11

HIGH PROTECTIVE EFFECT OF UVA FILTER REINFORCED SUNSCREENS AGAINST PHOTOTOXICITY OF CHLORPROMAZINE AND BENZOYL PEROXYDE.

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Most of the modern sunscreens protect efficiently the skin against UVB (280-320 nm). However, very efficient UVB blocking formulations allow longer sun exposure and thus may lead to UVA over exposure. UVA are known to be involved in the pathogenesis of various photo induced dermatosis, aging and skin cancer. Moreover, most of the exogenous photosensitizers, and in particular the phototoxic agents, are activated by UVA radiations.

The aim of the present study, was to assess the protective effect of three UVB + UVA high protection sunscreens reinforced in short UVA domain (Anthelios line, La Roche-Posay, Mexoryl ®SX filter) against phototoxicity of topical Benzoyl Peroxyde (BP) and Chlorpromazine.

These products were compared to two other commercial sunscreens with different UVB and UVA filtration systems. At day 1, both phototoxic agents were applied under 24 h-occlusion on the back of ten volunteers . At day 2, the treated zones were exposed to increasing doses of UVA radiation. At day 3, the minimal phototoxic dose (MPD) was determined for both products. Then, the MPD was assessed on sunscreens protected skin at day 3, 4 and 5, using UVA doses of 3, 5 and 8 times the unprotected MPD value.

The sunscreens can be ranked according to three levels of protection. First, two formula of the short UVA filter reinforced line, protected respectively 100% and 50% of the volunteers following 3 and 8 MPD irradiation doses. Second, the third formula belonging to the same line protected 100% of the subjects after 3 MPD and 50% after 8 MPD. Third, the two others sunscreens, based on different UVA filtering systems, protected 50 to 90% and 0 to 10 % following respectively 3 and 8 MPD UVA doses.

These results clearly showed that a broad spectrum UVA filtration reinforced in the short UVA domain offers a more efficient protection against phototoxicity Benzoyl Peroxyde and Clhorpromazine, even in conditions of very high UVA exposure.

HIGH PROTECTIVE EFFECT OF UVA FILTER REINFORCED SUNSCREENS AGAINST PHOTOTOXICITY OF CHLORPROMAZINE AND BENZOYL PEROXYDE

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INTRODUCTION

Most of the modern sunscreens protect efficiently the skin against ultraviolets B (UVB: 280-320 nm). However, very efficient UVB blocking formulations allow longer sun exposure and thus may lead to UVA overexposure. UVA (320-400 nm) are known to be involved in the pathogenesis of various skin diseases (photoageing, skin cancers, photodermatosis). Moreover, most of the exogenous photosensitizers, and in particular the phototoxic agents, are activated by UVA.

The aim of the present study was to assess the protective effect of three UVB+UVA high protection sunscreens reinforced in short UVA domain (Anthélios line, La Roche-Posay, Mexoryl® SX filter) against phototoxicity of topical benzoyl peroxyde and chlorpromazine. These products were compared to two other commercial sunscreens with different UVB and UVA filtration systems.

MATERIAL AND METHOD

Eighteen consenting healthy volunteers (13 females and 5 males), aged from 18 to 44 years (mean age = 28 ± 9 years) were included in this study.

Five commercially available sunscreen creams were tested:

Anthélios L, Anthélios 20, Anthélios T (La Roche-Posay Laboratoire Pharmaceutique). These products are based on a photostable combination of filters: UVB (methylbenzylidene camphor (Eusolex® 6300) + mineral screens) UVA short (Terephtalidene dicamphor sulfonic acid (Mexoryl® SX)) and UVA long (methoxydibenzoylmethane (Parsol® 1789)).
The fourth product (Product A) was a combination of UVB/short UVA and UVB filters (Oxybenzone, Octylmethoxycinnamate, Octylsalicilate), whereas the fifth product (Product B) contained special UVB filters (methoxycinnamic composed, phenylbenzimidazole) and long UVA filter (dibenzoylmethane derivative) and mineral screen (short UVA).

The light source was a solar simulator (IDEM 3000, Arquantiel, France) equipped with a high-pressure xenon-vapor lamp (1000 watts) and a combination of WG 335/3 mm + UG5/3 mm filters. This system offered mean UVA radiation (320-400 nm) intensity of 100 mW/cm².

Experimental design:

First of all, the test consisted to determine the Minimal Phototoxic Dose (MPD) on unprotected skin for each subject. Thus, on Day 1, 3 mg/cm² of a 10% benzoyl peroxyde gel (Panoxyl 10%, Stiefel) were applied under occlusion on a 20 cm² area of one side of the back. A petrolatum 0.1% chlorpromazine ointment (Trolab, Promedica) was applied in the same manner on the other side of the back. Twenty-four hours later (Day 2), each treated zone was exposed on five 1.5 cm² sites with increasing UVA doses (25% geometric progression). On Day 3, the MPD was determined for each irradiated zone. Following the MPD determination on unprotected skin, only ten subjects out of the eighteen showed clear-cut phototoxic reactions on both treated zones and were selected to continue the study.
Then, following the same procedure, the MPD was determined on sunscreen protected skin (Day 3, 4 and 5) using a UVA dose range of 3, 5 and 8 times the unprotected MPD. Clinical scoring system (0 to 4-scale) and colorimetry were used to assess the reactions 24 h and 48 h after irradiation. In addition, for each tested sunscreen, a colorimetric measurement was performed on a treated but non-irradiated site (control dose 0).

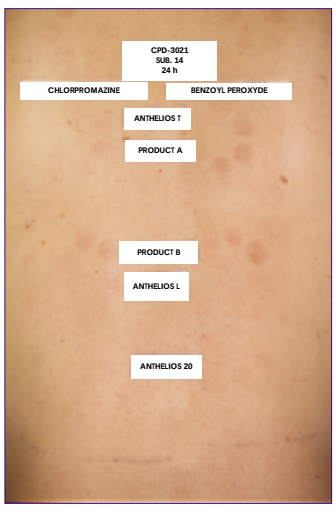

Photo 1

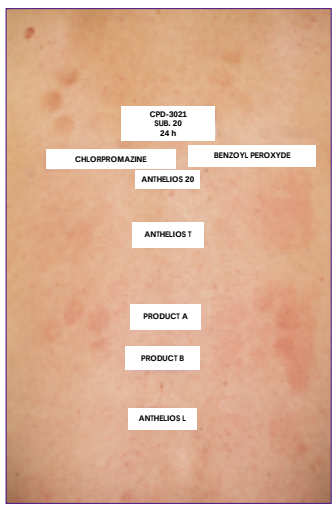

Photo 2

DOSES EXPRESSED IN MPD	Number of protected subjects 24 hours after irradiation (benzoyl peroxide)				
	Anthélios L	Anthélios 20	Anthélios T	Product A	Product B
3-MPD	100 %	100 %	100 %	80 %	90 %
5-MPD	100 %	90 %	70 %	40 %	20 %
8-MPD	90 %	80 %	40 %	10 %	10 %

Table 1:
Percentage of protected subjects as a function of the UVA dose (expressed in MPD) on benzoyl peroxyde treated zones.

RESULTS

The mean MPD value, obtained on the unprotected skin was 20.3 ± 2.7 J/cm² for benzoyl peroxyde and 13 ± 2 J/cm² for chlorpromazine.
Two products (Anthélios L and Anthélios 20) offered a very high level of protection against benzoyl peroxyde and chlorpromazine phototoxicity, whatever the UVA doses. Thus, very few phototoxic reactions were observed for these products. The percentage of protected subjects, observed 24 hours after irradiation, is summarized in Tables 1 and 2 as a function of UVA doses and tested products. No additional reactions were observed 48 hours after irradiation.

Figure 1 and 2 illustrate the results of colorimetric assessments (a*) performed 24 hours after irradiation on the irradiated and control zones for benzoyl peroxyde and chlorpromazine respectively.
Statistical comparisons (Student t-test for paired data) of sunscreens were carried out on the Δa* variable. Δa* corresponded to the a* values normalized from control value (unirradiated but treated zone), and expressed the increase of erythema due to phototoxic reaction. Results of statistical comparisons indicated that the three products reinforced in the short UVA domain produced generally significantly lower Δa* than products A and B.
Examples of typical reactions are given in photograph 1 and 2.

Thus, the sunscreens could be ranked in three levels of protection. First, two products, belonging to the short UVA filter reinforced line, protected 100% of subjects for 3xMPD and 80 to 90% for 8xMPD. Second, the third product of the same line protected also 100% of subjects for 3xMPD and about 50% for 8xMPD. Third, the two others sunscreens, based on different UVA filtrations, protected 50 to 90% of subjects for 3xMPD and only 0 to 10% for 8xMPD.

DOSES EXPRESSED IN MPD	Percentage of protected subjects 24 hours after irradiation (chlorpromazine)				
	Anthélios L	Anthélios 20	Anthélios T	Product A	Product B
			*		
3-MPD	100 %	100 %	100 %	50 %	80 %
5-MPD	100 %	100 %	88 %	30 %	20 %
8-MPD	90 %	100 %	55 %	0 %	10 %

** : tested on 9 subjects*

Table 2:
Percentage of protected subjects as a function of the UVA dose (expressed in MPD) on chlorpromazine treated zones

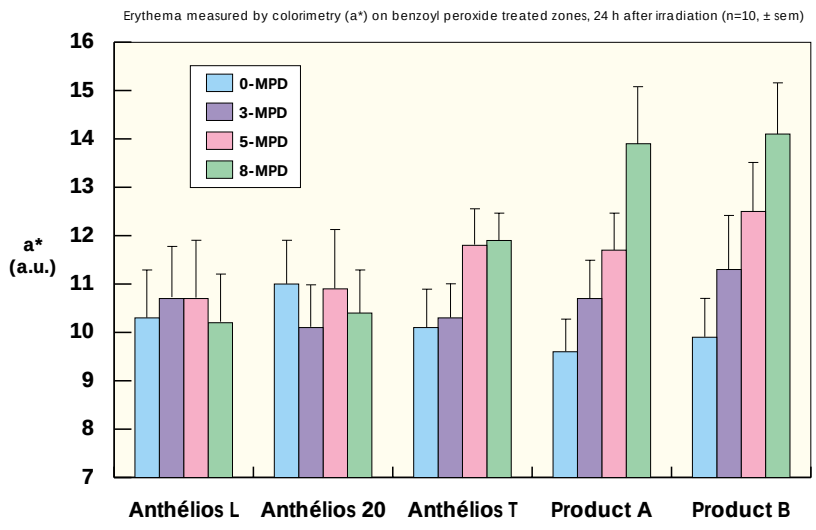

Figure 1:
Colorimetric assessment of erythema (a*) on benzoyl peroxyde treated zones, 24 hours after irradiation. (a.u.: arbitrary units, sem: standard error of the mean)

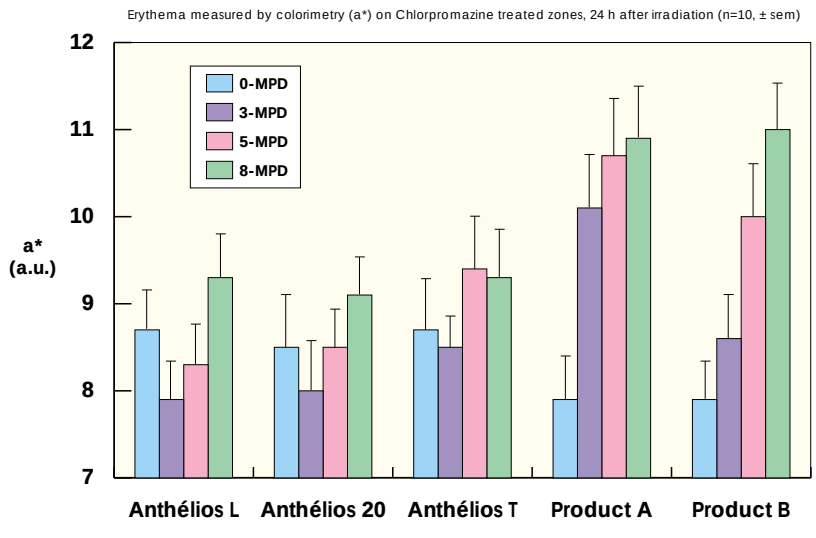

Figure 2:
Colorimetric assessment of erythema (a*) on Chlorpromazine treated zones, 24 hours after irradiation. (N=9 for Anthélios T, a.u .: arbitrary units, sem: standard error of the mean)

CONCLUSION

These results indicate that a broad spectrum UVA filtration reinforced in the short UVA domain (Mexoryl® SX filter) offers a more efficient protection against phototoxicity of benzoyl peroxyde and chlorpromazine, even in conditions of very high UVA exposure.

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12

PREVENTION OF SOLAR URTICARIA USING A BROADSPECTRUM SUNSCREEN AND DETERMINATION OF A SOLAR URTICARIA PROTECTING FACTOR (SUPF).

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Solar urticaria (SU) is a rare photodermatose whose preventive treatment remains difficult. An alternative would the use sunscreens products. Unfortunately, up to now, most them were found poorly effective as SU is known to be ellicited mainly by UVA.
We determined the Solar Urticaria Protection Factor (SUPF) using a broadspectrum sunscreen containing UVB (Eusolex 6300 + TiO_2) and UVA (Parsol 1789 + Mexoryl SX) filters (SPF (UVB) = 60; IPD/PPD (UVA) = 55/12). 10 patients susceptible to SU were investigated. The action spectrum of SU was determined in each patient following irradiation with a xenon arc solar simulator. Spectral bands used were: 360 +- 10 nm (long UVA), 335 +- 10 nm (short UVA), 310 +- 10nm (UVB). The Minimal Urticarial Dose (MUD) was assessed for each patient in his triggering spectral band. SUPF was then determined after topical application of the sunscreen formulation or its vehicle according to an arythmetical ratio of 2 MUD. Clinical assessment of erythema and swelling was performed in the early minutes following each irradiation dose.
6 patients responded to UVA (long UVA: 3; short UVA: 1; both: 2), 1 to UVB and 3 to UVA+UVB. The MUD ranged from 80 mJ to 1 J/cm^2 in the long UVA, from 40 mJ to 2 J/cm^2 in the short UVA and from 40 to 60 m J/cm^2 in the UVB. The SUPF of the vehicle ranged from 2 to 4, werheas that of the sunscreen formulation reached respectively 90 and 50 in the long UVA and in the short UVA, and 133 in the UVB.
These results demonstrate that SU can be effectively prevented when using a highly protective UVB and UVA sunscreen.

PREVENTION OF SOLAR URTICARIA USING A BROADSPECTRUM SUNSCREEN AND DETERMINATION OF A SOLAR URTICARIA PROTECTION FACTOR (SUPF)

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INTRODUCTION

Solar urticaria (SU) is a rare photosensitivity disorder.
Within 5 to 10 min of sun exposure, patients experience itching, erythema, and patchy or confluent whealing. Chronically exposed skin (face, harms) is generally less susceptible to be involved than areas normally covered. All solar wavelengths can be effective for SU induction.
Antihistamines or PUVA preventive treatments remain difficult. Another alternative could be the use of sunscreen products. Unfortunately, most of them are not sufficiently effective on the whole UV range, particularly in the UVA wave band which is mainly responsible for the elicitation of SU (1-4).
The aim of the present work was to determine the solar urticaria protection factor (SUFP) of a broadspectrum sunscreen highly efficient both in the UVB and UVA wavelengths.

MATERIALS AND METHODS

TEST PRODUCTS

- ANTHELIOS L La Roche Posay Pharmaceutical Laboratories (SPF 60, UVAPF 12*): UVB filter 5% (EUSOLEX® 6300), TIO_2 5%, UVA filters 6.75% (MEXORYL® SX and PARSOL® 1789), in O/W emulsion.
  * Persistent Pigment Darkening method (5).
- Vehicle (without filtering system).

PATIENTS

10 volunteers, 5 males and 5 females aged from 21 to 73 years, with skin type 2 and 3, unexposed to the sun or solar simulator since a minimum of 3 months.
Test area: the back

UV SOURCE

- 1000 W Xenon Arc solar simulator (Dermolum UM-W, MÜLLER, Germany) equipped with a monochromator, the UV-output of which was monitored with a thermopile.
- Spectral bands used for irradiation:

Experiment 1
- 285-320 nm (UVB)
- 320-400 nm (UVA)

Experiments 2 and 3
- 310 ± 10 nm (UVB)
- 335 ± 10 nm (short UVA)
- 360 ± 10 nm (long UVA)

CLINICAL ASSESSMENT

Clinical assessment of erythema and swelling was performed in the early minutes following each UV exposure dose.

STUDY DESIGN

For each experiment, the minimal urticarial dose (MUD) was determined after application of increasing doses of UVB and/or UVA.

Experiment 1

The susceptibility to SU of each patient was assessed in the UVB and in the UVA range.

Experiment 2

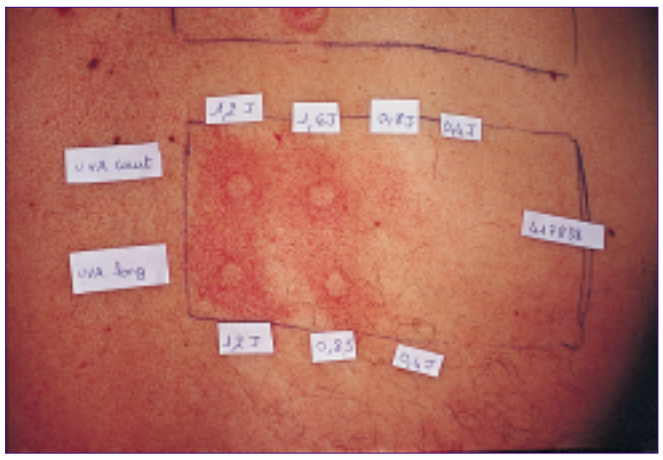
The minimal urticarial dose (MUD) on untreated area was determined for each patient and for each triggering spectral band.

Experiment 3

The protective effect of the sunscreen was assessed. Following the application of either 2 mg/cm^2 of the broadspectrum sunscreen or its vehicle, the MUD was determined again for each patient in each triggering spectral band defined in experiment 2.
SUPF was then determined for each patient as follow:

$$\text{SUPF} = \frac{\text{MUD with the sunscreen or its vehicle}}{\text{MUD without any product}}$$

The SUPF of the product is the arithmetical mean from all the individual SUPF found in each patient.



RESULTS

- **Experiment 1**

  7 patients responded to UVA exposure (long UVA: 3, short UVA: 1, both: 3), 1 to UVB and 2 to UVB + UVA.

- **Experiment 2**

  The MUD without product ranged from 0.08 to 1 J/cm^2 in the long UVA, from 0.04 to 2 J/cm^2 in the short UVA and from 4 to 60 mJ/cm^2 in the UVB.

- **Experiment 3**

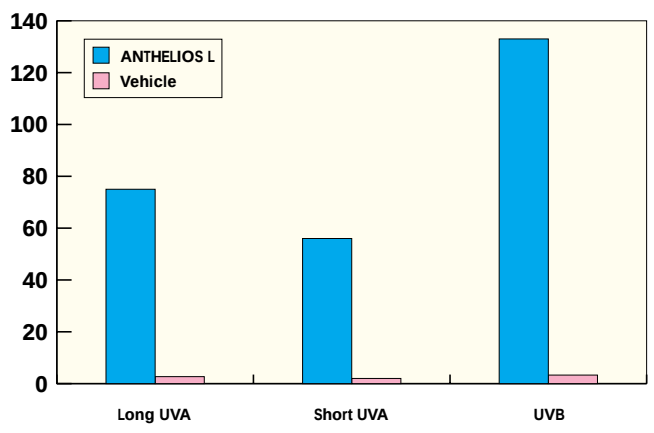
  The SUPFs of the vehicle were 2.7, 2 and 3.3, respectively in the long UVA, short UVA and UVB

  The SUPFs of the sunscreen were 75, 56 and 133, respectively in the long UVA, short UVA and UVB.

INDIVIDUAL RESULTS

VOLUNTEERS	N° 1 BRU...	N° 2 BEV...	N° 3 MAR...	N° 4 FER...	N° 5 DOS...	N° 6 DUF...	N° 7 LAM...	N° 8 CHA...	N° 9 PAR...	N° 10 BLA...
EXPERIMENT 1										
Spectral band of elicitation	UVA ------	UVA UVB	UVA ------	UVA ------	UVA ------	------ UVB	UVA ------	UVA UVB	UVA ------	UVA ------
EXPERIMENT 2										
MUD										
- long UVA (J/cm²)	1	0.5	------	0.3	1	------	0.7	0.08	0.4	0.4
- short UVA (J/cm²)	2	0.1	1.8	------	1	------	------	0.04	0.4	------
- UVB (mJ/cm²)	------	5	------	------	------	60	------	4	------	------
EXPERIMENT 3										
MUD with sunscreen										
- long UVA (J/cm²)	> 30	> 20	------	36	50	------	56	8	40.2	32
- short UVA (J/cm²)	40	5.8	0.2	------	40	------	------	2	45	------
- UVB (mJ/cm²)	------	700	------	------	------	9600	------	400	------	------
MUD with vehicle										
- long UVA (J/cm²)	4	1	------	0.9	2	------	2.8	0.16	0.8	1.2
- short UVA (J/cm²)	4	0.2	3.6	------	2	------	------	0.08	0.8	------
- UVB (mJ/cm²)	------	20	------	------	------	240	------	8	------	------
Broadspectrum sunscreen SUPF										
- long UVA	> 30	> 40	------	120	50	------	80	100	100.5	80
- short UVA	40	58	34	------	40	------	------	50	112.5	------
- UVB	------	140	------	------	------	160	------	2100	------	------
Vehicle SUPF										
- long UVA	4	2	------	3	2	------	4	2	2	3
- short UVA	2	2	2	------	2	------	------	2	2	------
- UVB	------	4	------	------	------	4	------	2	------	------

SOLAR URTICARIA PROTECTION FACTORS IN EACH TRIGGERING SPECTRAL BAND
(mean values)



CONCLUSION

These experiments settled that solar urticaria can be elicited by the different parts of the sun UV spectrum.

Moreover, most of the patients reacts to very low doses of UV light, particularly in the UVA wavelengths, confirming the extreme skin sensitivity to this photodermatosis.

Our results clearly showed that the use of sunscreens can be considered as an interesting alternative in the prevention of SU. However, to be effective against urticaria induction these sunscreens must provide highly efficient filtering properties, not only in the UVB but also in the UVA part of the solar spectrum.

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13

EFFICACY OF DIHYDROXYACETONE TREATMENT IN ADDITION TO A BROADSPECTRUM SUNSCREEN IN THE PREVENTION OF POLYMORPHOUS LIGHT ERUPTION

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In previous studies, we have enlighted (PLE) and the preventing effect of broadspectrum sunscreens with very high protective efficacy both in the UVB and UVA wavelenghts. We have also demonstrated that dihydroxyacetone (DHA), which reacts with skin surface proteins to produce brown polymers, could, in addition, potentiate the protective effect of conventional sunscreens, particularly in the UVA range.
The aim of the present work was to check in what an extent a simultaneous treatment of skin with DHA could improuve the efficacy of a sunscreen formulation recommended in PLE prevention.
14 female volunteers very susceptible to PLE were included in the study. In the 5 days preceding sun exposures, the volunteers were daily treated on one side of their chest (right or left) with a lotion containing 5% DHA. During the 7 days of sun exposures, which were performed in Tunisia, the daily application of DHA was maintained. Before each exposure, a SPF 60 and UVA-PF 16 (PPD method) sunscreen was applied onto the whole body. The UVA and UVB doses received were monitored using a Centra-Osram Uvmeter. A clinical examination was performed every evening and signs of PLE were recorded.
The results obtained in this experiment confirm the significant efficacy of the broadspectrum sunscreen used in the prevention of PLE, as compared with usual observations. Thus PLE was delayed and of lower intensity in 71.5 % of the cases or totaly prevented in 21.5% of the cases. In the DHA treated volunteers, this efficacy was increased up to 100 % of the cases. The assymetry of eruption between the two sides of the body, with or without DHA, was found obvious throughout the study.
In this preliminary work, we have demonstrated that recontructed skin or epidermis can constitute useful *in vitro* tools to study the phototoxicity potential of chemicals induced by UVA and to evaluate the efficacy of sunscreen formulations in the prevention of this adverse reaction.

EFFICACY OF DIHYDROXYACETONE TREATMENT IN ADDITION TO A BROADSPECTRUM SUNSCREEN IN THE PREVENTION OF POLYMORPHOUS LIGHT ERUPTION

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INTRODUCTION

In previous studies, we have enlighted the major role of UVA rays in eliciting Polymorphous Light Eruption (PLE) and the preventive effect of broadspectrum sunscreens with very high protective efficacy both in the UVB and particularly in the UVA wavebands. It has also been shown that dihydroxyacetone (DHA), which reacts with skin surface proteins in producing brown polymers, could potentiate the action of conventional sunscreens, particularly in the UVA range. The aim of this work was to assess to which extent a pretreatment of the skin with DHA could enhance the efficacy of a sunscreen product recommended for PLE prevention.

PRODUCTS TESTED

Selftanning lotion *: DHA 5% in O/W emulsion (AUTOHELIOS, LA ROCHE-POSAY Pharmaceutical Laboratories).

Broadspectrum sunscreen *: UVB filter 5%, UVA filters 6,75% (MEXORYL® SX and Parsol 1789), micronised TIO2 5% in O/W emulsion (ANTHELIOS L LA ROCHE-POSAY Pharmaceutical Laboratories). SPF 60 UVA PF 12 (PPD) 55 (IPD).

* AUTOHELIOS - ANTHELIOS L La Roche-Posay Pharmaceutical Laboratories

UVA PROTECTING FACTORS MEASUREMENTS

UVA protecting factors of the different products tested were determined using the Persistent Pigment Darkening Method (PPD) on 10 volunteers.

DHA pretreatment	Broadspectrum sunscreen UVB + UVA	DHA pretreatment + Broadspectrum sunscreen UVB + UVA
4 applications 2 applications / day during 2 days	1 application 2 mg/cm²	1 application 2 mg/cm²
UVA PF = 1.75	UVA PF = 16.3	UVA PF = 25.7

The DHA pretreatment potentiate the UVA protective efficacy of the broadspectrum sunscreen.

PREVENTION OF POLYMORPHOUS LIGHT ERUPTION

EXPERIMENTAL CONDITIONS

- *Patients*

14 female volunteers, very susceptible to PLE, mean age 39 years.
Duration of the PLE: 20 years.
Unexposed to the sun or solar simulator since a minimum of 4 months.

- *DHA pretreatment*

The selftanning lotion was applied once a day during 5 days prior sun exposure on one side of the body (left or right) (the arms excepted).

- *DHA treatment during sun exposures*

The selftanning lotion was reapplied every evening.
The broadspectrum sunscreen was applied before each sun exposure on the entire body.
The arms which serve as control, were treated with a sunscreen containing only UVB filters.

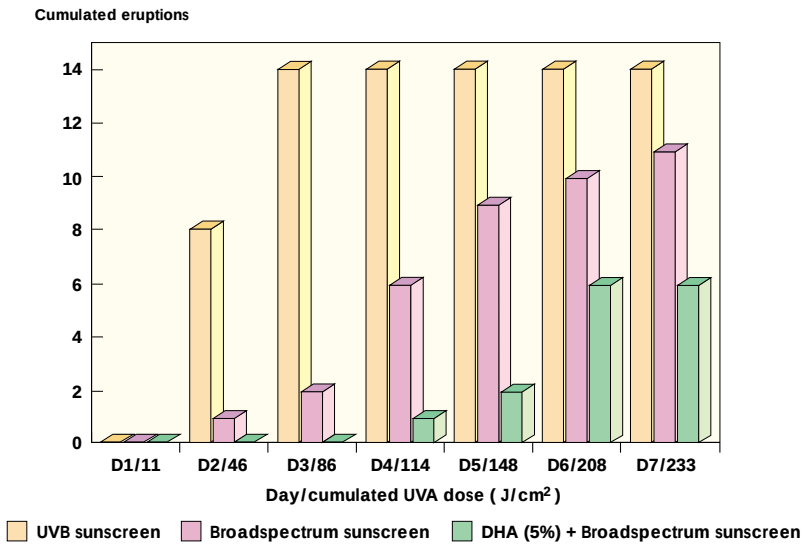
- *Sun exposures*

Sun exposures were performed during 7 days in June 1995 in Tunisia (Djerba, latitude 33° 50 N, longitude 10° 48 E).
Two exposures per day, one in the morning and one in the afternoon.
The UVB and UVA doses effectively received were monitored using a Centra Osram® UVmeter.

- *Clinical examinations*

A clinical examination were performed by the dermatologist every evening and the signs of PLE were recorded.

RESULTS



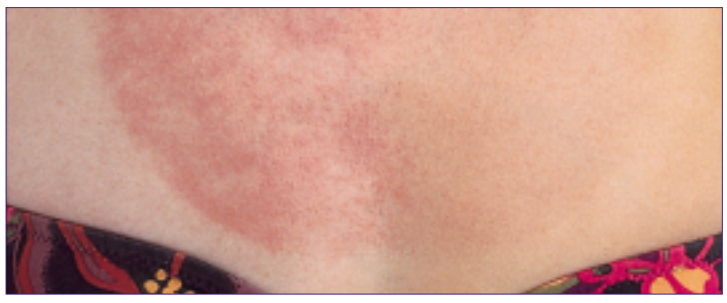
PLE was elicited on the arms of 14 volunteers protected by the UVB sunscreen: 8 eruptions at day 2 and 6 others at day 3. These early eruptions confirm the high susceptibility of the patients to PLE.

When the broadspectrum sunscreen was used an eruption was observed on the chest after 3 days on 2 patients only.

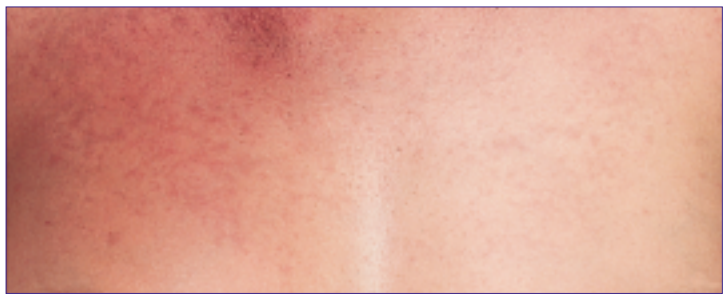
In intense conditions of sun exposures, PLE was significantly delayed and of lower intensity in 71.5 % of the cases and totaly prevented in 21.5 %. Finally satisfactory and excellent prevention was found in 93% of the patients.

With the additional DHA treatment the efficacy of the broadspectrum sunscreen was enhanced in 100% of the cases. Moreover PLE was either totally prevented or more delayed and of minimal intensity.

The asymmetry of eruption between the two sides of the body, with or without DHA treatment, was found evident throughout the study.



Without DHA



With DHA

CONCLUSION

The present study has clearly demonstrated that the use of a highly efficient UVB + UVA sunscreen can prevent from PLE. Moreover, this prevention is improved by treating the skin with DHA.

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14

PRETREATMENT OF HUMAN SKIN WITH A SUNSCREEN OR DIHYDROXY-ACETONE (DHA) PREVENTS PHOTO - PROVOCATION - INDUCED POLYMORPHOUS LIGHT ERUPTION (PLE) AND KERATINOCYTE (KC) ICAM-1 EXPRESSION.

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PLE represents an abnormal response of human skin to UVA-radiation (UVAR), which is characterized by the expression of proinflammatory molecules such as ICAM-1 on the surface of KC. We have assessed whether the induction of KC ICAM-1 expression and the development of skin lesions in PLE patients may be affected by topical application of a UVA/UVB filtering sunscreen (Eusolex 6300 + TiO_2 + Parsol 1789 + Mexoryl SX; Anthelios L) or pretreatment with DHA (Autohelios).
Skin lesions were induced by simultaneously using 2 different protocols: (i) exposure of previouly affected skin to 3x100 J/cm^2 UVA or (ii) to 20, 20, 30, 40, and 60 J/cm^2 UVA for 5 days.
We found that Anthelios L was higly effective in protecting against UVAR-induced skin lesions in 9/10 patients regardless of the photoprovacation protocol used. A strong KC ICAM-1 expression was observed in UVA-irradiated, but not in sunscreen pretreated + UVA-irradiated, or normal control skin. Pretreatment of skin areas with DHA also provided protection against UVAR-induced PLE lesions in 5/8 patients.
These studies indicate that both the broad spectrum sunscreen and, to a lesser extent, the DHA formulation tested, provide significant protection against the induction of skin lesions in PLE. Moreover, KC ICAM-1 expression and development of skin lesions in PLE patients are closely linked and may be causally related.
the major role of UVA in the induction of Polymorphous Light Eruption

PRETREATMENT OF HUMAN SKIN WITH A SUNSCREEN OR DIHYDROXY-ACETONE (DHA) PREVENTS PHOTOPROVOCATION-INDUCED POLYMORPHOUS LIGHT ERUPTION (PLE) AND KERATINOCYTE (KC) ICAM-1 EXPRESSION

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INTRODUCTION

Polymorphous light eruption represents an abnormal response of human skin to UV radiation, especially to UVA-radiation (UVAR), which is characterized by interindivudual polymorphic but intraindividual monomorphic skin lesions. In immunohistochemical studies PLE was characterized by increased and prolonged expression of proinflammatory molecules in the epidermis, such as ICAM-1 on the surface of keratinocytes (KC) (1).

Commonly used strategies to protect human skin against deleterious effects exerted by UV-radiation include topical application of sunscreen formulations as well as self-tanning ointments. In recently published studies (2), it has been demonstrated that dihydroxyacetone (DHA), which reacts with skin surface proteins in producing brown polymers, potentiates the efficacy of conventional broadspectrum sunscreens, particularly in the UVA range.

ANTHELIOS L is a recently developed sunscreen which contains both UVB and UVA filters and thus should be suitable to prevent the induction of lesions in PLE patients. In addition, AUTOHELIOS is a DHA containing ointment which induces an ocre-brown pigmentation with poorly defined photoprotective abilities.

Purpose: Does topical application of a UVA/UVB filtering sunscreen or pretreatment with DHA prevent the induction of experimentally induced skin lesions and ICAM-1 expression in PLE patients?

MATERIAL AND METHODS

PLE patients

n = 10, diagnosis clinically and histologically proven, unexposed to sun lignt or solar simulator irradiation for a minimum of 4 months.

Products tested

- ***Self tanning ointment:*** 5% DHA in O/W emulsion (AUTOHELIOS, La Roche-Posay Laboratoire Pharmaceutique).
- ***Sunscreen:*** O/W emulsion (ANTHELIOS L, La Roche-Posay Laboratoire Pharmaceutique) containing: 5% UVB filter (EUSOLEX® 6300), 6.75 % UVA filters (MEXORYL®SX - PARSOL® 1789), 5% micronized TiO_2, [SPF 60, UVAPF 12 (PPD) 55 (IPD)].
- ***UVA protecting factors***
  UVAPF of the products tested were previously determined according to the Persistent Pigment Darkening methods (PPD) on 10 healthy volunteers. The UVAPF obtained were:
  - DHA pretreatments = 1.75
  - Broadspectrum sunscreen = 12

Treatments

- ***Self tanning ointment:*** 1 application/day (day -4 to -1 before UVA irradiation protocols I or II).
- ***Sunscreen:*** 1 application (2 mg/cm²) 20 min before each irradiation protocols I or II.
- ***Control:*** Unprotected skin area (self tanning ointment or sunscreen).

Photoprovocation protocols

- ***UV-radiation:*** UVA 1 (340-400 nm); System Dr. Sellmeier 2000 device (Sellas, Ennepetal, Germany)
- ***Protocol I :*** Increasing UVA-doses during 5 consecutive days (20, 20, 30, 40, 60 J/cm²).
- ***Protocol II :*** One single UVA-dose (100 J/cm²)/day during 3 consecutive days.

End points

- Clinical examination was performed by the dermatologist and signs of PLE were recorder.
- Immunohistochemistry was performed on skin punch biopsies according to the labeled streptavidin-biotin method (LSAB) (3) using the ICAM-1 antibody Mab 84H10. The biopsies were taken from the untreated skin which were exposed to photoprovocation protocol II and from the ANTHELIOS L or AUTOHELIOS treated skin areas, which were also treated with the same photoprovocation protocol (n=5).

RESULTS

1 - Effect of topical application of UVA/UVB sunscreen

In 10/10 patients photoprovocation testing either with increasing UVA-doses up to 60 J/cm² or 1 x 100 J/cm² UVA on 3 consecutive days induced PLE-lesions in unprotected or untreated skin. In 9/10 patients application of the UVA/UVB protecting sunscreen ANTHELIOS L completely prevented the induction of PLE lesions using the photoprovocation protocol I. The broadband sunscreen ANTHELIOS L also prevented the experimental induction of PLE-lesions in 9/10 volunteers after 3 consecutive irradiations with 100 J/cm² UVA (Table 1), indicating that application of ANTHELIOS L was effective in the prevention of the induction of PLE lesions in the same volunteers regardless of the photoprovocation protocol used. In immunohistochemical studies [photoprovocation protocol II (n=5)] the KC ICAM-1 expression could be detected in experimentally provoked PLE-lesions, but not in sunscreen-protected skin areas (Table 2).

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Table 1:
Prevention of experimental induction of PLE lesions after topical application of ANTHELIOS L or pretreatment with AUTOHELIOS.

Volunteers	untreated skin (protocol I)	untreated skin (protocol II)	ANTHELIOS L treated skin protocol I	ANTHELIOS L treated skin protocol II	AUTOHELIOS pretreated skin protocol I	AUTOHELIOS pretreated skin protocol II
1	+ +	+ +	-	-	n.d.	n.d.
2	+ +	+ +	-	-	-	-
3	+ + +	+ + +	-	-	-	-
4	+ +	+ +	-	-	-	-
5	+ +	+ +	-	-	n.d.	n.d.
6	+	+ +	-	-	+	+
7	+	+	-	-	+	+
8	+ +	+ +	-	-	-	-
9	+ +	+ +	-	-	-	-
10	+ + +	+ + +	+ +	+ +	+ + +	+ + +

+ positive induction of PLE lesions, ++ strong induction of PLE lesions, +++ very strong induction of PLE lesions, - no induction of PLE lesions.

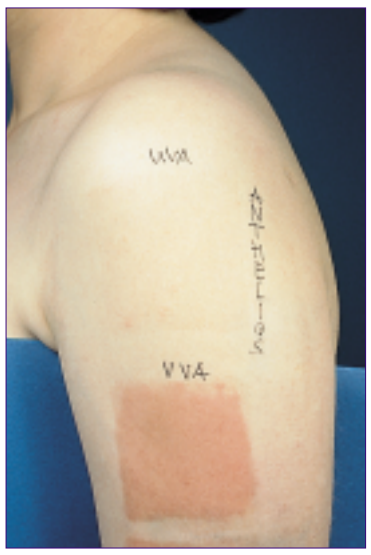
Table 2:
Prevention of experimental induction of KC ICAM-1 expression in the UVA-exposed skin of PLE patientsafter topical application of ANTHELIOS L or pretreatment with AUTOHELIOS.

Volunteers	untreated skin (protocol II)	ANTHELIOS L treated skin protocol II	AUTOHELIOS pretreated skin protocol II
2	+ +	-	-
3	+ + +	-	-
4	+ +	-	-
8	+ +	-	-
9	+ +	-	-

+ weak ICAM-1 expression, ++ moderate ICAM-1 expression, +++ very strong ICAM-1 expression, - no ICAM-1 expression.

1 - Effect of topical application of 5% DHA

In 5/8 patients pretreatment with AUTOHELIOS completely prevented the experimental induction of PLE-lesions which were provocated in all tested individuals using both protocol I and protocol II (Table 1). In experimentally induced PLE-lesions, increased KC ICAM-1 expression could be observed, whereas no KC ICAM expression could be found in DHA-pretreated and UVA-irradiated skin (photoprovocation protocol II) (Table 2).



You can see erythematous and papular reaction in UVA-irradiated skin area, but not in ANTHELIOS L protected skin area.

CONCLUSION

These studies indicate that both the sunscreen and, to a lesser extent, the DHA preparation tested provide significant protection against the experimental induction of skin lesions in PLE patients. They also suggest that induction of KC ICAM-1 expression and development of skin lesions in PLE patients are closely linked and may be causally related. In previous studies, a 1 week treatment of human skin with DHA was found to induce skin pigmentation, resulting in a UVA protection factor of 1.75. It is therefore unlikely that the protective effect of DHA is due to a sunscreen effect of the DHA-induced skin pigmentation. Because UVA-radiation-induced skin lesions in PLE patients and UVA-radiation-induced KC-ICAM-1 expression previously were shown to involve the generation of reactive oxygen species, it is tempting to speculate that DHA application to human skin may have anti-oxidative consequences (4).

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15

INFLUENCE OF HIGH PROTECTIVE SUNSCREENS ON THE PHOTOISOMERIZATION OF UROCANIC ACID IN HUMAN SKIN.

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Production of *trans*-urocanic acid (UCA) in the skin is due to the enzymatic deamination of histidine. Under UVB (290-320 nm) and UVA (320-400 nm) a *trans* to *cis* isomerization is observed. Because *cis*-UCA is involved in some immunosuppressive mechanisms, we have tested the efficiency of different sunscreens against this reaction in human skin by varying the Sun Protection Factor (SPF) and the UVA Protection Factor (UVAPF).
Four areas were delineated on the skin of the back of 15 volunteers. One was untreated. Two mg/cm^2 of each sunscreen were applied on the others 15 minutes before a single exposure to Solar Simulated Radiation (SSR) or UVA radiation. UCA isomers were sampled using the tape-stripping technic and quantified by liquid chromatography.
The results obtained have shown a very high influence of the UVA on the photoisomerization of UCA. This explains that a sunscreen highly protective in the UVB but poorly effective in the UVA (SPF 75, UVAPF 3) is not more efficient than a sunscreen having a low SPF value (SPF 8, UVAPF 2).
The best photoprotection is obtained with a sunscreen having a high absorption spectrum covering the UVB and UVA ranges (SPF 60, UVAPF 16).

INFLUENCE OF HIGH PROTECTIVE SUNSCREENS ON THE PHOTOISOMERIZATION OF UROCANIC ACID IN HUMAN SKIN

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INTRODUCTION

Taking into account the following properties of urocanic acid:

- Production of *trans*- urocanic acid (UCA) in the skin is due to the enzymatic deamination of histidine (1).
- Under UVB (290-320 nm) and UVA (320-400 nm) exposure *trans*- to *cis*-UCA and *cis*- to *trans*-UCA conversions occur (2, 3).
- UCA photoisomerization is independent of skin type. This indicates that UCA photoisomerization and erythema are independent processes (4).
- *cis*-UCA can be involved in some immunosuppressive mechanisms (5).

We have used the photoproduction of *cis*-UCA in human skin exposed to UVB+A or UVA radiation as a physiological dosimeter in order to compare the protection efficiency of some sunscreens having different Sun Protection Factor (SPF) and UVA Protection Factor (UVAPF).

MATERIALS AND METHODS

- **Subjects**

Fifteen healthy informed volunteers with skin type II participated in the study. Only volunteers non exposed to sunlight or solar simulator since a minimum of 3 months were selected.

- **UV Sources**

A Supersun Mutzhas lamp with an emission spectrum between 290-390 nm was used as UVB+A source and with an emission spectrum in the 320-400 nm range as UVA source.

Dosimetric measurements were performed using a Centra Osram UVmeter.

- **Sunscreens**

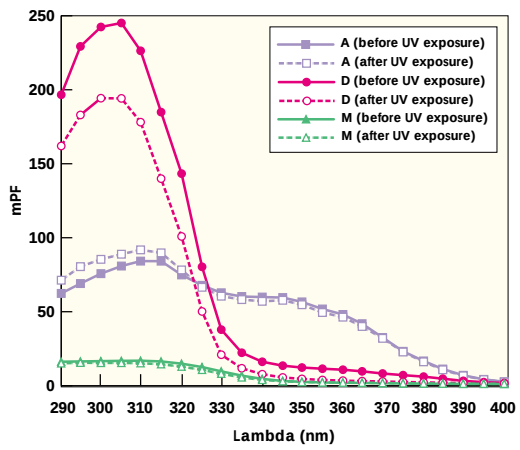
Three commercial sunscreens were evaluated in the study.

- Sunscreen A * (SPF 60 and UVA PF** 12),
- Sunscreen D (SPF > 60 and UVA PF 3),
- Sunscreen M (SPF 8 and UVA PF 2).

* Anthelios L - La Roche-Posay, Laboratoire Pharmaceutique - France

** Protection factor based on the Persistent Pigment Darkening (PPD) reaction (6).

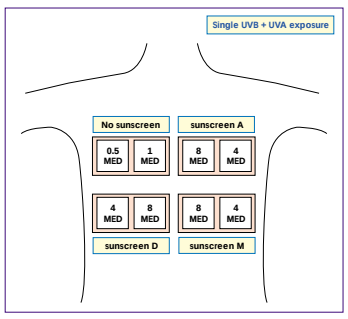
Monochromatic protection factor spectra of the 3 sunscreens tested before and after UV exposure

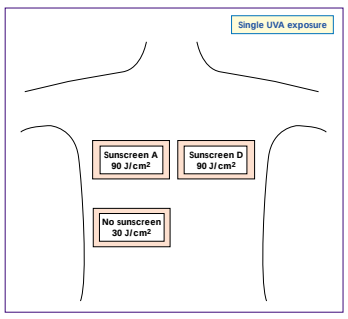


mPF spectra were obtained *in vitro* after application of 1 mg/cm^2 of sunscreen on a quartz plate. First measurements were performed 15 min after application of the sunscreen on the plate and before UV exposure. Second measurements were performed after 1 hour UV exposure (Suntest lamp, dose ~18 J/cm^2 UVB + UVA).
Sunscreens A and M were not influenced by UV exposure whereas protection efficiency of sunscreen D decreased significantly both in the UVB and UVA ranges.

- **Study design**

Two mg/cm^2 of each sunscreen were applied onto a defined area of the back 15 min before a single UVB+A (290-390 nm) or UVA (320-400 nm) exposure.

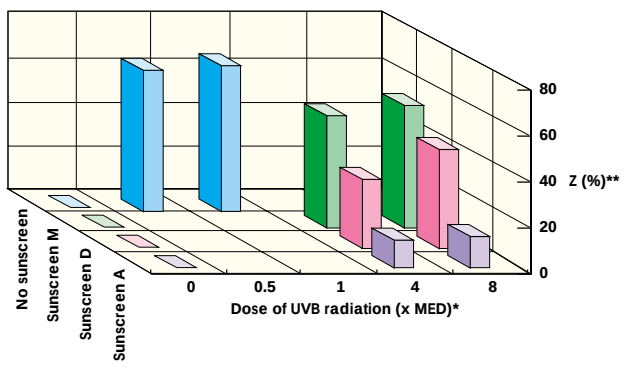




At the end of exposure, 6 successive tape strippings (4 cm^2 area) were performed on each area using adhesive disks (Haas, Sumoreau, France). *trans*- and *cis*-UCA in each strip were quantified by HPLC (4).

RESULTS AND DISCUSSION

1 - EFFECTS OF UVB+A EXPOSURE



RELATIVE AMOUNT OF *cis*-UCA AFTER A SINGLE UVB + UVA EXPOSURE

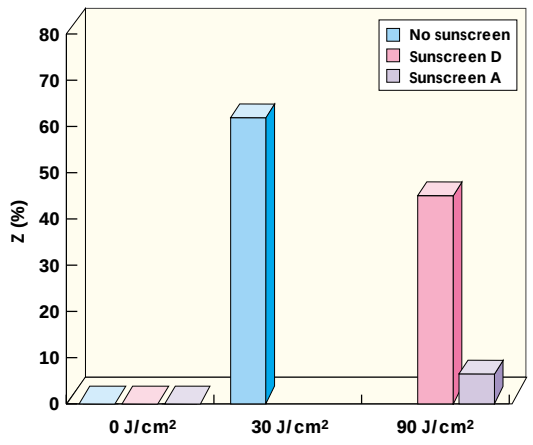
* (1 MED = 250 mJ/cm^2 UVB + 4.6 J/cm^2 UVA)
** Z (%) = percentage of UCA present under the *cis* form

Sunscreen A (SPF 60, UVA PF 12) is more efficient in preventing *cis*-UCA formation than sunscreen D (SPF >60, UVA PF 3) and sunscreen M (SPF 8, UVA PF 2). Such an observation confirms that:

- UVA are highly effective in producing *cis*-UCA.
- UCA photoisomerization and erythema are independent processes.

It results from this that the protective efficacy of a sunscreen should not be described using a single erythemal protection factor (SPF)(7) but requires information about its effectiveness in the UVA range.

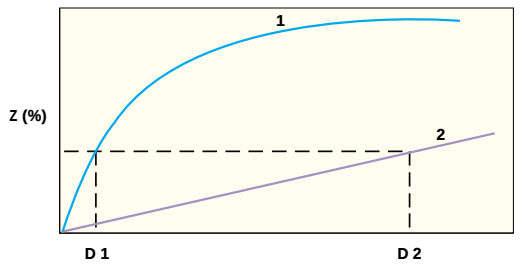
2 - EFFECTS OF UVA EXPOSURE



RELATIVE AMOUNT OF *cis*-UCA AFTER A SINGLE UVA EXPOSURE

This experiment confirmed the high contribution of the UVA in the production of *cis*-UCA. Only the highly protective broad-spectrum sunscreen A decreased significantly *cis*-UCA production induced by a single UVA exposure.

3 - PREVENTION OF *cis*-UCA PRODUCTION



INFLUENCE OF THE DOSE ON THE PRODUCTION OF *cis*-UCA

Z (%) represents the percentage of *cis*-UCA present at a given irradiation dose.
Indices « 1 » and « 2 » correspond to non protected and sunscreen protected areas, respectively.

Prevention of *cis*-UCA production can be assessed by using a « *cis*-UCA protection factor » such as:

cis-UCA protection factor = D2 / D1.

COMPARISON OF *cis*-UCA PROTECTION FACTOR, SPF, AND UVA PF OF THE SUNSCREENS TESTED

SUNSCREEN	UVA PF	*cis*-UCA PROTECTION FACTOR	SPF
A	12	250	60
D	3	40	>60
M	2	20	8

These values clearly indicate that a significant decrease in the *cis*-UCA formation requires the use of broad-spectrum (UVB plus UVA),highly protective sunscreens.

Because there is no direct relationship between UCA photoisomerization process and erythema, we suggest this reaction may be used as a complementary parameter in the assessment of the UV protection provided by sunscreens.

As a consequence of the influence of UVA in producing *cis*-UCA, a link between the UVA Protection Factor and the *cis*-UCA Protection Factor seems to be observed.

CONCLUSION

A significant decrease in the *cis*-UCA production rate can be obtained only using potent sunscreen providing high UVB and UVA protection.

Such enhanced protection was provided by an optimised photostable filtering system covering the entire UV spectrum (UVB + UVA), composed of MEXORYL® SX, PARSOL® 1789, EUSOLEX® 6300 and TiO_2.

Furthermore, this study clearly indicates that the protection efficiency of a sunscreen cannot be described with a single UV protection factor but requires information about its effectiveness both in the UVB and in the UVA ranges.

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