Cutaneous malignant melanoma (CMM) is a complicated disease that is dependent on a number of factors that influence its incidence in ways that are quantitatively uncertain (1). Such factors include genetic background, including skin type and hair color, and the presence and distribution of nevi, and lifestyle habits such as sun exposures—where, time of day and year, frequency, intensity, use of sunscreens etc. A common denominator is sun exposure, as best indicated by a comparison in Australia of CMM on exposed body areas vs. sun protected sites—96-97% on exposed sites—, and from a comparison of the incidence rates in the U.S. of CMM in whites compared to blacks—92-96% among whites (2). CMM is not a disease of outdoor workers and it differs from non-melanoma skin cancer in that it is associated with episodic exposures rather than chronic ones.

CMM is a public health concern because its incidence, among whites, has been increasing at the rate of 4-5% per year for approximately 50 years (3) so that this once very rare disease is now (excluding non-melanoma skin cancer) the 4th most common cancer in Australia and New Zealand and the 10th most common one in the U.S. (4).

The incidence of CMM increases with proximity to the Equator—an observation in line with the conclusion that sun exposure is the most important etiologic agent. However, the latitude effect does not implicate UVB because the intensities of all
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spectral regions increase toward the Equator. An understanding of the useful public health measures to lower the incidence of CMM would benefit greatly if the spectral region of sunlight implicated in melanoma incidence were known. Such knowledge requires animal models to evaluate the incidence as a function of wavelength. There are marsupial models, a transgenic mouse model, and a fish model (5). To date, only the fish model has been employed to obtain an action spectrum (6,7).

The fact that xeroderma pigmentosum individuals—deficient in DNA repair—have a prevalence of CMM that is several thousand-fold greater than in the normal population (8) is an indication that DNA is a target for light induced CMM. DNA absorbs strongly in the UVB. However, it is conceivable that melanin in melanocytes could absorb energy at all wavelengths and, by an indirect means, affect DNA at wavelengths greater than UVB. Again, an animal model would be helpful.

2. A Fish Model

The fish model of Setlow, Woodhead, and Grist (6) uses backcross hybrids of the genus Xiphophorus (X. maculatus (9) and X. couchianus (3)). These hybrids have melanocytes and are very sensitive to melanoma induction. Melanomas are observed after single exposures to much less than a human minimal erythemal dose of monochromatic UV (9). The high sensitivity is presumed to reflect the presence of only a single tumor suppressor gene per melanocyte—approximately $10^4$ at the 7 days of age when the fish are irradiated. Tumors are scored by eye and histologically at 4-6 months. At each wavelength—302, 313, 365, 405, 436, and 547 nm—a dose response curve is obtained. Figure 1 shows preliminary results for 547 nm. The initial slopes of such curves gives the sensitivity (cross-section in $m^2/J$ converted to $m^2/incident photon$) that, normalized to 1.00 at 302 nm, gives an action spectrum for
melanoma induction (Figure 2A). It is obvious that the melanoma sensitivity spectrum is much higher in the UVA than the erythemal sensitivity (10). To obtain the relative effect that would be observed in a sunlight spectrum, the action spectrum points must be multiplied by the sunlight spectrum (Figure 2B).

3. Implications of the Fish Spectrum

If the CMM spectrum were similar to the fish spectrum, the most effective sunlight inducing wavelength would be in the UVA region. In this case, the use of sunscreens to minimize erythema by UVB, or by UVB plus UVA, could result in a much enhanced melanoma inducing exposure if individuals increased their exposure to obtain a minimum erythema dose (Table 1).

<table>
<thead>
<tr>
<th>Sunscreen Type</th>
<th>Melanoma-Inducing Exposure Rate</th>
<th>Melanoma-Inducing Exposure per MED</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sunscreen</td>
<td>1.00</td>
<td>1.0</td>
</tr>
<tr>
<td>SPF 8 (UVB)</td>
<td>0.75</td>
<td>6.0</td>
</tr>
<tr>
<td>SPF 8 (UVB/UVA)</td>
<td>0.47</td>
<td>3.8</td>
</tr>
<tr>
<td>SPF 15 (UVB/UVA)</td>
<td>0.65</td>
<td>9.7</td>
</tr>
<tr>
<td>SPF 25 (UVB/UVA)</td>
<td>0.35</td>
<td>8.7</td>
</tr>
</tbody>
</table>

1. Mid-summer, mid-day, 41°N.
2. I am indebted to Brian Diffey, Medical Physics, Newcastle upon Tyne, for the absorption spectra of these sunscreens.
3. Minimum erythema dose.
4. Skin protection factor of 8, absorption in the UVB (Diffey).
5. Absorption mostly in the UVB, but some, dependent on sunscreen formulation, in the UVA and a little in the visible (Diffey).

Since greater than 90% of the effective sunlight dose with a putative CMM spectrum is in the UVA and visible regions, ozone depletion (affecting mostly UVB) will be inconsequential.
4. **Epidemiological Data**

There are three types of epidemiological studies that support the important role of UVA in CMM. 1) The use of sunscreens is associated with a significant risk of melanoma (11,12). 2) A comparison of the ratio of squamous cell carcinoma (SCC) in Australia to Norway gives a ratio of approximately 20, consistent with the much higher flux of UVB in Australia. However, for CMM the ratio is only about 2 (13,14). Since animal and molecular data indicate that UVB is the important spectral region in SCC, the UVB cannot be strongly associated with CMM. 3) A role for melanin and UVA is also supported by the observation of high SCC in albinos African blacks (lots of UVB) but little CMM in this population (lots of UVA but no melanin) (15).

An argument against the importance of UVA in CMM is that mutations observed in the CDKN2 gene in melanoma cell lines derived from human tumors were similar to those observed after UVB exposure of cells in vitro and in SCC (16), and not similar to those observed in mammalian cells exposed to UVA in vitro (17). However, no mutations in this gene were observed in the 30 melanoma surgical specimens studied, indicating that the mutations in cell lines might be a result of growth in culture (18).

It should be noted that relevant processes other than initiation may be affected by exposure to sunlight. For example, immunosuppression in mice is inhibited by the spectral region, mostly UVB, that forms cyclobutane pyrimidine dimers in DNA, as judged by the observation that repair of the dimers by an exogenously applied repair enzyme for dimers minimizes the suppression (19).
Fig. 1 Preliminary dose-response data for melanoma induction by 547 nm.

Fig. 2 A) Action spectra (normalized to 1.00 at 302 nm) for melanoma induction in fish and erythema induction in humans (10). B) The relative sunlight effective doses (action spectra values multiplied by sunlight fluence rate) versus wavelength for fish melanoma and human erythema.
5. Acknowledgements

The melanoma data presented here were a collaborative effort of the author and Avril D. Woodhead, Eleanor Grist, Neva Setlow, and Keith Thompson. This work was supported in part by the Office of Health and Environmental Research of the U.S. Department of Energy.

6. References


