An *In Vivo* Photocarcinogenesis Study Demonstrating the Validity of the SCUP-m Action Spectrum for UVR-Induced Skin Cancer

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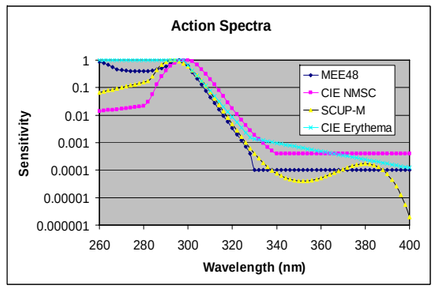
Abstract

The recently published Commission Internationale De L'eclairage (CIE) Standard Action Spectrum for Non-Melanoma Skin Cancer (S 019/E:2006) is based on studies in laboratory animals and the resulting Skin Cancer Utrecht Philadelphia-man (SCUP-m) action spectrum (weighting function) modified to account for anatomical differences in human skin. Recent spectral and mathematical analyses confirmed that the SCUP-m weighting function accurately describes the tumor responses attributable to the ultraviolet radiation (UVR) sources used, and **predicted that blocking the UVR scatter from the xenon long-arc solar simulator (i.e., including radiation < 290 nm) would have little or no measurable impact on tumor response in hairless mice**. We now provide data from the **first direct laboratory test of that hypothesis**. The methodology differed from previous studies only by virtue of modifying the lamp housing to prevent the small but measurable amount of scattered radiation from reaching the mouse cages. Mice in two groups received weekly (Monday-Friday) UVR exposures totaling either 600 or 1200 Robertson Berger Units, equivalent to 300 or 600 J/m2 (CIE erythema-weighted, respectively. The median latent periods (for Tumors ≥ 1mm planar diameter) were 37 and 23 233ks respectively. **This response is well within the parameters of our published historical control data, all of which were based on the xenon lamp prior to its modification.** This direct evidence lends further experimental support to the spectral specifications in CIE Standard S 019/E :2006. The result further discounts recent speculation that UVR scatter from the xenon UVR source substantially contributed to the observed tumor response, and thus skewed the calculated weighting function.

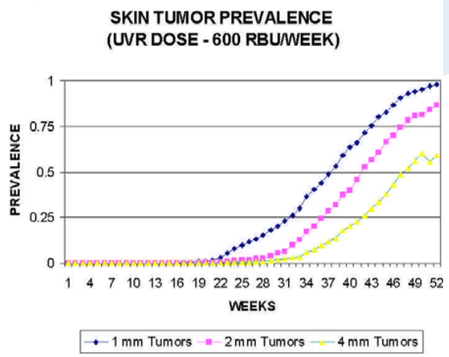
Introduction and Background

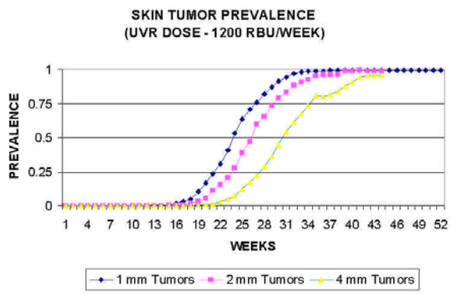
Currently the weighting function ("action spectrum') most widely employed for erythema risk assessment is documented in the CIE standards (ref 1). The following figure compares that erythema action spectrum with a standard action spectrum for photocarcinogenesis and the predecessors from which it was derived (ref 2-5).. The 'Philadelphia" component of the laboratory tumor data set depended on several UVR sources, one of which was a long-arc xenon lamp fitted with Schott optical filters. Published results recognized the presence of some scattered or stray ultraviolet radiation, and incorporated an estimate of impact of that unfiltered component.



The original xenon arc lamp is illustrated below.

Data from nine studies utilizing this light source are summarized in the following two tumor prevalence figures.





The average tumor prevalence for tumors > 1, >1 and > 4 mm in planar diameter for mice (combined sexes) exposed to this source at 600 or 1200 RBU/week for the first 40 weeks of the stud. Each curve (cumulative distribution function) represents the mean prevalence of the nine studies.

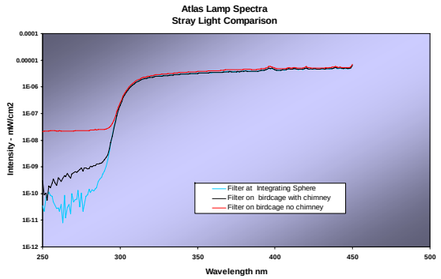
Improved technology permitted more precise measurements as a determination of whether the unfiltered UVR "scatter" from the xenon arc source influences overall calculations of effectiveness, using the SCUP-m weighting function.

Metal shrouds were added above and below the filter holder to eliminate the principal source of unfiltered UVR but not interfering with the air flow required to cool the xenon arc and is illustrated below.

A photocarcinogenesis study in the standard format of 72 albino hairless mice per group was performed with this modified lamp.

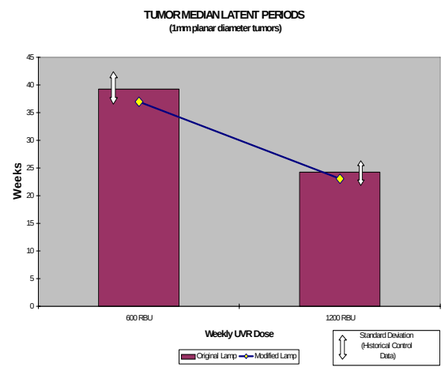
Atlas 6500 watt long arc Xenon lamp modified to eliminate scatter above and below the filter holder.

The emission spectra illustrated below (determined using an Optronic Laboratories OL 753 Spectroradiometer) confirm the nature and quantity of UVR scatter, most of which can be eliminated by lamp modification illustrated here. The red line represents the original unmodified lamp; the black line represents the same lamp with modification; the blue line represents an idealized measure made by placing the filter immediately adjacent to the integrating sphere.



TUMOR ONSET: MEDIAN LATENT PERIOD (WEEKS) Tumors 1mm Planar Diameter		
Weekly UVR Dose	**600 RBU**	**1200 RBU**
New Study (Modified Lamp)	**37 weeks**	**23 weeks**
Historical Control Data (Original Lamp) ± Std Dev	**39.28 ± 3.15 weeks**	**24.25 ± 1.65 weeks**

With the use of the modified lamp, the tumor onset times were within less than one standard deviation of those calculated for the previous nine studies using the original, unmodified lamp that emitted the "UVR scatter". The data from this study is presented in the above table and the below chart.



Utility and Application

Reliable weighting functions for spectral effectiveness have long been considered essential to quantifying both the benefits and the risks associated with exposure to sources of electromagnetic radiation. Of the many photobiological endpoints already recognized, this project bears on skin erythema and tumor production (i.e., photocarcinogenesis). Natural and artificial sources of ultraviolet radiation are associated with skin cancer production (ref 5-8,11) and the availability of weighting functions provides a basis for risk assessment and safety education.

Conclusions

- The experimental data used to develop CIE Standard S 019/E:2006 had previously been described in the SCUP-m action spectrum. Our analysis confirms that the SCUP-m weighting function accurately describes the tumor responses attributable to the UVR sources used.
- The effect of stray radiation is a non-significant contribution to the biological endpoints observed and does not alter the conclusions on the utility or accuracy of the SCUP-m action spectrum as the experimental basis for developing a tool for assessing risk to man.
- Data from a recent study using a modified xenon arc lamp (shielded to minimize the scatter of unfiltered radiation) are indistinguishable from historical control data (nine previous studies using the lamp prior to modification).
- A poster presentation critical of the 1982 studies (ref 6) appears to be based on incomplete data, on a flawed interpretation of "dose-reciprocity", and on a failure to take into account the time-dose relationship (equation) which was an essential component of the proposed weighting function.

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