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# **Blue light impairs the repair of UVB-induced pyrimidine dimers in a human skin model**

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## 1 **ABSTRACT**

2 In the recent years, interest is growing in the biological cutaneous effects high-energy visible  
3 light (400-450 nm). In the present study, we explored the impact of blue light (BL) on the repair  
4 of pyrimidine dimers, the major class of premutagenic DNA damage induced by exposure to  
5 sunlight. We unambiguously demonstrate that the exposure of *in vitro* reconstructed human  
6 epidermis to environmentally relevant doses of BL strongly decreases the rate of repair of  
7 cyclobutane pyrimidine dimers and pyrimidine (6-4) pyrimidone photoproducts induced by a  
8 subsequent UVB irradiation. Using the highly sensitive and specific liquid chromatography /  
9 tandem mass spectrometry assay, we did not observe induction of pyrimidine dimers by BL  
10 alone. Finally, we showed that application, during the BL exposure step, of a formula containing  
11 a new filter, named TriAsorB and affording BL photoprotection, prevented the decrease in DNA  
12 repair efficiency. These results emphasize the potential deleterious effects of BL on DNA repair  
13 and the interest in providing adequate skin protection against this wavelengths range of sunlight.

14

## 15 INTRODUCTION

16 Ultraviolet (UV) irradiation leads to harmful effects including skin aging and skin cancer due to  
17 increased production of cellular reactive oxygen species and by direct DNA damage. Damaged  
18 DNA, if not properly repaired, is a source of mutations, and interferes with many cellular  
19 mechanisms such as replication, transcription, and cell cycle. Recent studies have highlighted  
20 the impact of the visible light on the skin. An action spectrum of visible light in HaCat  
21 keratinocytes showed that the deleterious effect decreased in the order violet > blue > green >  
22 red (1). These observations demonstrate the major role played by high-energy visible light  
23 spectral range (400-450 nm). Large amounts of information have been in particular gathered on  
24 blue light (BL) and revealed damaging effects on cutaneous cells mainly by inducing an  
25 oxidative stress. In keratinocytes cultured *in vitro*, violet and BL have been shown to induce  
26 oxidative stress, mitochondrial dysfunctions and blockade of autophagy and DNA damage (2,  
27 1, 3). Similar observations were made in melanocytes (4). Another interesting feature of visible  
28 light is that it is more abundant and penetrates deeper into the skin layers than UV. BL have  
29 been implicated in erythema, hyperpigmentation and premature skin aging (5-9). Induction of  
30 oxidative stress is also documented (2). This evidence that BL is active in skin raises the concern  
31 about a possible worsening impact of BL on effect of UV.

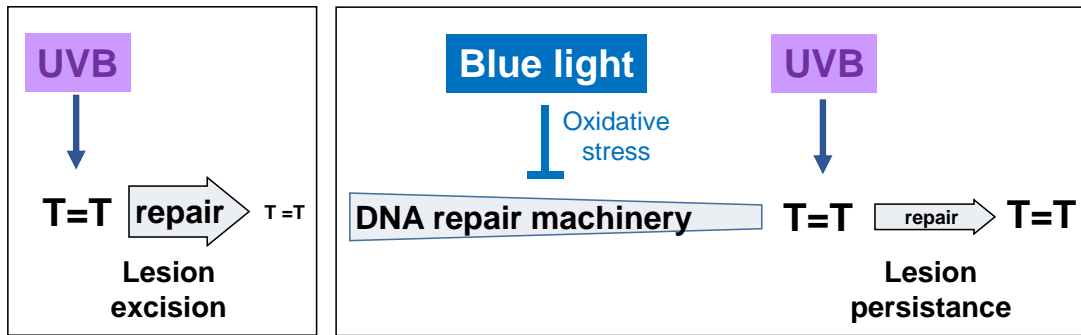
32 A major issue in the deleterious effect of sunlight is its genotoxicity, which is directly linked to  
33 induction of skin cancer. *In vitro*, BL has been shown to damage DNA by oxidation processes  
34 (10, 11, 1, 3). The latter are triggered by BL mediated photosensitization reactions involving  
35 endogenous chromophores (2, 12). Superoxide anion is the main species produced (2), likely  
36 through excitation of flavins (13). BL has also been shown to induce chromosome aberrations

37 *in vitro* (3). BL-induced DNA damage is yet approximately 3 orders of magnitude less efficient  
38 at damaging DNA than UVB at inducing cyclobutane pyrimidine dimers (CPDs) (10, 11). More  
39 recently, a study on human volunteers showed that the induction of dark CPDs was efficient at  
40 380 nm but not in the visible light range (14). These results strongly suggest that the DNA  
41 damage induced by BL do not significantly contribute directly to the initiation of skin cancer.  
42 However, BL may be indirectly genotoxic by preventing the repair of DNA damage induced by  
43 other wavelengths ranges, especially carcinogenic UVB.

44 In order to test this hypothesis, we designed a realistic protocol where reconstructed human  
45 epidermis (RHE) were first exposed to BL and then to UVB. We further took advantage of the  
46 photoprotective efficacy against BL of the new sunfilter Phenylene Bis-Diphenyltriazine  
47 (TriAsorB<sup>®</sup>) to unambiguously establish the role of BL. This organic sunscreen has a critical  
48 wavelength  $\approx$  390 nm. The filter effectively absorbs visible light especially in the region from  
49 400 to 450 nm bandwidth. The absorbance decreases with increasing wavelength and dropped  
50 at about 0.1 at 450 nm with a  $\lambda_{Vis-CW} = 594$  nm (15). Moreover, TriAsorB is also able to reflect  
51 BL with a peak of reflectance at about 450 nm and a progressive decrease up to 700 nm (15). Its  
52 filtering efficacy against BL radiations has been demonstrated by inhibition of the formation of  
53 8-oxo-7,8-dihydroguanine in reconstructed human skin after exposure to 80 J.cm<sup>-2</sup> of BL at  
54 427 $\pm$ 30 nm. Moreover, TriAsorB formulation as a SPF50<sup>+</sup> sunscreen in combination with other  
55 UV filters prevented cellular photodamage and BL-induced oxidatively generated DNA lesions  
56 (9).

57

58 **GRAPHICAL ABSTRACT**



59

60 Exposure of reconstructed human epidermis with blue light decreases the rate of repair of  
61 pyrimidine dimers induced in DNA by a subsequent UVB irradiation. This deleterious effect is  
62 prevented by application of a sunscreen exhibiting blue light photoprotection.

63

64

## 66 **MATERIALS AND METHODS**

### 67 **TriAsorB and SPF50<sup>+</sup> sunscreen formulations**

68 The commercially available SPF50<sup>+</sup> sunscreen containing TriAsorB<sup>®</sup> (Laboratoires Eau  
69 Thermale Avène, France) is a combination with three other UV filters: diethylamino  
70 hydroxybenzoyl hexyl benzoate (Uvinul A+<sup>®</sup>, BASF SE), ethylhexyl triazone (Uvinul T150<sup>®</sup>,  
71 BASF SE) and bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S<sup>®</sup>, BASF SE), as  
72 recently reported (9). This sunscreen contains Avène thermal spring water, C12-15 alkyl  
73 benzoate, caprylic/capric triglyceride, dicaprylyl carbonate, diethylamino hydroxybenzoyl  
74 hexyl benzoate (Uvinul A+), glycerine, ethylhexyl triazone (Uvinul T150), phenylene bis-  
75 diphenyltriazine (Triasorb), bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S),  
76 potassium cetyl phosphate, stearyl alcohol, VP/eicosane copolymer, caprylyl glycol, glyceryl  
77 stearate, PEG-100 stearate, PPG-1-PEG-9 lauryl glycol ether, glyceryl dibehenate, xanthan gum,  
78 benzoic acid, tribehenin, polyacrylate-13, glyceryl behenate, sorbitan isocitrate, polyisobutene,  
79 tocopheryl glucoside, polysorbate 20, Red 33, and tocopherol (patented association WO581;  
80 WO984).

81 A formulations containing 5% TriAsorB<sup>®</sup> was prepared according the following INCI: Ethylic  
82 alcohol, Avène thermal spring water (Avène aqua), C12-15 alkyl benzoate, caprylic/capric  
83 triglyceride, dicaprylyl carbonate, glycerin, potassium cetyl phosphate, polyacrylate-13, PEG-  
84 100 stearate, stearyl alcohol, VP/eicosane copolymer, phenoxyethanol, glyceryl behenate,  
85 glyceryl dibehenate, benzoic acid, xanthan gum.

## 86 **Growth of reconstructed human epidermis**

87 In this study, the model used was a follicular model of RHE *in vitro*. The epidermis was  
88 reconstructed from keratinocytes derived from the outer epithelial sheath of human hair follicles  
89 obtained from healthy volunteers who had given informed consent. The 3D reconstruction  
90 method was previously described by Guiraud et al. (16) and Bacqueville et al. (17). The outer  
91 epithelial sheath cells of human hair follicles are a readily available and non-invasive source of  
92 keratinocytes for epidermal reconstruction. Briefly, the cells were isolated from the outer  
93 epithelial sheath of the hair follicles and then cultured before seeding on culture inserts  
94 (CLS3460, Corning®) immersed in culture medium. The culture inserts are then placed at the  
95 air/liquid interface in an incubator at 37°C with 5% CO<sub>2</sub> to induce epidermal differentiation and  
96 maturation of the *stratum corneum*. The culture medium is renewed every 24 hours. The RHE is  
97 formed in 16 days with a surface area of 1.12 cm<sup>2</sup>.

## 98 **Blue light and UVB irradiations of skin model**

99 TriAsorB and SPF50<sup>+</sup> sunscreen formulations were evaluated for BL photoprotection. They  
100 were applied at a dose of 2 mg.cm<sup>-2</sup> to the surface of a polymethyl methacrylate (PMMA) plate.  
101 This plastic is naturally transparent and has greater light transmission than glass. The PMMA  
102 plate is then deposited on the RHE model just before exposure to BL radiation using a blue light  
103 LED lamp (Kessil PR160) (15, 9). The power of the LED lamp is 257.4 W.m<sup>-2</sup> and the  
104 wavelength is 427±30 nm. The RHE models were exposed to BL at a dose of 60 or 92 J.cm<sup>-2</sup> for  
105 a duration of 39 min and 1 hour, respectively.

106 After this BL stress, the PMMA plate was removed and the skin was then exposed to UVB by  
107 using a Biosun RMX irradiator (Vilber Lourmat, Germany) equipped with a monochromatic



108 illumination lamp at 312 nm. The lamp power is approximately 3 mW.cm<sup>-2</sup>. RHE models were  
109 exposed to a single dose of 50 mJ.cm<sup>-2</sup>. To assess DNA repair, tissues were finally harvested  
110 just after UVB exposure (t0) or 48 hours after the UVB stress (t48h), and all were frozen at -80°C  
111 before analysis by liquid chromatography coupled to tandem mass spectrometry (HPLC-  
112 MS/MS).

113 All experiments were performed in 3 independent biological replicates (N=3) with n=3 or 4  
114 technical replicates for each series (n=3), except for the conditions UVB stress alone (UVB  
115 control) and BL stress plus UVB stress (BL + UVB) (N=6, n=3 or 4).

### 116 **DNA extraction and quantification of photoproducts**

117 DNA was then extracted from the RHE with the DNeasy tissue kit (Qiagen) following the  
118 manufacturer instructions. Briefly, samples were grinded in a tissue lyzer with steel beads in  
119 buffer ATL. Samples were then incubated for 3 h at 55°C in the presence of proteinase K,  
120 followed by a RNA treatment for 2 min. The lysis was completed by a 10 min incubation at  
121 70°C with AL buffer. Ethanol was added and DNA trapped on silica gel column. It was washed  
122 twice and finally collected in water. The recover fraction was freeze-dried. The residue obtained  
123 was enzymatically hydrolyzed and analyzed by HPLC-MS/MS as previously reported (18).

### 124 **Statistical analyses**

125 Non-parametric analyses were performed on the Prism-GraphPad software (San Diego, CA). A  
126 Kruskal-Wallis multiple comparison was first performed. It was followed by comparison  
127 between selected conditions by use of a post-hoc Dunn test. Reported results are median ± 25<sup>th</sup>-  
128 75<sup>th</sup> percentiles range.

## 129 RESULTS

### 130 Quantification of photoproducts after UVB and Blue light + UVB exposure

131 Cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6-4) pyrimidone photoproducts  
132 (64PPs) were quantified in the DNA of RHE collected either immediately (t0) or 48 hours after  
133 irradiation (t48h) (Table 1). No photoproduct was detected in the DNA of unirradiated RHE or  
134 exposed only to BL. The distribution of photoproducts at t0 just after UVB exposure was similar  
135 to previous results: i) CPDs are 3 times more frequent than 64PPs, ii) the order of formation of  
136 CPDs is  $TT > TC > CT$ , iii) TC 64PP is more frequent than TT 64PP and iv) very little Dewar  
137 valence isomers are produced with UVB (19, 20). The observations at t48h for DNA repair after  
138 pure UVB are also those expected, namely that 64PPs are removed from DNA faster than CPDs  
139 (21-24). In addition, not all CPDs were repaired with the same efficiency. The decreasing order  
140 of removal rate was  $CT > TC > TT$  (24). BL exposure at either 60 or 92 J.cm<sup>-2</sup> before UVB  
141 irradiation did not affect the level of photoproducts quantified at t0 as inferred from the absence  
142 of statistically significant differences. Interestingly, the frequency of pyrimidine dimers was  
143 lower 48h post-exposure. These differences were statistically significant for 64PPs under all  
144 conditions and for CPDs after pure UVB irradiation. However, statistical significance was not  
145 reached for samples exposed to BL before UVB.

146 **Table 1:** Level of photoproducts (dimer per  $10^6$  normal bases)\*. The dose of blue light was either 60 or  
 147 92  $J.cm^{-2}$  (BL60 or BL92, respectively). Results were obtained from 6 to 3 biological replicates involving  
 148 3 or 4 technical replicates.

dimer	UVB t0	UVB t48h	BL60+UVB t0	BL60+UVB t48h	BL92+UVB t0	BL92+UVB t48h
TT CPD	84.1±31.8	47.1±24.4***	74.1±17.4	67.2±18.8	94.4±39.6	73.3±48.1
TT 64PP	5.7±2.5	0.3±0.3***	6.0±1.5	1.1±1.2**	6.6±2.7	0.9±1.0***
TC CPD	37.9±17.2	22.3±9.0***	39.5±8.6	35.0±11.3	42.8±23.8	38.0±21.1
TC 64PP	35.1±16.8	1.7±2.2***	40.3±18.1	5.5±7.9**	36.2±32.0	3.8±5.3***
CT CPD	12.2±8.9	4.0±4.1***	13.1±11.0	8.8±7.5	10.9±10.7	6.4±6.9

149 \* Data are median  $\pm$  25th-75th percentiles range. (Statistical significance of the difference between t0  
 150 and t48h: \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ )

151

## 152 Effect of blue light on DNA repair

153 For a better assessment of the impact of BL on DNA repair, repair efficiency was calculated for  
 154 each value. Equation (1) was used:

$$155 \quad (1) \quad \%_{\text{repair}} = 100 * (\text{average}(\text{dimer}_{t_0}) - \text{dimer}_{t_{48h}}) / \text{average}(\text{dimer}_{t_0})$$

156 where average(dimer<sub>t0</sub>) is the average of the level of a photoproduct under specific conditions  
 157 at t0, dimer<sub>t48h</sub> is a value of the level of the same photoproduct and conditions at 48h, and %repair  
 158 is the index of repair efficiency.

159 The %<sub>repair</sub> parameter was calculated for all individual photoproducts (Table 2) as well as for the  
 160 sum of either all CPDs or all 64PPs (Fig. 1) following the exposure to pure UVB, BL 60  $J.cm^{-2}$

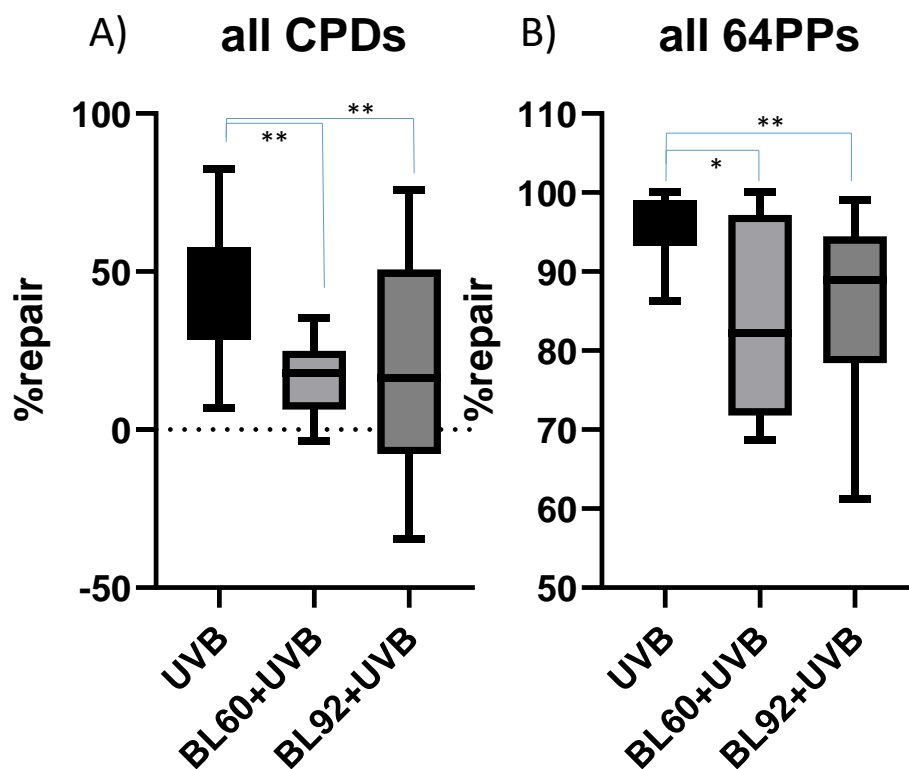
161 + UVB and BL 92 J.cm<sup>-2</sup> + UVB. A statistically significant decrease in the repair efficiency was  
 162 observed in all cases, whatever the BL dose applied before UVB irradiation. Remarkably, the  
 163 deleterious effects of BL on DNA repair were even observed for 64PPs that are very efficiently  
 164 excised. The differences between %<sub>repair</sub> for the 60 and 92 J/cm<sup>2</sup> BL treatments did not reach  
 165 statistical significance.

166 **Table 2:** Repair efficiency (%<sub>repair</sub>)\* for the different exposure protocols. The dose of blue light was either  
 167 60 or 92 J.cm<sup>-2</sup> (BL60 or BL92, respectively). Statistical significance of the differences was obtained by  
 168 comparison with pure UVB.

dimer	UVB	BL60+UVB	BL92+UVB
TT CPD	42.0±28.0	18.6±29.1*	7.9±71.1*
TT 64PP	94.4±5.6	82.0±19.9*	84.6±16.5***
TC CPD	42.4±23.4	16.4±26.8*	7.7±51.2**
TC 64PP	94.9±6.7	84.0±23.1*	88.8±15.9*
CT CPD	68.6±31.8	36.7±54.6**	49.8±53.4*

169 \* Data, expressed in %, are median ± 25th-75th percentiles range. Results were obtained from 6 to 3  
 170 biological replicates involving 3 or 4 technical replicates. (Statistical significance of the difference with  
 171 respect to pure UVB exposure: \* p< 0.05; \*\* p< 0.01; \*\*\* p< 0.001).

172



173

174 **Figure 1.** %<sub>repair</sub> of A) all CPDs and B) all 64PPs determined in RHE exposed under different conditions.

175 The dose of blue light was either 60 or 92 J.cm<sup>-2</sup> (BL60 or BL92, respectively). Results are median ±

176 25<sup>th</sup>-75<sup>th</sup> percentiles range. (Statistical significance of the difference with respect to pure UVB

177 exposure: \* p < 0.05; \*\* p < 0.01).

178

## 179 Photoprotection against BL-induced DNA repair impairment

180 Quantification of DNA repair was then performed with BL-absorbing/reflecting sunscreens

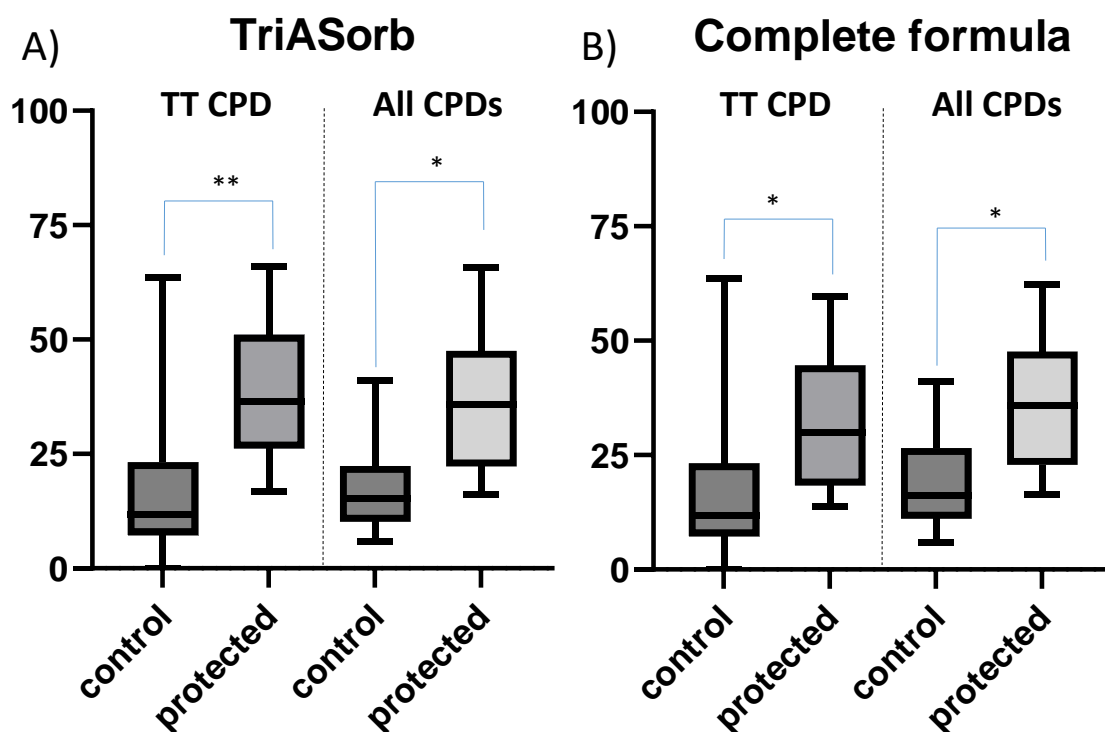
181 spread on a PMMA plate, placed above the RHE only during the BL irradiation. Data were

182 obtained with BL at the 60 J.cm<sup>-2</sup> dose. Both a TriAsorB 5% formulation and a commercial

183 SPF50<sup>+</sup> sunscreen containing this UVB + UVA + BL filters were investigated for their

184 photoprotective properties against the deleterious effects of BL radiations on DNA repair. A

185 significant improvement of DNA repair was observed for sunscreen formulations. This was well  
 186 shown for the DNA repair of TT CPD and the combination of all CPDs (Fig. 2) for which the  
 187 efficiency of repair was doubled by using a photoprotection during BL exposure. A protective  
 188 effect was also observed for TC CPD with both formulations. Interestingly, a positive effect of  
 189 TriAsorB 5% was observed for either TT 64PP or all 64PPs combined.



190

191 **Figure 2.** Improvement of the repair efficiency (% repair) of TT CPD or all CPDs in the presence of  
 192 photoprotectors during the BL exposure. A) unprotected compared to TriAsorb-protected RHE; B)  
 193 unprotected compared to complete formula-protected RHE. Reported statistical significance of the  
 194 differences was obtained by comparison with sample to BL 60 J.cm<sup>-2</sup> without photoprotection and then  
 195 UVB. Data, expressed in %, are median ± 25<sup>th</sup>-75<sup>th</sup> percentiles range. Results were obtained from 3  
 196 biological replicates involving 3 or 4 technical replicates (statistical significance between  
 197 photoprotected and control RHE: \* p < 0.05; \*\* p < 0.01).

198

## 199 **DISCUSSION**

200 The present results unambiguously demonstrate, for the first time, that BL hampers the repair of  
201 pyrimidine dimers in the DNA of reconstituted human skin tissue. This phenomenon was  
202 observed on CPDs, the repair rate of which was c.a. 50% in UVB-irradiated sampled and half  
203 of this value when a preliminary BL exposure was applied. Interestingly, a statistically  
204 significant effect was also obtained for 64PPs for which 95% of the damage was removed after  
205 48h from UVB-irradiated RHE. These results provide additional evidence of possible  
206 deleterious effects of high energy visible light (400-450 nm) since the LED lamp used in this  
207 study was centered at  $427\pm 30$  nm. In terms of underlying mechanism, the present observations  
208 are reminiscent of those made with UVA in a similar experimental design in primary cultures of  
209 human skin cells (23, 25). Explanation for this effect of UVA is likely associated with the  
210 capacity of these radiations at oxidizing and degrading DNA repair proteins (26-28). In this  
211 respect, we can speculate that BL could act as UVA by altering DNA repair process following  
212 protein oxidation. Further studies will be required to confirm this hypothesis. It may be added  
213 that no pyrimidine dimer could be detected by HPLC-MS/MS in the DNA of RHE exposed only  
214 to BL. This result is in agreement with our previous results in human skin (14) but contrasts with  
215 that obtained with the less specific comet assay in cultured keratinocytes (3). Other works in cell  
216 culture also failed at detecting CPDs at wavelengths higher than UVA (10, 11).

217 The other major result of the present study is that BL exposure of the skin model through a blue  
218 light absorbing/reflecting sunscreen specifically prevented decrease in repair capacities. It is  
219 now well established that sunscreens do prevent formation of DNA photoproducts, especially at  
220 high SFP. This was shown both *in vivo* (29-31), in RHE (9) and *ex-vivo* in skin explants (32-34,

221 17). For example, the sunscreen used in the present work decreased by 95% the yield of  
222 pyrimidine dimers in a human skin model exposed to simulated sunlight (9). Yet, a fraction of  
223 UV photons is not absorbed/reflected by the photoprotectors. In addition, sunscreens may be  
224 washed out and people do not use them permanently even under sunny conditions. Therefore,  
225 the formation of DNA damage cannot be completely avoided. Consequently, preventing the  
226 decrease of the repair efficiency by sunscreens containing blue light absorbing/reflecting  
227 components is an interesting strategy in terms of photoprotection.

228

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330 **TABLES**

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335 **FIGURE CAPTIONS**

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