APPENDIX 1. TOPICAL SUNSCREENS

1. General

Sunscreens are physical and chemical topical preparations which attenuate the transmission of solar radiation into the skin by absorption, reflection or scattering. Physical sunscreens (sunblocks), for example zinc oxide or titanium dioxide, function by reflecting and scattering and provide protection against a broad spectrum of UV and visible wavelengths. They are normally nontoxic and have few known adverse effects. Chemical sunscreens contain one or more colourless UV-absorbing ingredients which generally absorb UVB radiation more strongly than UVA. The application of any sunscreen thus normally changes the spectrum of radiation that reaches the target cells. General information is available on sunscreens that have been or are in use (Liem & Hilderink, 1979; Boger *et al.*, 1984; Murphy & Hawk, 1986; Pathak, 1986, 1987; Ramsay, 1989; Lowe & Shaath, 1990; Taylor *et al.*, 1990) and on procedures for testing them (Azizi *et al.*, 1987; Kaidbey & Gange, 1987; Urbach, 1989).

Although most sunscreens are designed to attenuate UVR, some contain additives such as bergamot oil (containing 5-methoxypsoralen; see IARC, 1986, 1987) to enhance pigmentation and photoprotection (Young *et al.*, 1991). The role of such preparations remains controversial.

The generally accepted parameter for evaluating the efficacy of sunscreen preparations is the sun protection factor (SPF), which is defined as the ratio of the least amount of UVR required to produce minimal erythema after application of a standard quantity of the sunscreen product film to the skin to that required to produce the same erythema without sunscreen application. The US Food and Drug Administration (1978) published recommendations for the testing of proprietary sunscreens. Many factors influence SPF values; particularly important are the spectral power distribution of the source used for SPF testing and a clear definition of the end-point used for assessment (see Urbach, 1989). Variations in these factors can lead to considerable differences in measured SPF values for the same product.

SPF values generally reflect the degree of protection against solar UVB radiation, but their protective capacity against UVA must also be defined. Several in-vivo and in-vitro methods have been proposed for defining protection against UVA, but there is no consensus on which is the most appropriate.

Correctly used, sunscreens are effective in preventing erythema. Little information is available, however, on their protective value against harmful immunological changes, photoageing or skin cancer or on their potential long-term adverse effects. The protective and adverse effects of sunscreen use are summarized below.

2. Protective effects

2.1 *Against DNA damage*

UVR inhibits normal (semi-conservative) DNA synthesis. Knowledge about the prevention of DNA damage is based on the results of studies of a small number of sunscreens. In a limited in-vitro study, two commercially available sunscreens (Spectraban, SPF 15.0 and Spectraban, SPF 5.6 [components unspecified]) were tested for their ability to protect against the inhibition of semi-conservative DNA synthesis or the induction of unscheduled DNA synthesis by UVB (300 nm) radiation (Arase & Jung, 1986). Protective factors were found to correlate with the stated SPF values of the sunscreens.

The ability of sunscreens to protect against UV-induced inhibition of DNA synthesis has also been tested in epidermal mouse skin. In a study of seven commercially available sunscreens [components unspecified], the calculated protection factors corresponded fairly well with the SPF values provided by the manufacturers (Walter, 1981). In a study of a single sunscreen (7.5% octyl methoxycinnamate, 4.5% benzophenone-3; SPF, 15), the induction of pyrimidine dimers in human skin *in situ* by a solar simulator (280–400 nm) was measured as a function of fluence (up to 10 times the MED), with or without application of the sunscreen. Dimer induction was reduced by 40-fold in sunscreen-treated skin (Freeman *et al.*, 1988).

2.2 *Against acute and chronic actinic damage*

Protection against erythema is well substantiated by extensive human experience; however, other cellular and metabolic activities may not be afforded the same degree of protection (Pearse & Marks, 1983). In a histological assessment of mouse skin damage, Kligman *et al.* (1982) found that sunscreens provided protection against the effects of chronic sunlamp irradiation. Furthermore, the application of sunscreens (SPF 6 or 15) allowed previously damaged dermis to be repaired despite continued irradiation (Kligman *et al.*, 1983). A UVB sunscreen (2-ethylhexyl 4′-methoxycinnamate, SPF 8) was shown to protect against biochemical changes induced in collagen by Westinghouse FS20 sunlamp irradiation of mouse skin over 12 weeks (Plastow *et al.*, 1988).

2.3 *Against immunological alterations*

Various investigators have examined the efficacy of sunscreens to inhibit photoimmunological reactions in the skin. Inhibition of the development of UV-induced suppression of contact hypersensitivity has been reported (Morison, 1984), but in other studies sunscreens have been ineffective in preventing immunosuppression (Gurish *et al.*, 1981; Hersey *et al.*, 1987; Fisher *et al.*, 1989; van Praag *et al.*, 1991), or mixed results have been obtained depending on the sunscreen used (Reeve *et al.*, 1991). [The Working Group concluded that no consistent relationship could be assumed between protection against photoimmunological events and erythema and other changes in the skin.]

2.4 *Against tumour formation*

Some sunscreens have been shown to protect mice against UV-induced skin tumour formation (Knox *et al.*, 1960; Kligman *et al.*, 1980; Wulf *et al.*, 1982; Gallagher *et al.*, 1984; Morison, 1984). Demonstration of effectiveness against skin tumour formation is, however,

not required by regulatory bodies in evaluations of sunscreens. Sunscreen use may encourage people to have longer overall exposure to sunlight, because protection by the sunscreen reduces the effective irradiance. Kelfkens *et al.* (1991) observed that exposure of mice to a daily dose of UVB over a longer period gives a higher tumour yield than the same dose given over a shorter period. Accordingly, any assessment of the overall impact of sunscreens in reducing human skin cancer should take into account both the efficacy of sunscreens in reducing UV-induced damage to the skin and concomitant human behavioural changes with respect to time spent in the sun. In some case–control studies (e.g., Holman *et al.*, 1986; Beitner *et al.*, 1990), use of sunscreens has been associated with an increased risk for melanoma. This association is probably the result of confounding of sun exposure by skin type or amount of exposure, because individuals who easily get sunburned or expose themselves heavily (and who are at increased risk of skin cancer) may use sunscreens more frequently than other people.

3. Adverse effects

3.1 *Acute toxicity*

Acute toxic side-effects of specific sunscreen agents include contact irritation, allergic contact dermatitis, phototoxicity, photoallergy and staining of the skin (Schauder & Ippen, 1986; Pathak, 1987; Knobler *et al.*, 1989).

3.2 *Chronic toxicity*

Relatively little information is available on the mutagenic and carcinogenic potential of sunscreen agents. This deficiency was reviewed in a report by the US National Cancer Institute (1989), which recommended the following six compounds for chronic testing in the US National Toxicology Program rodent test programme: cinoxate, 2-ethylhexyl 2-cyano-3,3-diphenyl-acrylate, 2-ethylhexyl *para*-methoxycinnamate, homosalate, methyl anthranilate and oxybenzone. The bases for selecting these compounds, together with extensive references, are given in the report. In short, neither epidemiological data nor long-term mammalian carcinogenicity studies are available on these compounds. The results of in-vitro testing were assessed as either negative or inconsistent among test systems or among batches of a compound (because of impurities). 2-Ethylhexyl *para*-methoxycinnamate was implicated as a potential tumour initiator in one study in which hairless mice were painted with the compound over a nine-week period and subsequently treated with the tumour promoter, croton oil (Gallagher *et al.*, 1984). Subsequent work by Reeve *et al.* (1985), however, failed to confirm these results, and Forbes *et al.* (1989) found no evidence of tumour initiation by the compound in an initiation–promotion experiment in mice.

trans-Urocanic acid (an additive in some commercial sunscreen products) increased the yield of simulated solar UV-induced tumours in hairless mice (Reeve *et al.*, 1989). The significance of this finding for human exposure has not been evaluated.

3.3 *Reduced vitamin D synthesis*

Vitamin D production is almost completely blocked in subjects who use UVB sunscreens (Matsuoka *et al.*, 1987). This finding may be significant for elderly individuals, who are

already at risk for vitamin D_3 deficiency (MacLaughlin & Holick, 1985), but its significance for clinical disease remains unknown (Fine, 1988).

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