Sunscreen And Immunosuppression

To the Editor:

Recently, Walker and Young (1997) reported that ultraviolet (UV) B sunscreens offer the same UVB protection factors against inflammation and immunosuppression in the mouse. The authors studied the relationship between photoprotection of inflammation and immunosuppression with monochromatic (Philips TL-01 tubes, \( \lambda_{max} = 311 \) nm) UVB radiation. The UVB dose-response curve for murine edema was similar to that for human erythema. The protection afforded by the UVB filters, octyl dimethyl para-amino-benzoic acid and 2-ethylhexyl-4'-methoxycinnamate (2-EHMC), revealed that topical or tape application of sunscreen protected totally against UV-induced inflammation but only partially against UV-induced immunosuppression. Furthermore, a sunscreen protection factor (SPF) of 4, in vivo, was determined for 2-EHMC for both inflammation and immunosuppression.

These findings, however, are confusing. On the one hand, the investigators used minimally significant increases in skin edema or suppression of contact hypersensitivity (CHS) to define minimal inflammatory (MID) and minimal immunosuppressive doses (MISD) (p < 0.05). In both unprotected and 2-EHMC-protected mice, the MID and MISD were the same and were determined to be 773 \( \mu \)g/cm\(^2\) and 3091 \( \mu \)g/cm\(^2\), respectively. On the other hand, the comparison of protective effects of UVB sunscreens showed that 2-EHMC-treated mice exposed to 2.8 MID (2184 \( \mu \)g/cm\(^2\)) showed significant suppression of CHS (33%) when compared to unirradiated and untreated controls (p < 0.05). Dose-response studies with 2-EHMC, however, showed that irradiation with about 2150 \( \mu \)g/cm\(^2\) resulted in less than 10% suppression of CHS.

We recently conducted a study regarding the protective potency of UVB sunscreen against solar-simulated radiation (SSR)-induced immunosuppression in which we determined immunologically relevant end points within the epidermis and skin-draining lymph nodes.\(^1\) On 6 consecutive days, hairless C3H mice (n = 5) were irradiated with SSR (Muzihas Supersun 5000 UV lamp equipped with a special filter system, 290 nm < \( \lambda < 400 \) nm) with or without sunscreen protection (COLIPA standard PI [2.7% octyl-methoxycinnamate] versus placebo). On days 6–9, mice were topically exposed to the model contact allergen, oxazolone, on the dorsal surface of both ears to induce a primary CHS response. On day 10, ears and local draining lymph nodes were removed to assess lymph node cell proliferation and activation of antigen-presenting cells, T cells, and B cells in epidermal and lymph node cell (LNC) suspensions. Moreover, SSR-induced immunomodulation was assessed by measuring dorsal double skinfold thickness. The results obtained showed that the murine SPF of 3.7, based on skin edema, correlated well with a human SPF of 4, which was determined by skin erythema measurement. Dose-response studies with unprotected or placebo-treated animals revealed that the MISD was comparable to 80% of the MID\(_{unprotected}\). MID\(_{D}\) and MID\(_{B}\) were determined as minimal significant suppression of in vivo lymph node cell proliferation or increase in dorsal skin edema. Flowcytometric analysis of epidermal cell and LNC suspensions showed that contact allergen-induced upregulation of co-stimulatory molecules, such as B7-1 and intercellular adhesion molecule-1, on I-A\(^+\) epidermal cells and LNC was markedly reduced after irradiation with 60% of the MID\(_{unprotected}\), whereas infiltration of CD4\(^+\) cells into the epidermis was initially suppressed after exposure to 1 MID\(_{unprotected}\). Moreover, oxazolone-induced upregulation of the intercellulin-2 receptor \( \alpha \)-chain (CD25) on CD4\(^+\) LNC was maintained up to irradiation with 1.5 MID\(_{unprotected}\). In comparison, UVB sunscreen-protected mice exhibited a MISD of 60% of the MID\(_{protected}\). Furthermore, this SSR dose dramatically suppressed co-stimulatory molecule expression on epidermal cells and LNC and T-cell migration into the epidermis.

In recent years, several studies have been performed regarding protective potency of sunscreens against UV-induced immunosuppression, and contrasting results have been published (Wolf et al., 1993; Bestak et al., 1995, Roberts and Beasley, 1995). So far, it is widely accepted that the ability of sunscreens to provide immunoprotection depends critically on the dose of UV radiation and can be overcome at high UV radiation doses. Furthermore, the spectrum of the light source is important in evaluating sunscreen efficacy for any end point because of the high sensitivity of biologic effects of UVR to small changes at certain wavelengths.

In conclusion, we agree with the investigators that dose-response curves for murine edema and human erythema are similar, although different light sources were used. Moreover, our findings confirm that UVB sunscreens protect only partially against UV-induced immunosuppression and that subdental doses of UV radiation were able to induce substantial immunosuppression. In contrast to Walker and Young’s finding that UVB SPF\(_s\) against UV-induced murine edema and immunosuppression are the same, data from our study showed that the SPF against SSR-induced immunosuppression was lower than the one against inflammation. Differences between our findings and those of Walker and Young might be due to the use of different light sources (monochromatic UVB versus SSR) and different end points. These contrasting results support the concept that UVA radiation plays a critical role in UV-induced immunosuppression. In our opinion, the use of SSR and the assessment of immunologically relevant end points such as \( \text{in vivo} \) lymph node cell proliferation and analysis of the activation of antigen-presenting cells (I-A\(^+\)/CD80[87-1], I-A\(^+\)/CD54[intercellular adhesion molecule-1]), T (CD4\(^+\)/CD25\(^+\)), and B (I-A\(^-\)/CD45R[8220\(^+\)]) cells in skin and skin-draining lymph nodes during primary CHS responses, may be more appropriate to achieve results that could be extrapolated to humans exposed to sunlight. Finally, we would like to stress the conclusion that complete immunoprotection will be achieved only by sunscreens with broad-
band absorption spectrum and a higher SPF than necessary for the prevention of erythema.

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Reply:
We thank Homey et al for their interest in our work. Their observations are correct. When we tested the ultraviolet B (UVB) sunscreen 2-ethylhexyl-4’-methoxycinnamate (2-EHMC) after a single challenge dose of 2184 mJ/cm², there was a 33% suppression of the contact hypersensitivity (CHS) response (n = 8) as is shown in Fig 6 of our paper (Walker and Young, 1997). However, our dose-response studies (Fig 7) with sunscreen application showed that the same dose resulted in about 10% suppression of CHS (n = 4). This difference in the results (which was not significant; p = 0.2) may be attributed to the smaller group size in the dose-response study; one aberrant result with smaller sample sizes can significantly alter the group mean. This is clear from the error bars (±SEM), which are larger than for the dose-response study. Furthermore, the challenge dose of 2184 mJ/cm² is at the base of the “exponential” part of the sigmoid dose-response curve, where small variations in UVB dose (e.g., from animal movement) are likely to result in proportionately larger errors. Our data demonstrate that there is no significant difference in the shape of the dose-response curves for immunosuppression with or without sunscreen application once we allowed for attenuation of UVB dose by the sunscreen according to its protection factor against edema. Failure to afford complete immunoprotection with our challenge dose of 2184 mJ/cm² was due to a lower dose threshold for UVB-induced immunosuppression compared with edema, despite similar protection factors for both end points. Our data emphasize the importance of dose-response studies rather than reliance on an arbitrary challenge dose of UV radiation (UVR), as is commonly done by some investigators.

Homey et al have tested the protection afforded by the same UVB sunscreen [sun protection factor (SPF) = 4] against solar simulated radiation-induced immunosuppression using by six successive exposures to solar-stimulated radiation (SSR) (Mutzhas Supersun 5000). They confirm our observations that murine edema is a good model for human erythema and that the dose threshold for UVR-induced immunosuppression (using different end points) is lower than that for inflammation. In contrast to our data, they report that protection against immunosuppression is lower than that for inflammation. We look forward to the publication of their studies, but in the meantime it is difficult to make a comment without a more detailed account of their experimental protocol than is given in their abstracts. However, they have assessed the SPF for immunoprotection after multiple SSR exposures, which cannot be readily compared with the presumed more conventional assessment of inflammation after a single exposure. For example, it is possible that multiple subedema doses of UVB may cumulatively induce significant immunosuppression, as other workers have demonstrated that immunosuppression (suppression of CHS) in the mouse is independent of dose fractionation (Noonan et al, 1981). Thus we cannot agree with Homey et al that the lower SPF for immunosuppression necessarily indicates that UVA plays a critical role in immunosuppression.

Homey et al correctly state the importance of using SSR. However, the emission spectrum of the Mutzhas Supersun source that they used is a rather poor simulation of solar UVR (a continuum), as it contains several high-intensity monochromatic spikes. We would like to stress that we chose an essentially monochromatic UVB source (Philips TL01 tubes) so that the absorption spectra of the UVB sunscreens we used completely overlapped the emission spectrum of the source. This ensured that the observed suppression of CHS was not due to UVR wavelengths transmitted by the sunscreen. Our aim was to study the reported apparent lack of correlation between sunscreen photoprotection of inflammation and immunosuppression. The use of a monochromatic source eliminated any confounding factors due to possible differences in the action spectra of edema and immunosuppression.

Sunscreens are routinely evaluated by their ability to prevent erythema from a single SSR exposure. If we are to determine the role of sunscreen photoprotection against solar UVR-induced immunosuppression, we must determine the relationships between SSR-induced erythema and immunosuppression in humans. Furthermore, it is also important to establish the effect of chronic suberythemal SSR exposure on the induction of both these end points. We do agree with Ruzicka et al, however, that incomplete immunoprotection requires a higher SPF than is necessary for the prevention of erythema. This holds true when the dose threshold for immunosuppression is lower than that for erythema even if, as demonstrated by us, the protection end points are the same.

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