark-skinned the person for single and multiple UV-exposures for both Solar Simulator and nUVB (table 8 and 12)(Paper II, III).

Except for 5 UV-exposures, the correlation coefficient r is almost stationary for PPF – thus independent on exposure frequency (1, 6, 12 exposures) for Solar and nUVB (table 7 and 9). While the correlation coefficient r for Fitzpatrick skin type is more unstable, but actually except for 5 UV-exposures is higher for repetitive exposures compared to single UV-exposure. Thus with pigmentation (MMD) as endpoint, we hereby show that skin type, as expected, is better related to multiple UV-exposures than to a single UV-exposure. This indicates that people refer to multiple exposures, when they recall their sun sensitivity (concerning the pigmentation part) for Fitzpatrick skin type classification. We conclude that for single as well as for multiple UV-exposures PPF is clearly more predictive of induction of pigmentation than skin type for Solar and nUVB.

The daily UV-dose to clinically evaluated minimal pigmentation (MMD) is lowered (by approximately 50 %) after 5 exposures. For UVA1 MMD being 0.4 SED for all skin types (table 12). After 6 or 12 exposures the daily dose to minimal pigmentation is only respectively a half or a third compared to a single exposure for all the UV-sources (Paper III, IV, table IV). But the cumulative dose is still higher after multiple UV-exposures.

Ratio of MMD/MED on nates and/or back after a single UV-exposure to Solar Simulator and nUVB

The ratio of MMD/MED was determined as an average in our population after a single UV-exposure to respectively Solar and nUVB. Table 10 shows that the mean ratio of MMD/MED was

approximately 1.5. On average the UV-dose to 1 MMD is approximately 50 % larger than the UV-dose to 1 MED when using Solar or nUVB as UV-source.

Table 10. Mean MMD/MED ratio after a single UV-exposure to Solar and nUVB. (Solar: n=65, skin type distribution: 3 I, 8 II, 19 III, 19 IV, 16 V, nUVB: n=69, skin type distribution: 3 I, 8 II, 21 III, 20 IV, 17 V).

	Solar Simulator		nUVB
	Nates	Back	Back
MMD/MED ratio	1.4 (0.31)	1.5 (0.40)	1.6 (0.41)

(standard deviation)

The above is provided that the intercept = 0. However this is not reasonable to assume. The lowest value of SED to MED is also defined as 1 SED (65). By linear regression we found a good correlation between SED to MMD and SED to MED ($p < 0.0001$). The equations are:

Solar (nates): MMD = 1 + 1.2 MED $\Rightarrow$ MMD/MED = 1.2 + 1/MED ($r = 0.89$)

Solar (back): MMD = 3.4 + 0.86 MED $\Rightarrow$ MMD/MED = 0.86 + 3.4/MED ($r = 0.85$)

nUVB (back):MMD = 2.7 + 0.86 MED $\Rightarrow$ MMD/MED = 0.86 + 2.7/MED ($r = 0.79$)

Our results demonstrate that a high erythema grade is needed to induce pigmentation in very fair-skinned persons. In example, some of the skin type I volunteers were actually able to tan after a single UV-exposure to Solar or nUVB, but the tanning was then preceded by a higher erythema grade than MED. Whereas the ratio of MMD/MED becomes smaller in darker skinned persons, hence pigmentation is preceded by a low erythema grade. In the very dark/black persons the ratio will be 1, thus MED = MMD. For nUVB, MED = MMD when SED to MED = 19, thus a person with PPF = 19. In the darkest Indian in our study (PPF=19) MED = MMD for nUVB. For Solar MED = MMD, when SED to MED = 24.3, thus a person with PPF = 25 – a theoretically completely black person.

Reliability of the clinical evaluation of pigmentation (MMD)(Paper II)

The MMD is not an exact dose since the true dose will be between the registered one and the lower preceding dose. Moreover, the reliability of the clinical evaluation of pigmentation (MMD) was investigated by comparing it to the objective increase in pigmentation% measured by skin reflectance.

Table 11. The dose to clinically evaluated 100 % MMD and 50 % of MMD corresponds to the indicated objectively measured pigmentation% increase (reflectance). 50 % of MMD corresponds to a pigmentation increase of approximately 1 pigmentation%. The objectively measured pigmentation% is more pronounced after 5 UV-exposures than after one exposure for 100 % MMD. However this is statistically significant only for nUVB (p=0.007) and UVA1 (p=0.03).
Average of all volunteers (skin types II-V, n= 49-52).

Clincally evaluated MMD	UV-exposures	Pigmentation% increase					
		nUVB	Solar	bUVA	UVA1	**mean**	P
100 %	1	3.1	3.0	3.1	2.2	**2.9**	n.s.
	5	5.3	3.7	4.1	3.7	**4.2**	n.s.
	p	0.007	n.s.	n.s.	0.03	0.003	
50 %	1	0.5	1.1	1.5	1.7	**1.2**	n.s.
	5	1.4	-0.2	1.4	0.9	**0.9**	n.s.
	P	n.s.	n.s.	n.s.	n.s.	n.s.	

After 1 exposure the measured increase in pigmentation-% equivalent to the clinical (visual) evaluation was the same for all of the UV-sources (table 11). Likewise after 5 UV-exposures. The objectively measured increase in pigmentation% was higher after 5 UV-exposures compared to 1 UV-exposure, but this was only statistically significant for some UV-sources, nUVB ($p=0.007$), UVA1 ($p=0.03$) and for a mean of all UV-sources ($p=0.003$).

If there had been concordance between the objective increase in pigmentation and the clinical evaluation of pigmentation, this difference would not occur. This means that the reflectance instrument (UV-Optimize) is more sensitive at distinguishing pigmentation than the eye. The reason why more pigmentation is needed after 5 compared to 1 UV-exposure to be perceived by the eye is unknown. Regarding nUVB we speculate that thickening of stratum corneum induced by the UV-exposures changes the optics of the skin and thereby changes how pigmentation is perceived after more exposures. As thickening of stratum corneum mainly is caused by UVB (53, 73) another yet unknown phenomena may play a role for UVA1.

Discussion

Our results indicate, in contrary to expected, that people seem to refer to the constitutive pigmentation, when they reply to the question of Fitzpatrick skin type with regard to both erythema (MED) and tanning (MMD). However, due to the limited area available on nates it was only examined for one UV-source, the Solar Simulator.

In skin types II and III UVA proved to be more melanogenic than erythemogenic (MMD<MED) (44, 45). Accordingly sub-erythemogenic UVA-doses induced pigmentation in skin types II and III, whereas tanning from UVB-irradiation only occured when preceded by erythema (45, 94). These relations are confirmed in our study in a broader pigmentation spectrum (skin types I-V). However, our study confirm the relation MED<MMD found for UVB in skin types II and III (44, 45), but we found that for dark skin types this relation is graduated. Hence, according to our equations (p. 12), there is a graduation, so a high erythema grade is needed to induce pigmentation in very fair-skinned persons, whereas the ratio of MMD/MED becomes smaller in darker skinned persons and finally in very dark/black persons the ratio will be 1, thus MED = MMD. However, after a single UV-exposure to Solar the relation was MMD < MED for back/nates in the darkest Indian (who was skin type V and dropped out after the single UV-exposure), whereas the relation for nUVB in this person was perfectly in accordance with the equation, hence MED = MMD at PPF = 19. Other exceptions were observed after a single exposure to Solar, hence MMD = MED on nates (n= 4) or back (n= 12) in volunteers with broad skin type representation.

The reason could be that the Solar Simulator also emits UVA. A single study find that MMD<MED in skin types II-IV, when full spectrum light was used (37).

Only results from 3 out of 10 volunteers with skin type I could be used. According to the definition (1) they should not develop pigmentation after a single exposure. For those who did develop pigmentation, it was preceded by a higher erythema grade than (+).

Pigmentation after multiple UVB-exposures is difficult to obtain in fair-skinned persons, since tanning from UVB-irradiation only occurs when preceded by erythema (45, 94). Multiple exposures to very small UVB-doses will not induce erythema and therefore no pigmentation is induced as in most of the Scandinavians after exposure to the lowest doses 0.4 and 0.2 MMD. On the other hand, after a higher dose which induces erythema and

thereby pigmentation, the erythema does not disappear from day to day leading to excessive erythema. This explains why many of the Scandinavians were excluded during the repetitive exposures to the highest dose 0.8 MMD of Solar and nUVB (Paper III). With this knowledge in mind ideally more doses in between 0.4 MMD and 0.8 MMD, in example 0.5 MMD and 0.7 MMD, would have been a better choice.

By using individualized MMD doses our intention was to diminish the risk of erythema and focus on pigmentation. With pigmentation as our endpoint, we could not have used equal SED doses (or equal physical doses, i.e. mJ/cm2) for all UV-sources, as this would lead to very large dose steps leading to severe burns in the fair-skinned volunteers, or the doses would be so low that the darker-skinned volunteers would not develop pigmentation after exposures to UVB-emitting sources.

The intention of not allowing sun-exposure 3 months prior to participation was to use the facultative pigmentation at baseline level. Ideally we could have measured the unexposed skin next to the exposed squares to ensure that a general decrease in pigmentation of the volunteer did not occur during the study. Such a decrease would indicate that the volunteer actually had been sun-exposed less than 3 months prior to the study, and thereby was not in steady-state at the initiation of the study. Actually our results indicate that this could be the case for some of the volunteers despite our exclusion criteria (Papers III, IV).

This study, in a broader pigmentation spectrum, confirms the bad relation between objective UV-sensitivity (MED) and Fitzpatrick skin type (i.e. 24, 25, 27, 29, 31-33) also after multiple UV-exposures. We show that the well known considerable variation in UV-sensitivity (MED) within each skin type group and corresponding overlap between different skin types, not only exists for the erythema parameter, but also for the pigmentation response (MMD) in volunteers with a broad spectrum of pigmentation (Paper II, fig. 2 and 3).

WHICH OF THE UV-SOURCES RELATE BEST TO SKIN TYPE?

SED to MMD - dependency on wavelength (Paper II)

The UV-dose (SED) needed to produce a minimal pigmentation (1 MMD) after respectively 1 and 5 UV-exposures was investigated and related to UV-source (table 12)(Paper II).

Table 12. Average UV-dose (SED) to give a minimal pigmentation (MMD) in skin types II-V.

	Solar	nUVB	bUVA	UVA1
1 UV-exposure	9.3 (3.9-14.8)	6.5 (3-13)	2.2 (1.2-5)	0.9 (0.7-1.6)
5 UV-exposures	5.6 (2.0-11.1)	4.0 (1.6-7.6)	1.1 (0.4-2.6)	0.4 (0.1-0.9)

Mean and range.
1 UV-exp. Solar/nUVB: n = 58, bUVA/UVA1: n = 62
5 UV-exp. Solar/nUVB: n = 49, bUVA/UVA1: n = 52

Table 12 shows that, when we look at the average SED to MMD for all volunteers, in general a much lower UV-dose is needed to produce a minimal pigmentation as the UVB-content of the lightsource declines and the UVA-content increases. The Solar Simulator was the least melanogenic of the 4 UV-sources (the highest UV-dose (SED) to give 1 MMD) and UVA1 was the most melanogenic. This relation was the same when we evaluated it for each skin type group (table 8). This means that the melanogenic effect is highly dependent on wavelength. The differences between the UV-sources were highly significant ($p<0.0001$). The difference in SED to MMD between Solar Simulator (the least melanogenic) and UVA1 (the most melanogenic) is more pronounced after 5 UV-exposures ($p=0.001$)(table 12).

In skin types I-V we found that the relation between MMD and Fitzpatrick skin type/PPF after a single UV-exposure is strongly dependent on wavelength and is only significant, when shorter-waved UV-radiation is used; UVB and broadband UVA radiation (table 7). The relation is best for, in the mentioned order, nUVB ($r = 0.55/0.72$ (Fitzpatrick skin type/PPF)), Solar ($r = 0.51/0.71$) and bUVA ($r = 0.37/0.33$). For the longwaved UVA1 source MMD is independent on skin type/PPF.

In skin types II-V we found the same relation after 5 UV-exposures (Paper II), but now the relation between Fitzpatrick skin type and MMD was only significant for nUVB (table 7), whereas the relation between PPF and MMD was significant for nUVB and Solar after 5, 6 and 12 UV-exposures. However, after 6 and 12 UV-exposures the relation between Fitzpatrick skin type and MMD was highly significant for both nUVB and Solar.

Discussion

The reason why Solar was less melanogenic than nUVB despite its higher UVA-content is that the Solar Simulator emits shorter waved UVB compared to the nUVB. The short-wave UVB counts heavily to the SED and the UVA dose only contributes to the SED by 14 %. Moreover does the Solar emit short-wave UVA that is less melanogenic than UVA1. nUVB was the most erythemogenic and a lower SED was needed to produce MED than for the Solar Simulator (Paper I).

We conclude, that SED to MMD is only dependent on skin type/PPF, when tanning is preceded by erythema (MED<MMD) (45, 94). Whereas MMD at 365 nm has been found to be independent of skin type, tested for skin types I, II and V (40), which we confirm for UVA1 (peakwavelength at 365 nm) and moreover find true also for multiple UV-exposures. MED or MMD at 305 nm appeared to be a sensitive indicator of skin type (single exposure)(40). We find that MED after single and multiple UV-exposures to nUVB (peak wavelength at 311 nm) and Solar Simulator could be used as indicator of skin type. MMD could also be used, but MED was preferred. At 315 nm Kollias et al found that MED = MMD, but MED was defined as erythema with a well demarcated border (40).

Which wavelengths can be recommended for objective skin type determination? The longwaved UVA1 should definitely not be used, as there is no relation between MMD and Fitzpatrick skin type/PPF. For shorter UVA wavelengths (broadband UVA) the relation between MMD and Fitzpatrick skin type/PPF was only significant after 1 UV-exposure and the correlation coefficient was low ($r = 0.37$ skin type, $r = 0.33$ PPF). For practical purposes bUVA also has the disadvantage of quite long exposure time. The Solar Simulator and the nUVB have the highest correlation coefficients, and the correlation for both UV-sources was stronger after multiple UV-exposures compared to single UV-exposure. In addition, after 6 or 12 UV-exposures steady-state pigmentation is presumed to be reached, like a natural tanning on a sunny holiday. Repetitive UV-exposures to Solar and nUVB are apart from their burning tendency also very timeconsuming and therefore not suitable for clinical praxis; contrarily to single exposure, which is easy to implement.

The correlation between skin type and MED was best for Solar compared to nUVB, whereas the correlation between skin type and MMD was best for nUVB, but the differences in correlation coefficients were relatively small after a single exposure. We

conclude that, both nUVB and Solar are useable for objective skin type determination after 1 UV-exposure. MED was better correlated to both Fitzpatrick skin type and PPF compared to MMD. Therefore an MED determination could be performed preferrably on nates as there was a closer relation between constitutive pigmentation and skin type compared to facultative pigmentation for Solar Simulator. We presume the same is true for nUVB. If nUVB is chosen for objective skin type determination, two aspects should be considered: 1) The spectral distribution of this narrowband UVB-source with peak wavelength at 311 nm is very different from the spectral distribution of sunlight. 2) nUVB is more carcinogenic than broadband UVB-sources as for example TL12 (95). Therefore we propose to use broadspectrum UVB, e.g. TL12 instead of narrowband UVB (TL01) due to a spectral distribution with closer similarity to sunlight and less carcinogenicity.

WHICH OBJECTIVE PARAMETERS DOES FITZPATRICK SKIN TYPE REPRESENT?

By multinominal logistic regression analyses we also analyzed how well the objective parameters used in this study were related to Fitzpatrick skin type and examined which of them were most successful to predict this subjective skin type.

Solar and nUVB

Concerning one UV-exposure on the back the following parameters were examined: pre-exposure pigmentation, SED to MED and SED to MMD. The results from multinominal logistic regression analyses showed that in skin types I-V prediction of Fitzpatrick skin type is only related to pre-exposure pigmentation (Pseudo-R2= 0.73 $\Rightarrow$ r = 0.85). If pre-exposure pigmentation is removed from the analysis, the model is weakened (r = 0.58) and it turns out that only SED to MED is significant. The results are identical if skin type V is excluded from the analysis and if the two UV-sources are analysed separately or together.

After multiple UV-exposures on the back pre-exposure pigmentation, SED to MED after 4 UV-exposures and SED to MMD after 5 UV-exposures were examined. Together, all of the 3 investigated parameters were significant (r = 0.86).

Solar, nUVB, bUVA and UVA1

The significance of pre-exposure pigmentation and SED to MMD for prediction of Fitzpatrick skin type was analysed likewise for all 4 UV-sources after 1, 5, 6 and 12 UV-exposures. Also when all 4 UV-sources are analysed for one UV-exposure, and SED to MED is absent, prediction of Fitzpatrick skin type is still only related to pre-exposure pigmentation (r= 0.84). If pre-exposure pigmentation is removed from the analysis SED to MMD is only significant for nUVB (1, 5, 6, 12 exp.), Solar (for 1, 6, 12 exp.) and bUVA (only for 1 exp.)(r= 0.54) in accordance with the single calculations (table 7, 9). For UVA1 SED to MMD was not able to predict Fitzpatrick skin type at all.

In summary, after a single UV-exposure prediction of Fitzpatrick skin type is only related to degree of pre-exposure pigmentation. After multiple UV-exposures (nUVB and Solar) together the three investigated parameters all significant.

Two examples were chosen to show to what extent the model succeeds to predict the Fitzpatrick skin type (table 13).

a) **bUVA single exp. Observed**	**Predicted** Fitzpatrick skin type					
	I	II	III	IV	V	Percent correct
I	6	1	3	0	0	60 %
II	4	0	6	2	0	0 %
III	1	0	12	8	0	57.1 %
IV	1	1	8	9	3	40.9 %
V	0	0	0	2	17	89.5 %
Overall percentage (%)	14.3	2.4	34.5	25.0	23.8	52.4 %

b) **nUVB multiple exp. Observed**	**Predicted** Fitzpatrick skin type					
		II	III	IV	V	Percent correct
II		3	0	0	0	100 %
III		0	11	2	0	84.6 %
IV		0	3	6	2	54.5 %
V		0	0	4	3	42.9 %
Overall percentage (%)		8.8	41.2	35.3	14.7	67.6 %

Table 13.
How well the model succeeds to predict the Fitzpatrick skin type given the objective parameters a) pre-exposure pigmentation and SED to MMD after a single exposure to bUVA and given the objective parameters b) pre-exposure pigmentation, SED to MED after 4 UV-exposures and SED to MMD after 5 UV-exposures to nUVB.

Table 13 shows that the model for single UV-exposure is most succesfull at predicting skin types I and V, hence the extremes in each end of the pigmentation spectrum, as skin type only was related to pre-exposure pigmentation. The rate of correct predictions of skin types III, IV was fairly low, and skin type II was never predicted after a single UV-exposure except for nUVB, where only 1 out of 8 (12,5 %) was correctly predicted. After multiple UV-exposures skin type IV could not be predicted after 6 or 12 UV-exposures for all UV-sources.

Moreover it shows that the model, for all UV-sources, overall succeeds better to classify people correct after multiple UV-exposures compared to a single UV-exposure.

The overall percentage of correct predictions lies between 48.8 % and 66.7 %.

When the model does not predict correctly it generally chooses the adjacent skin type, in example a true skin type IV could be classified as skin type III or V by our model.

Discussion

Even though erythema tendency after a single sun exposure partly is the definition of the Fitzpatrick skin type, our results show that skin types I-IV could not be related to SED to MED after a single UV dose. Instead our results indicate that they relate the questions of tendency to burn and ability to tan simply to their degree of pigmentation. Only after multiple UV-exposures SED respectively to MED and MMD were significant. Which could indicate that, when people try to recall their erythema tendency and tanning ability, they refer to multiple UV-exposures.

The reason why skin type II was the most problematic skin type to predict after a single UV-exposure may in part be, that few skin types II were represented (n = 8 for Solar and nUVB) and that many fair-skinned persons acknowledge that they will usually burn after the first sun exposure, but will tan well afterwards which makes it impossible to choose between skin type II and III. Those who always burn after the first sun exposure, but tan although with difficulty, might pay more attention to the tanning and therefore choose skin type II instead of I. As mentioned earlier it can be difficult to imagine if a tan will occur after only one sun-exposure, as tanning after repeated exposures may be more familiar to the majority. In this study four volunteers of skin types II had no tanning after a single UV-exposure to nUVB/Solar and

therefore were to be considered as skin types I. This indicates that it still seems less attractive to be pale and a poor suntanner. For these reasons in particular prediction of skin type II is difficult.

The reason why skin type IV could not be predicted after 6 or 12 UV-exposures for all UV-sources may in part be due to the composition of volunteers: Scandinavians and Indians/Pakistani. No Hispanics or Asians were represented at 6 or 12 UV-exposures, but at 1 and 5 UV-exposures. Furthermore few skin types IV were represented at 6 and 12 UV-exposures (n = 4).

Skin type V is, according to the definition of Fitzpatrick, determined entirely on the individual pigmentation degree. Our analyses also indicate this, when we determine Fitzpatrick skin type from objective parameters.

The model is most successful in predicting skin type V. This may be due to the fact that it is much easier to relate to an individual pigmentationdegree than to try to recall how the skin would react upon a single sun exposure early in the summer and combine these two reactions into one of only 4 classifications. Furthermore this group has almost twice as high pigmentation degree compared to the typical Scandinavian.

Despite the literature, that generally indicate that the relation between MED and Fitzpatrick skin type is bad or at least doubtful, our assumption that people mainly refer to tanning ability, when they determine their skin type seem to be wrong. The correlation between Fitzpatrick skin type and SED to MED was better than for SED to MMD for both single exposure and after 4 or 5 UV-exposures examined for Solar and nUVB (tables 4, 5, 6, 7, 9).

Fitzpatrick skin type in epidemiological context (risk for skin cancer) stands for burns and ability to tan may represent “cumulative” dose as mentioned in the introduction. SED to MED is equivalent to burns. PPF may also indirectly represent cumulative dose – the more pigmented the skin the less UVR penetrates the epidermis and will be able to induce skin cancer. Our results that indicate that skin type predominantly is determined by the skin pigmentation and that the second most important objective parameter is SED to MED (and not SED to MMD) explain why Fitzpatrick skin type still plays an important role in epidemiology with regard to risk of skin cancer.

Agreement between single calculations and multinominal regression analyses

Generally the results from single calculations were concordant with the results from multinominal regression analyses. But for single UV-exposure, when pre-exposure pigmentation was removed from the multinominal regression analyses only SED to MED was significant. This simply shows that SED to MMD is even worse to predict Fitzpatrick skin type. When analysed by multinominal regression pre-exposure pigmentation, SED to MED and SED to MMD were all significant after multiple UV-exposures (for Solar and nUVB), whereas SED to MED by single calculation was better correlated to skin type than SED to MMD. These differences may be due to technical aspects. E.g. the parameters can be intercorrelated as for SED to MED and SED to MMD for nUVB and Solar.

PREDICTION OF PPF

Likewise an attempt was made to predict PPF - the measured skin type. Based on SED to MED, SED to MMD and Fitzpatrick skin type we predicted PPF by multiple regression analyses and found high correlation coefficients. In the following section it is outlined how successful each of these parameters were in predicting PPF.

Solar and nUVB

Concerning one UV-exposure prediction of PPF was influenced by SED to MED and Fitzpatrick skin type ($p< 0.0001$)(Solar nates $r = 0.93$, Solar back $r = 0.89$ and nUVB back $r = 0.92$). SED to MMD was not significant.

After exposure to Solar, the two parameters worked equally well as predictors of PPF (SED to MED $r = 0.79$, Fitzpatrick skin type $r = 0.80$). Whereas PPF was stronger correlated to Fitzpatrick skin type ($r = 0.87$) than to SED to MED ($r = 0.79$) after exposure to nUVB.

After multiple UV-exposures on the back SED to MED after 4 UV-exposures, SED to MMD after 5 UV-exposures and Fitzpatrick skin type were examined. Again prediction of PPF was related to two parameters, SED to MED and Fitzpatrick skin type ($p< 0.05$)(Solar $r = 0.82$ and nUVB $r = 0.79$). SED to MMD was not significant.

PPF was stronger correlated to Fitzpatrick skin type than to SED to MED for both Solar ($r = 0.76$ versus $r = 0.65$) and nUVB ($r = 0.74$ versus $r = 0.55$).

Prediction of PPF is stronger for single UV-exposure compared to multiple UV-exposures (Solar $r = 0.89$ versus $r = 0.82$, nUVB $r = 0.92$ versus $r = 0.79$). These results only apply to nUVB and Solar as MED only was determined for these 2 UV-sources.

Solar, nUVB, bUVA and UVA1

The significance of SED to MMD and Fitzpatrick skin type for prediction of PPF was analysed likewise for all 4 UV-sources after 1, 5, 6 and 12 UV-exposures. Skin type was highly significant except after 12 UV-exposures to nUVB. SED to MMD was significant for Solar (1, 5, 6, 12 exp.), nUVB (1, 12 exp.), bUVA (5, 12 exp.) and not significant for UVA1 when analyzed together with skin type (r ranged from 0.77-0.92). When SED to MMD was analyzed as the only parameter it was only significant for Solar and nUVB (r ranged from 0.35-0.83) after all exposures and for bUVA ($r = 0.44$) only after a single exposure and the correlation was weak.

Discussion

At prediction of Fitzpatrick skin type a single parameter, the pre-exposure pigmentation, was the most important factor for classification. At prediction of PPF SED to MED and skin type work equally well after a single UV-exposure to Solar, whereas skin type is better correlated to PPF after a single nUVB-exposure and after 4 and 5 UV-exposures to both UV-sources. It was expectable that SED to MED was well correlated to PPF, as the purpose of the PPF system is to predict the number of SED to MED. It is surprising that skin type is so highly correlated to PPF, and generally even better correlated to PPF compared to SED to MED.

FITZPATRICK SKIN TYPE COMPARED TO PPF

We found that PPF is better related to the objective parameters for UV-sensitivity (MED and MMD) than Fitzpatrick skin type. Accordingly, prediction of PPF seems to be more successful than prediction of Fitzpatrick skin type by multiple regression analyses, at the same time the correlation to Fitzpatrick skin type is very convinsing and PPF may thus be preferable to Fitzpatrick as a measure of skin sensitivity to sunlight. The reason for this may be due to the fact that PPF is based on a linear scale (240 steps), which re-moves the dilemmas and uncertainty in the person at subjective skin type determination. Skin reflectance measurements with calculation of PPF are thus preferred, though provided that people do not suffer from photodermatoses with abnormal UV-sensitivity. In such patients with possible abnormal

UV-sensitivity a phototest with Solar or broadspectrum UVB is preferred to PPF.

CONCLUSIONS

This research work was initiated to investigate what the Fitzpatrick skin type actually represents with regard to the skin's reaction to UVR. To our knowledge this study is the first to combine volunteers with a broad spectrum of pigmentation and the use of repetitive UV-exposures to obtain this aim.

In contrary to what we expected, our results indicate that people do refer to the constitutive pigmentation (nates), but as expected do refer to multiple exposures rather than a single exposure to the sun, when classifying their Fitzpatrick skin type. This applied to both erythema (MED) and pigmentation response (MMD).

Only when tanning is preceded by erythema, there is a relation between UV-dose to pigmentation (SED to MMD) and skin type/PPF. In this study thus only after nUVB and Solar. For nUVB and Solar there was a linear relation between erythema (MED) and tanning ability (MMD) with the intercept different from zero. The correlation was better between SED to MED and skin type, than between SED to MMD and skin type. This applied to single and multiple exposures, suggesting that people pay more attention to the question of burning tendency than to the tanning ability in spite of what we expected based on the literature.

The long-waved UVA1 and broadband UVA should definitely not be used for objective skin type determination, as there was no relation between MMD and skin type/PPF. Both nUVB and Solar could be considered for objective skin type determination. As an alternative to nUVB, we propose to use broadspectrum UVB (e.g. TL12) as it has a spectral distribution closer to sunlight.

This study confirms that Fitzpatrick skin type is an unreliable predictor of UV-sensitivity with regard to MED- and MMD test. Fitzpatrick skin type in epidemiological context (risk for skin cancer) stands for burns and ability to tan, which may represent "cumulative" dose. In our study SED to MED is equivalent to burns. PPF may also indirectly represent cumulative dose – the less pigmented the skin the more UVR penetrates the epidermis and can accumulate. Our results indicate that Fitzpatrick skin type predominantly is determined by the skin pigmentation and that the second most important objective parameter is SED to MED (and not SED to MMD). This explains why Fitzpatrick skin type, eventhough being an unreliable predictor of UV-sensitivity, still plays an important role in epidemiology with regard to estimation of risk of skin cancer. However, these parameters are even better determined by PPF, which at the same time is highly correlated to Fitzpatrick skin type and PPF can be continued (objectively and fast). We conclude that it should be considered to concentrate on skin reflectance measurements with calculation of PPF, as PPF is preferred to predict the individual UV-sensitivity rather than the subjective Fitzpatrick skin type, confirmed for both nates and back, single as well as repetitive UV-exposures.

FUTURE PERSPECTIVES

It could be interesting to ask the volunteers two questions:"How easily do you burn?" and "how easily do you tan?" without the usual restrictions of combinations but still with the same gradation giving four answering possibilities for each question, so they could combine the answers freely, thus giving 4*4 = 16 combinations of answers for skin types I-IV. Furthermore, there should be no specification of whether it concerns one or repetitive sun exposure.

With our finding in mind, that Fitzpatrick skin type predominantly is determined by the individual skin pigmentation and that the second most important objective parameter is the tendency to burn (SED to MED), maybe one question: "how easily do you burn?" would cover the skin type. A visual analogue scale (VAS-scale) ranging from 0-10 could be used for grading the burning tendency. However, this has not been tested yet.

In a similar group with a wide pigmentation range (skin type I-V) it could be interesting to use exactly the UV-dose stated by Fitzpatrick, a rather unspecified dose, defined as

"3 MEDs or about 45 to 60 minutes of noon exposure in northern (20º to 45º) latitudes in the early summer" equivalent to 90 mJ/cm2 (In Denmark equivalent to 9 SED). Thus the same physical dose for all persons, for a single exposure to a Solar Simulator and afterwards examine their erythema response respectively 1 day after and tanning response 1 week after to see how these objectively determined parameters, the persons are asked to try to recall, actually corresponds to their self-evaluated skin type. The erythema response could be evaluated by reflectance measurements or by clinical evaluation, but as only one point should be assessed and the clinical scale only offers 4 possible erythema grades, reflectance measurements may be preferred. Eventually different UV-sources could be used.

SUMMARY

The overall aim of this Ph.D. project was to clarify what the subjective Fitzpatrick skin type represents with regard to the skin's reaction to UVR. Fitzpatrick skin type is used as an expression of the constitutive UV-sensitivity. It has been used for guiding dose-levels in phototherapy and is an important risk factor for skin cancer.

The subjective Fitzpatrick skin type and the measured skin type PPF (pigment protection factor, calculated based on a skin reflectance measurement, predicts the UV-dose (SED) to give 1 MED) were investigated parallelly in relation to the clinically determined dose to erythema (MED) and/or pigmentation (MMD) to determine which one related best. PPF is an established method for assessing UV-sensitivity by predicting SED to MED. UV-dose to MED and/or MMD was determined after single UV-exposure to Solar Simulator on nates (n= 84) and after single and multiple (5, 6 or 12) UV-exposures (n = 24-62) on the back to four UV-sources (nUVB, Solar, bUVA and UVA1). SED to MMD was also related to wavelength. MED was only determined after a single and four UV-exposures to narrowband UVB (nUVB) and Solar Simulator (Solar). Volunteers with a broad range of constitutive pigmentation (skin types I-V) were included. Equal MMD doses (predetermined after a single UV-exposure) were used at the multiple exposures.

The absolute increase in pigmentation after 6 and 12 UV-exposures, where steady-state pigmentation was reached, was independent of skin type and therefore could not enter into the calculations. But it proved that the MMD determinations after single exposure were correct and could be used at multiple UV-exposures.

In contrary to what we expected, our results indicate that people may refer to the constitutive pigmentation, when they reply to the question of Fitzpatrick skin type. This applied to both erythema and pigmentation response as both dose to MED and MMD showed a better correlation to nates than to the back.

As expected, our results from the back indicate that people seem to refer to sun sensitivity after multiple exposures to the sun rather than a single sun exposure, when they reply to the

question of Fitzpatrick skin type. Hence, both SED to MED and SED to MMD are better correlated to skin type after respectively 4 and 5 exposures to Solar Simulator and nUVB compared to 1 exposure.

Only when tanning is preceded by erythema there is a relation between SED to MMD and skin type/PPF. Thus only after nUVB and Solar. For nUVB and Solar there was a linear relation between erythema and tanning ability with the intercept different from zero. In spite of what we expected based on the literature, the correlation was better between SED to MED and skin type than between SED to MMD and skin type. This applied to single and multiple exposures and to single calculations and multiple regression analyses.

The long-waved UVA1 and broadband UVA should definitely not be used for skin type determination, as there was no relation between MMD and skin type/PPF. Both nUVB and Solar can be considered.

Finally, based on the objective parameters: pre-exposure pigmentation measured by skin reflectance, MED and MMD we tried to predict the Fitzpatrick skin type by multinominal logistic regression analyses to evaluate the significance of the different parameters for the subjective skin type classification and thereby hopefully enlighten what Fitzpatrick skin type represents. For single UV-exposure only the pre-exposure pigmentation worked as a predictor of Fitzpatrick skin type, and that is what PPF is based on. When this parameter was removed, only SED to MED was significant. Our model succeeds better to classify people correct after multiple UV-exposure compared to a single UV-exposure.

PPF was predicted likewise and was highly correlated to SED to MED, as expected, and even higher correlated to Fitzpatrick skin type. SED to MMD was not significant.

This study confirms that Fitzpatrick skin type is an unreliable predictor of UV-sensitivity with regard to MED- and MMD test. Fitzpatrick skin type in epidemiological context (risk for skin cancer) stands for burns and ability to tan may represent "cumulative" dose. SED to MED is equivalent to burns. PPF may also indirectly represent cumulative dose – the less pigmented the skin the more UVR penetrates the epidermis and will be able to accumulate and induce skin cancer.

Our results indicate that Fitzpatrick skin type predominantly is determined by the skin pigmentation and that the second most important objective parameter is SED to MED (and not SED to MMD). This explains why Fitzpatrick skin type, eventhough being an unreliable predictor of UV-sensitivity, still plays an important role in epidemiology with regard to estimation of risk of skin cancer.

This study showed that PPF can predict the UV-sensitivity also with regard to the tanning ability (MMD), can be applied to multiple UV-exposures and to a broader pigmentation spectrum. PPF is preferred to predict the individual UV-sensitivity rather than the subjective Fitzpatrick skin type, confirmed for both nates and back, single as well as repetitive UV-exposures. It should therefore be considered to concentrate on skin reflectance measurements.

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