Differential Protection by Two Sunscreens from UV Radiation-Induced Immunosuppression

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A controversy has arisen concerning the ability of sunscreens to protect mice from the immunosuppressive effects of UV radiation. We have assessed the photoprotection in hairless mice of two sun protection factor (SPF)15 sunscreens containing different UVB (280-320-nm) absorbers, namely, octyl-N-dimethyl-p-aminobenzoate (o-PABA) or 2-ethylhexyl-p-methoxycinnamate (2-EHMC). Following three minimum erythemal exposures to UV radiation, both systemic suppression of contact hypersensitivity to 2,4-dinitrofluorobenzene and induction of susceptibility to transplanted UV radiation-induced tumor cells was established. Topically applied 2-EHMC sunscreen protected totally from both forms of immunosuppression, but the o-PABA sunscreen failed to protect, although both sunscreens were equally effective in protection from UV radiation-induced erythema and edema. *J Invest Dermatol 97:624-628, 1991*

The immunosuppressive action of UV radiation was first described in relation to the preferential growth in UV-irradiated host mice, of transplanted UV radiation-induced syngeneic tumor tissue or cultured cells [1]. This requirement for pre-irradiation of the recipient mouse for successful tumor growth revealed the highly antigenic nature of UV radiation-induced tumors. The majority of UV radiation-induced tumors in mice have been shown to be of this regressor type [2], in contrast to chemically induced skin tumors that exhibit progressor character and will grow when transplanted into a naive syngeneic host mouse. The suppression by UV radiation of the ability to recognize and reject the UV radiation-initiated tumor has been suggested as a prerequisite for the outgrowth of tumors initiated in the epidermis.

In addition, other impairments of immune function have now been attributed to UV radiation, such as the suppression of the contact hypersensitivity (CHS) response to skin-sensitizing agents [3], and of the delayed-type hypersensitivity responses to epicutaneously presented infectious agents such as *Herpes virus* [4], *Candida* [5], and *Leishmania* [6]. The common defect in the UV radiation-induced tumor-susceptible state and suppressed CHS appears to be in antigen presentation; a population of suppressor T cells specific for the antigen can be demonstrated, and splenic T-cell preparations can adoptively transfer the immunosuppression to naive recipient mice [2,7].

Sunscreens that absorb radiation in the UVB (280-320 nm) waveband are known to protect from many of the UVB radiation-induced forms of epidermal damage, in both human and mouse skin [8-13]. However, their effect on UV radiation-induced immunosuppression is controversial. In an early study, Gurish et al [14] found that under conditions where a topically applied sunscreen containing p-aminobenzoate (PABA) or its ester, octyl-N-dimethyl-p-aminobenzoate (o-PABA), prevented UV radiation-induced histologic damage to C3Hf/HeN mice, there was no protection from induction of the tumor-susceptible state. Lynch et al [15] have also shown lack of photoprotection by PABA against UV radiation-induced depletion of Langerhans cells and against suppression of CHS in these mice. In contrast, Morison [16] was later able to demonstrate partial photoprotection by a topically applied PABA-containing sunscreen against UV radiation-induced suppression of CHS in C3H mice, and against UVB radiation-induced tumor susceptibility in BALB/c mice, following higher UVB exposures that caused histologic changes in the skin that were only partially abrogated by the sunscreen. He was also able to demonstrate protection by a PABA-containing sunscreen from sunlight-induced tumor susceptibility after chronic exposure of C3H mice [17]. Most recently, however, Fisher et al [18] have presented evidence that an o-PABA-containing sunscreen did not protect from the suppression of CHS by relatively low doses of UVB radiation in hairless mice.

Thus, the protective capacity of UVB radiation-absorbing sunscreens against the immunosuppressive effects of UV radiation has not been clarified. In these experiments we compare the effects of two sunscreens, which are commercially available and separately represent the two major UVB radiation-absorbing compounds in use today (o-PABA and 2-ethylhexyl-p-methoxycinnamate, 2-EHMC), on the immune functions of UV-irradiated hairless mice. Immunity is assessed by both the CHS response to the sensitizer 2,4-dinitrofluorobenzene (DNFB), and by establishment of the tumor-susceptible state as shown by the growth of UV radiation-induced squamous carcinoma cells transplanted intradermally.

MATERIALS AND METHODS

Mice Inbred Skh:HR-1 hairless albino male mice, aged between 31 and 51 d, were evenly age distributed into groups of 11 to 17. They were housed in wire-topped plastic boxes on inert vermiculite bedding (Boral Ltd., Camellia, NSW) and were maintained at 25°C

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Abbreviations:

CHS: contact hypersensitivity
DNFB: 2,4-dinitrofluorobenzene
2-EHMC: 2-ethylhexyl-p-methoxycinnamate
PABA: p-aminobenzoate
o-PABA: octyl-N-dimethyl-p-aminobenzoate
UVA: 320-400 nm
UVB: 280-320 nm

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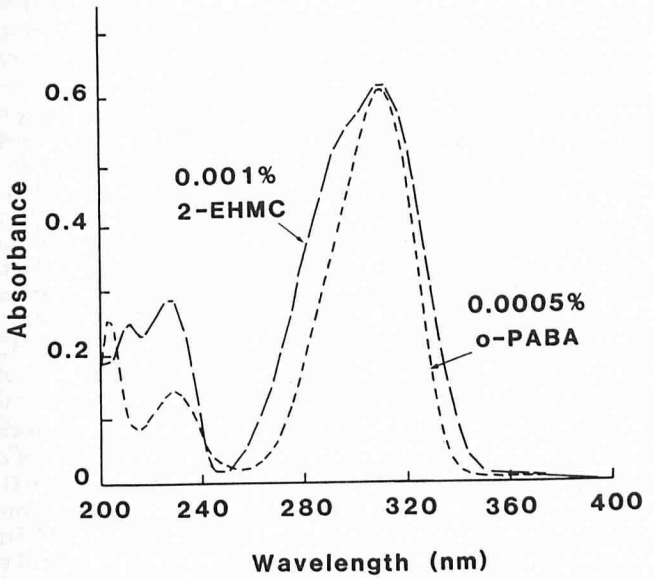

Figure 1. UV absorption spectrum of ethanolic solutions of two pure UVB radiation-absorbers, 2-EHMC, and o-PABA.

with 12 h of light (GEC F40GO gold light, which does not emit any UV radiation) alternating with 12 h of dark. They were fed standard laboratory mouse pellets (Allied Feeds, Rhodes, NSW) and water ad libitum.

Sunscreens The sunscreens are marketed by different suppliers as SPF 15 products. One sunscreen contained 7.5% 2-EHMC and 4.5% benzophenone-3 as UVB and UVA (320–400 nm) radiation-absorbers, respectively (Zia Photobiological Inc., Cedar Crest, NM). The second sunscreen contained 6.5% o-PABA and 3% benzophenone-3 (Johnson & Johnson Australia, Pty. Ltd., St. Leonards, NSW). The sunscreens were applied liberally at 2–3 mg/cm^2 to the dorsal aspect of the face, head, trunk, tail, and feet of the mice, 30 min before UV irradiation, by which time the lotions had been absorbed by the skin.

Samples of the pure UVB-absorbing ingredients were kindly donated, o-PABA from ICI Australia Operations, Villawood, NSW, and 2-EHMC from Givaudan Pty. Ltd., Dee Why, NSW. The absorption spectra were recorded on dilute ethanolic solutions, using a Beckman DU-7 Spectrophotometer, and are presented in Fig 1.

UV Irradiation Mice were irradiated with a single Oliphant FL40SE UVB fluorescent tube in a reflective batten, providing 2.62×10^{-4} W/cm^2 UVB radiation at the mouse dorsum, measured between 250–315 nm using an International Light IL 1700 radiometer. The mice received 0.1179 J/cm^2 UVB radiation on each of 3 consecutive days, being exposed unrestrained with the wire cage tops removed, and with the ears protected by electrical tape. The erythema reaction was observed 24 h after a single exposure and after the third exposure, and was also assessed by the degree of edema at these times, by measuring the double skinfold thickness with a spring micrometer (Mercer, UK). Significance was assessed by Student t test.

Contact Hypersensitivity Mice in groups of 17 (2-EHMC sunscreen) or 11 (o-PABA sunscreen) received one of three treatments on days 1, 2, and 3: sunscreen alone, UVB exposure alone, or sunscreen followed by UVB exposure. On days 8 and 9, mice were sensitized with 50 μl of a freshly prepared solution of 0.3% (v/v) DNFB (Sigma Chemical Co., St. Louis, MO) in A.R. acetone, applied to the ventral skin [19]. Circular cardboard collars were fitted to the mice prior to sensitization, to prevent removal of the DNFB by grooming; these were removed on day 10. The mice were challenged on day 15 with 5 μl 0.2% DNFB/acetone applied to both surfaces of each pinna. Ear swelling was measured with a spring micrometer (Mercer, UK) 18–19 h later, and compared with mice that had received the initial treatments (sunscreen, UVB, or sunscreen plus UVB) and the challenge treatment, but had not been sensitized. Net ear swelling was calculated as the average ear thickness of sensitized mice minus the average ear thickness of non-sensitized mice. Significance of the responses was assessed by Student t test.

Tumor Cell Line A tumor cell line was established from a squamous cell carcinoma, grade 4 [20], induced in an inbred albino hairless mouse by chronic, minimally erythemal, simulated solar UV radiation during a 10-week treatment period. The tumor was excised, cut into small fragments, and suspended in Eagles minimum essential growth media containing 10% fetal calf serum, at 37°C in humidified air with 5% carbon dioxide. The cell line that derived from this tumor had spindle-cell morphology, and regressor characteristics in that transplanted cells grew preferentially in previously UV-irradiated syngeneic recipients.

Tumor Susceptibility Cells stored at −170°C were revived and passaged twice in minimum essential growth media before being harvested, washed, and resuspended in serum-free media for inoculation. The recipient mice, which had been previously used for the CHS assay, were rested until day 21 following the first UVB exposure or sunscreen treatment. Each mouse received 10^5 cells in 0.1 ml media, injected intradermally in the lateral dorsal skin. Tumor growth was monitored for up to 30 d, and subjected to χ^2 analysis. The diameter of the tumors was measured with vernier calipers (Matui, Japan), and significance was assessed by Student t test.

RESULTS

Erythema and Edema Response The irradiation of the mice at this dose resulted in a minimal erythema of the dorsal skin area after a single exposure (Table I). A single exposure slightly but significantly ($p < 0.05$) increased the average skinfold thickness from 45.9 to 57.3 mm $\times 10^{-2}$ (24.9% increase) or from 38.6 to 46.8 mm $\times 10^{-2}$ (21.1% increase), indicating a minimal edemal response. In the presence of either sunscreen, no erythema was detectable and the average irradiated skinfold thickness remained within the range of skin thicknesses of the unexposed control mice.

After three UV radiation exposures, a moderate erythema was evident (Table I), and the average skin thickness was increased from 48.3 to 74.3 mm $\times 10^{-2}$ (53.9% increase) or from 37.1 to 55.4 mm $\times 10^{-2}$ (49.3% increase), indicating a marked and significant ($p < 0.05$) edema response. The presence of either sunscreen again prevented a detectable erythema and maintained the average skin thickness within the range of skin thicknesses of the unexposed control mice. Therefore, both sunscreens protected completely from the erythema and edema resulting from three consecutive minimally erythemal exposures.

CHS Response The CHS response is illustrated by the net ear swelling (Fig 2). Irradiation resulted in the highly significant ($p < 0.001$) reduction of the average ear swelling from 7.3 to 1.9 mm $\times 10^{-2}$ (74% suppression), but in the presence of the 2-EHMC sunscreen, there was complete protection ($p < 0.001$) from this suppression. In contrast, when irradiation had similarly reduced the average ear swelling from 9.8 to 1.8 mm $\times 10^{-2}$ (81% suppression; $p < 0.001$), the presence of the o-PABA sunscreen was not protective and the net ear swelling remained reduced, at 1.5 mm $\times 10^{-2}$ (85% suppression; $p < 0.001$).

Tumor Susceptibility The growth of the transplanted cultured UV radiation–induced tumor cells in mice pretreated with sun-

Table I. Erythema Reaction and Average Double Skinfold Thickness at 24 h After 1 or 3 Treatments with Sunscreen, UVB Radiation, or Sunscreen plus UVB Radiation

	One Treatment		Three Treatments	
Treatment (n)	Erythema	Thickness (mm × 10^{-2} ± SD)	Erythema	Thickness (mm × 10^{-2} ± SD)
2-EHMC sunscreen (16)	Nil	45.9 ± 5.3	Nil	48.3 ± 4.6
UVB (17)	Minimum	57.3 ± 3.7	Moderate	74.3 ± 6.5
2-EHMC sunscreen plus UVB (17)	Nil	54.2 ± 6.9	Nil	53.8 ± 4.1
o-PABA sunscreen (11)	Nil	38.6 ± 3.7	Nil	37.1 ± 3.2
UVB (11)	Minimum	46.8 ± 2.7	Moderate	55.4 ± 6.7
o-PABA sunscreen plus UVB (11)	Nil	39.0 ± 4.7	Nil	37.6 ± 3.2

screen, UV radiation, or sunscreen plus UV radiation, is illustrated in Table II as the successful growth per number of mice inoculated. It can be seen that this tumor cell line has regressor growth characteristics, and in the first transplantation experiment, grew in a significantly greater number of irradiated mice (70.6%) than unirradiated mice (35.3%; $p = 0.04$). In the second experiment, the tumor grew in a greater number of irradiated mice (63.6%) than unirradiated mice (36.4%), but this difference was not statistically significant ($p = 0.2$). When mice had been irradiated in the presence of the 2-EHMC sunscreen, only 35.3% were able to sustain tumor growth, identical with the unirradiated control mice. In contrast, when mice had been irradiated in the presence of the o-PABA sunscreen, 72.7% were able to sustain tumor growth, demonstrating a trend towards the increased susceptibility also observed in the mice irradiated without the sunscreen. There was thus significant ($p = 0.05$) protection from tumor susceptibility in the mice irradiated through the 2-EHMC sunscreen, when compared with mice irradiated through the o-PABA sunscreen.

The average tumor diameters at 30 d (2-EHMC sunscreen) and 26 d (o-PABA sunscreen) post-transplantation are also shown in Table II. Tumors that grew in non-irradiated recipients tended ($p < 0.01$) to be smaller (average 2.4 or 2.9 mm diameter) than tumors that grew in UV-irradiated recipients (6.1 or 5.0 mm diameter). The tumors that grew in mice irradiated in the presence of the 2-EHMC sunscreen remained smaller (2.6 mm diameter; $p < 0.01$), similar to growth in the non-irradiated recipients, but the tumors that grew in mice irradiated in the presence of the o-PABA sunscreen appeared as large (5.0 mm diameter) as those growing in the UV-irradiated recipients, although this was not statistically significant.

Thus, whereas the 2-EHMC sunscreen afforded protection from UV radiation-induced susceptibility to tumor growth, and reduced the growth rate of tumors in irradiated mice, the o-PABA sunscreen was completely non-protective.

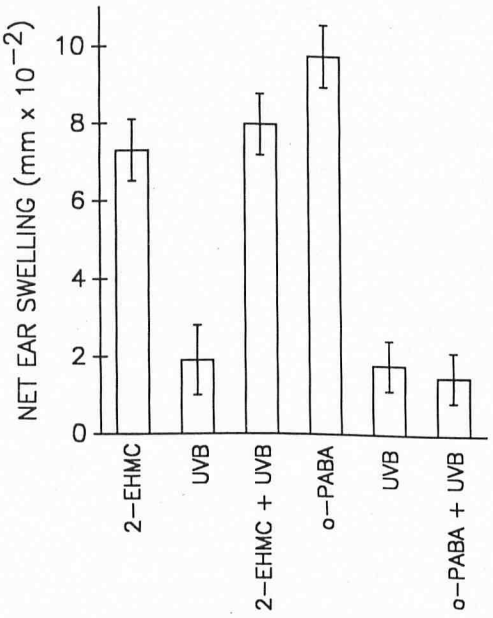

Figure 2. Contact hypersensitivity response to DNFB, expressed as net ear swelling (mm × 10^{-2}), measured 18–19 h after challenge. Mice had been treated with sunscreen (2-EHMC or o-PABA), UVB radiation, or sunscreen plus UVB radiation. *Error bars,* SEM.

DISCUSSION

These findings support the accumulating evidence that sunscreens containing PABA or o-PABA as the UVB absorber do not protect from at least two of the immunosuppressive effects of UV radiation. In contrast, under the same conditions of SPF and minimally erythemal exposure to UVB radiation, a 2-EHMC–containing sunscreen was highly protective. Both sunscreens, however, protected efficiently from the erythema and edema reactions to the UV radiation.

The different effects of each sunscreen may be explained by differing physical or chemical properties of the UV-absorbing ingredients. Because the UVA absorber benzophenone-3 was common to both sunscreens, but the induction of tumor susceptibility and suppression of CHS do not occur above 315 nm [17,21], the presence of this ingredient could be ignored. One variable that may affect localization of the ingredients in the epidermis, as suggested by Fisher et al [18], and thus perhaps their physical ability to influence receptors for immune impairment, is the vehicle, which differed between the

Table II. Induction of Susceptibility to Transplanted Tumor Cell Growth, Following 3 Treatments with Sunscreen, UVB Radiation, or Sunscreen plus UVB Radiation

Treatment	Tumors Growing/ Number of Mice Inoculated		Average Tumor Diameter (mm ± SEM)
			At Day 30
2-EHMC sunscreen	6/17	35.3%	2.4 ± 0.8
UVB	12/17	70.6%	6.1 ± 1.1
2-EHMC sunscreen plus UVB	6/17	35.3%	2.6 ± 0.9
			At Day 26
o-PABA sunscreen	4/11	36.4%	2.9 ± 1.2
UVB	7/11	63.6%	5.0 ± 1.3
o-PABA sunscreen plus UVB	8/11	72.7%	5.0 ± 2.4

two sunscreens. Information from the earlier studies has also been subject to differences in the vehicle of commercial sunscreens. However, we have recently reported similar lack of photoprotection by o-PABA but protection by 2-EHMC, when applied as ethanolic solutions to hairless mouse skin, in an assay of photoenhancement of chemical carcinogenesis [22].

The absorbance maximum for both o-PABA and 2-EHMC is at 310 nm; however, the absorption spectrum for o-PABA can be seen to be slightly sharper than 2-EHMC when the two spectra are normalized at 310 nm, which would lead to greater breakthrough of the peripheral wavebands, which might be of biologic significance.

At least two mechanisms for the suppression by UV radiation of CHS have been suggested. Applegate et al [23] have provided evidence that in the marsupial *Monodelphis domestica,* the immunosuppressive lesion might be the pyrimidine dimer, which is the major DNA lesion induced in mammalian skin following UV irradiation [24]. It is interesting to note that at 293 nm, which is the peak of the action spectrum for pyrimidine dimer formation [25], the absorbances are 61.3% and 86.3% of the peak absorbance at 310 nm, for o-PABA and 2-EHMC, respectively. Therefore, at equivalent SPF, o-PABA can be predicted to offer less protection from dimer formation than 2-EHMC, and hence less protection from the associated suppression of CHS. On the other hand, Fisher et al [18] demonstrated the same degree of suppression of CHS in hairless mice in the presence of SPF 6 and SPF 15 o-PABA–containing sunscreens, which suggests that, at least in the mouse, breakthrough UVB radiation at 293 nm is not the causative mechanism.

A second immunologically sensitive reaction has maximum activity at 270 nm, i.e., the UV absorbance and photoisomerization of the normal epidermal component, *trans* urocanic acid, to its *cis* form [26]. Independently of the evidence for the etiologic role of the pyrimidine dimer in UV radiation-induced suppression of CHS in the marsupial, this UVB photoproduct has also been proposed as the mediator of the immunosuppressive action of UV radiation in various strains of mouse, and several of the suppressive functions of UV radiation can be simulated in mice by *cis* urocanic acid alone, including the suppression of CHS [27]. It is possible that 2-EHMC offers greater protection from urocanic acid photoisomerization than o-PABA, by virtue of its broader absorption spectrum.

Chemical reactivity of the sunscreens with critical cellular molecules may account for the protective differential. It is known that PABA sensitizes the formation of pyrimidine dimers by UVB radiation in vitro and in vivo [28,29]; it is likely therefore that o-PABA would also increase the pyrimidine dimer damage, and thus the CHS-suppressing lesion. It has been suggested that photoexcited states of PABA might also directly modify DNA bases [30], and photoactivated PABA has induced DNA repair in mouse fibroblasts [31]. However, cinnamic acid derivatives, related to 2-EHMC, are also capable of photoactivated dimerization and reaction with thymine bases [32], and have been shown to enhance UV-induced mutagenesis by inhibition of excision repair in bacteria [33]. It is obviously of great interest to determine the effects of these two sunscreens on the UV radiation-induced formation of the critical DNA lesion that appears to underlie the suppression of CHS, at least in the marsupial.

The photosuppression of CHS responses in the mouse is a transient impairment, and the mechanism has been suggested to account for recurrent skin eruptions in humans that are manifested following sunlight exposure, e.g., *Herpes simplex* virus activation, as discussed by Norval et al [34]. However, we have shown in hairless mice that the same UV radiation exposure also induces the long-lived tumor-susceptible state, which has been demonstrated previously to require a much greater exposure to UV radiation in haired mice [16,17,35]. The tumor-susceptible state that follows chronic or high-dose UV irradiation is an indicator of a permanently impaired immune capacity to reject antigenic UV-induced tumor cells, and can be detected at least 5 months post-irradiation in haired mice [36,37] and at least 8 months post-irradiation in hairless mice (personal observations). The o-PABA–containing sunscreen did not protect from either form of immunosuppression. It is important now to determine the comparative protection by the two sunscreens from carcinogenesis in response to chronic UV irradiation, especially as there is evidence that sunscreens may simply prolong tumor induction, and that they inhibit tumor promotion but permit tumor initiation to occur in mouse epidermis [13,38].

It will be interesting to establish whether the underlying mechanism of tumor susceptibility is the same at low and high exposures, and whether the mechanism is common to the suppression of CHS. Certainly pyrimidine dimer formation has been correlated with both UV radiation-induced carcinogenesis and suppressed CHS, but *cis* urocanic acid activity likewise mediates suppressed CHS, and enhances UV radiation-induced carcinogenesis in hairless mice [27]. Whether these two radiation-induced alterations might interact in the induction of immunosuppression, or whether they indicate a mechanistic difference between the marsupial and the mouse, are questions still to be elucidated.

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REFERENCES

1. Fisher MS, Kripke ML: Systemic alteration induced in mice by UV light irradiation and its relationship to UV carcinogenesis. Proc Natl Acad Sci USA 74:1688–1692, 1977
2. Fisher MS, Kripke ML: Suppressor T lymphocytes control the development of primary skin cancers in UV-irradiated mice. Science 216:1133–1134, 1982
3. Noonan FP, DeFabo EC, Kripke ML: Suppression of contact hypersensitivity by UV radiation and its relationship to UV-induced suppression of tumor immunity. Photochem Photobiol 34:683–690, 1981
4. Howie S, Norval M, Maingay J: Exposure to low dose UV radiation suppresses delayed type hypersensitivity to *Herpes simplex* virus in mice. J Invest Dermatol 86:125–128, 1986
5. Denkins Y, Fidler IJ, Kripke ML: Exposure of mice to UVB radiation suppresses delayed type hypersensitivity to *Candida albicans.* Photochem Photobiol 49:615–619, 1989
6. Giannini MSH: Suppression of pathogenesis in cutaneous leishmaniasis by UV irradiation. Infect Immun 51:838–843, 1986
7. Noonan FP, Kripke ML, Pedersen GM, Greene MI: Suppression of contact hypersensitivity in mice by UV irradiation is associated with defective antigen presentation. Immunology 43:527–533, 1981
8. Kligman LH, Akin FJ, Kligman AM: Sunscreens prevent ultraviolet photocarcinogenesis. J Am Acad Dermatol 3:30–35, 1980
9. Pearse AD, Marks R: Response of human skin to UV radiation: dissociation of erythema and metabolic changes following sunscreen protection. J Invest Dermatol 80:191–194, 1983
10. Snyder DS, May M: Ability of PABA to protect mammalian skin from UV light-induced skin tumours and actinic damage. J Invest Dermatol 65:543–549, 1975
11. Kligman LH, Akin FJ, Kligman AM: Prevention of ultraviolet damage to the dermis of hairless mice by sunscreens. J Invest Dermatol 78:181–189, 1982
12. Gallagher CH, Greenoak GE, Reeve VE, Canfield PJ, Baker RSU, Bonin AM: UV carcinogenesis in the hairless mouse skin. Influence of the sunscreen 2-ethylhexyl-p-methoxycinnamate. Aust J Exp Biol Med Sci 62:577–588, 1984
13. Reeve VE, Greenoak GE, Gallagher CH, Canfield PJ, Wilkinson FJ: Effect of immunosuppressive agents and sunscreens on UV carcinogenesis in the hairless mouse. Aust J Exp Biol Med Sci 63:655–665, 1985
14. Gurish MF, Roberts LK, Krueger GG, Daynes RA: The effect of various sunscreen agents on skin damage and the induction of tumor susceptibility in mice subjected to ultraviolet radiation. J Invest Dermatol 76:246–251, 1981

15. Lynch DH, Gurish MF, Daynes RA: Relationship between epidermal Langerhans cell density, ATP-ase activity and the induction of contact hypersensitivity. J Immunol 126:1892–1897, 1981
16. Morison WL: The effect of a sunscreen containing paraaminobenzoic acid on the systemic immunological alterations induced in mice by exposure to UVB radiation. J Invest Dermatol 83:405–408, 1984
17. Morison WL, Kelley SP: Sunlight suppressing rejection of 280- to 320-nm UV-radiation-induced skin tumors in mice. J Natl Cancer Inst 74:525–527, 1985
18. Fisher MS, Menter JM, Willis I: Ultraviolet radiation-induced suppression of contact hypersensitivity in relation to Padimate O and Oxybenzone. J Invest Dermatol 92:337–341, 1989
19. Alcalay J, Ullrich SE, Kripke ML: Local suppression of contact hypersensitivity in mice by a monofunctional psoralen plus UVA radiation. Photochem Photobiol 50:217:220, 1989
20. Canfield PJ, Greenoak GE, Macasaet EN, Reeve VE, Gallagher CH: The characterization of squamous cell carcinoma induced by ultraviolet irradiation in hairless mice. Pathology 20:109–117, 1988
21. DeFabo EC, Kripke ML: Wavelength dependence and dose rate independence of UV radiation-induced immunologic unresponsiveness of mice to a UV-induced fibrosarcoma. Photochem Photobiol 32:183–188, 1980
22. Reeve VE, Bosnic M, Boehm-Wilcox C: Effect of UV radiation and UVB (280-315nm) absorbing sunscreen ingredients on 7,12-dimethylbenz(a)anthracene-initiated skin tumorigenesis in hairless mice. Photoderm Photoimmunol Photomed 7:222–227, 1990
23. Applegate LA, Ley RD, Alcalay J, Kripke ML: Identification of the molecular target for the suppression of contact hypersensitivity by UV radiation. J Exp Med 170:1117–1131, 1989
24. Patrick MH, Rahn RO: Photochemistry of DNA and polynucleotides: photoproducts. In: Wang SY (ed.). Photochemistry and Photobiology of Nucleic Acids, Vol. II, Academic Press, NY, 1976, pp 83–87
25. Ley RD, Peak MJ, Lyon LL: Induction of pyrimidine dimers in epidermal DNA of hairless mice by UVB: an action spectrum. J Invest Dermatol 80:188–191, 1983
26. DeFabo EC, Noonan FP: Mechanism of immune suppression by UV radiation *in vivo*. I. Evidence for the existence of a unique photoreceptor in skin and its role in photoimmunology. J Exp Med 157:84–98, 1983
27. Reeve VE, Greenoak GE, Canfield PJ, Boehm-Wilcox C, Gallagher CH: Topical urocanic acid enhances UV-induced tumour yield and malignancy in the hairless mouse. Photochem Photobiol 49:459–464, 1989
28. Sutherland BM: P-aminobenzoic acid-sunlamp sensitization of pyrimidine dimer formation and transformation in human cells. Photochem Photobiol 36:95–97, 1982
29. Sutherland JC, Griffin KP: P-aminobenzoic acid can sensitize the formation of pyrimidine dimers in DNA: direct chemical evidence. Photochem Photobiol 40:391–394, 1984
30. Gasparro FP: PABA: friend or foe? Photodermatol 3:61–63, 1986
31. Long SD, Little JB: Sunscreen agents induce DNA repair in mouse embryo fibroblasts. J Environ Path Toxicol Oncol 5:193–200, 1984
32. Morrison H: Photochemistry and photobiology of urocanic acid. Photodermatol 2:158–165, 1985
33. Shimoi K, Nakamura Y, Noru T, Tomita I, Fukushima S, Inoue T, Kada T: Methyl cinnamate derivatives enhance UV-induced mutagenesis due to the inhibition of DNA excision repair in *E. coli B/r*. Mutation Res 146:15–22, 1985
34. Norval M, Simpson TJ, Bardishiri E, Howie SEM: Urocanic acid analogues and the suppression of the delayed type hypersensitivity response to *Herpes simplex* virus. Photochem Photobiol 49:633–639, 1989
35. DeFabo EC, Kripke ML: Dose-response characteristics of immunologic unresponsiveness to UV-induced tumors produced by UV irradiation of mice. Photochem Photobiol 30:385–390, 1979
36. Kripke ML, Fisher MS: Immunologic parameters of ultraviolet carcinogenesis. J Natl Cancer Inst 57:211–215, 1976
37. Spellman CW, Daynes RA: Properties of ultraviolet light-induced suppressor lymphocytes within a syngeneic tumor system. Cellular Immunol 36:383–387, 1978
38. Wulf HC, Poulsen T, Brodthagen H, Hou-Jensen I: Sunscreens for delay of ultraviolet induction of skin tumors. J Am Acad Dermatol 7:194–202, 1982