

**USAARL Report No. 89-11**



**Effects of Ultraviolet Radiation  
on the Oxygen Uptake Rate of the Rabbit Cornea**

**(Reprint)**

**By**

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**July 1989**

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**United States Army Aeromedical Research Laboratory  
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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
1a. REPORT SECURITY CLASSIFICATION Unclassified			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY			3. DISTRIBUTION / AVAILABILITY OF REPORT Approved for public release, distribution unlimited		
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE					
4. PERFORMING ORGANIZATION REPORT NUMBER(S) USAARL 89-11			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
6a. NAME OF PERFORMING ORGANIZATION U.S. Army Aeromedical Research Laboratory		6b. OFFICE SYMBOL (if applicable) SGRD-UAS-VS	7a. NAME OF MONITORING ORGANIZATION U.S. Army Medical Research and Development Command		
6c. ADDRESS (City, State, and ZIP Code) Fort Rucker, AL 36362-5292			7b. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, MD 21701-5012		
8a. NAME OF FUNDING / SPONSORING ORGANIZATION		8b. OFFICE SYMBOL (if applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER		
8c. ADDRESS (City, State, and ZIP Code)			10. SOURCE OF FUNDING NUMBERS		
		PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
11. TITLE (Include Security Classification) Effects of Ultraviolet Radiation on the Oxygen Uptake Rate of the Rabbit Cornea					
12. PERSONAL AUTHOR(S) Lattimore, Morris R., Jr.					
13a. TYPE OF REPORT		13b. TIME COVERED FROM _____ TO _____		14. DATE OF REPORT (Year, Month, Day) 1989 July	15. PAGE COUNT 6
16. SUPPLEMENTARY NOTATION This work was done at the University of Houston and this report is a reprint of a publication in Optometry and Vision Science, Volume 66, Number 2, 1989					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP	cornea, metabolic activity, oxygen uptake rate, protection, ultraviolet radiation		
06	04				
06	05				
19. ABSTRACT (Continue on reverse if necessary and identify by block number) Ultraviolet radiation (UVR) has been demonstrated to be involved in a number of adverse ocular effects. One aspect of UVR-induced corneal stress only recently documented is an alteration of epithelial energy metabolite levels. In this study, in order to examine wavelength and dose dependency issues concerning metabolic effects of UVR, exposures were made at four different wavelengths (290, 300, 310 and 360 nm) and five different mean radiant exposures (0.05, 0.10, 0.15, 0.20 and 0.25 J·cm <sup>-2</sup> ). Pre- and postexposure levels of relative metabolic activity of the corneal epithelium were monitored <u>in vivo</u> by recording the corneal oxygen uptake rate with a micropolarographic electrode. A paired difference analysis demonstrated a decrease in relative corneal metabolic activity that was both wavelength- and dose-dependent. These relative metabolic effects provide some insight toward the understanding of underlying damage mechanisms, and imply a broader radiant energy susceptibility range of the eye than previously thought.					
20. DISTRIBUTION / AVAILABILITY OF ABSTRACT <input checked="" type="checkbox"/> UNCLASSIFIED/UNLIMITED <input type="checkbox"/> SAME AS RPT. <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION Unclassified		
22a. NAME OF RESPONSIBLE INDIVIDUAL Chief, Scientific Information Center			22b. TELEPHONE (Include Area Code) (205) 255-6907	22c. OFFICE SYMBOL SGRD-UAX-SI	

## Effects of Ultraviolet Radiation on the Oxygen Uptake Rate of the Rabbit Cornea

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### ABSTRACT

Ultraviolet radiation (UVR) has been demonstrated to be involved in a number of adverse ocular effects. One aspect of UVR-induced corneal stress only recently documented is an alteration of epithelial energy metabolite levels. In this study, in order to examine wavelength and dose dependency issues concerning metabolic effects of UVR, exposures were made at four different wavelengths (290, 300, 310 and 360 nm) and five different mean radiant exposures (0.05, 0.10, 0.15, 0.20, and 0.25 J·cm<sup>-2</sup>). Pre- and postexposure levels of relative metabolic activity of the corneal epithelium were monitored *in vivo* by recording the corneal oxygen uptake rate with a micropolarographic electrode. A paired difference analysis demonstrated a decrease in relative corneal metabolic activity that was both wavelength- and dose-dependent. These relative metabolic effects provide some insight toward the understanding of underlying damage mechanisms, and imply a broader radiant energy susceptibility range of the eye than previously thought.

**Key Words:** cornea, metabolic activity, oxygen uptake rate, protection, ultraviolet radiation

The electromagnetic spectrum has been divided into a number of discrete regions based on wavelength. The regions labeled as UV, visible, and infrared are of immediate interest for those concerned about ocular effects of nonionizing radiant energy. Shorter wavelength radiation has a higher potential energy<sup>1</sup> and, therefore, a greater capacity for tissue damage, if absorbed. As a result, the UV region has gained more investigative attention than the others. The UV region has been subdivided into several bands based on apparent biologic effect: UV-C, 200 to 290 nm; UV-B, 290 to 320 nm; and UV-A, 320 to 400 nm. Although these divisions are not agreed upon absolutely because of some phenomenological variation, generally the terminology

has been accepted. Research techniques have become increasingly sophisticated, allowing the detection of subtle functional changes that can occur in response to corneal stress or insult. These methodologies have introduced the possibility of detecting changes in corneal function as a result of UV radiant exposures that may not necessarily result in histologically detectable damage.

The action spectrum for histologically detectable corneal damage from exposure to UVR has been said to begin at 210 nm and extend to 315 nm.<sup>2-7</sup> Previously the corneal radiant exposure data above 320 nm have not been considered part of the action spectrum of the cornea because the exposure levels necessary to produce minimal histologic damage to the cornea are comparably high.<sup>8</sup>

However, recent data demonstrate an alteration of corneal epithelial energy metabolites in the pigmented rabbit exposed *in vivo* to UVR up to 360 nm at radiant exposures that exceeded, were at, or were below histologic damage threshold values.<sup>9</sup> This finding suggests the need for increased investigative attention toward the effects of UVR. Most discussions of UVR center on histologic findings and cell death; the study of previously undetectable functional changes may reveal information concerning the underlying damage mechanism(s) of UVR, and shed light on possible recovery processes.

The four experimental wavelengths (290, 300, 310, and 360 nm) were chosen based on an interest in maintaining an environmental relevance, inasmuch as 290 nm UVR and above can be found at the earth's surface.<sup>10</sup> An additional factor was the intention of creating a distinctive span of effects because the corneal thresholds for histologic damage ( $H_c$ ) vary considerably. The corneal radiant exposure  $H_c$  in the rabbit ranges from 0.012 J·cm<sup>-2</sup> at 290 nm to 0.022 J·cm<sup>-2</sup> at 300 nm to 0.05 J·cm<sup>-2</sup> at 310 nm to near 65 J·cm<sup>-2</sup> at 360 nm. By varying both the wavelength and the radiant exposure, it was predicted that effects on the oxygen uptake rate might vary from severe at 290 nm to moderate at 300 and 310 nm to nonexistent at 360 nm. Lastly, the source output happens to peak in these regions, thereby helping minimize some of the time differences typical of a noncoherent source exposure.

Presented at the Annual Meeting of the American Academy of Optometry, Denver, Colorado, December, 1987.

Received July 18, 1988; revision received October 12, 1988.

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## METHODS

### Exposure Instrumentation

Source calibration and radiometric quantification duplicated the procedures described by Pitts et al.<sup>6</sup> The UVR source was a 5000 W xenon-mercury (Xe-Hg) high pressure arc lamp, powered by a 10 kW direct current power supply regulated to  $\pm 0.5\%$ , and capable of delivering from 0 to 80 amps at 25 to 65 V to the arc electrodes. The lamp housing was cooled by a double blower system. The radiation from the source was focused at a double monochromator entrance slit by the housing optics. A 10 cm quartz-enclosed water chamber was placed between the focusing lenses and the monochromator to remove the infrared radiation. The exit optical beam was focused by a quartz lens with a beam size of 1.6 by 1.8 cm at the plane of the experimental animal's cornea.

The desired UVR waveband was obtained with a Czerny-Turner double grating monochromator (model 25-100; Jarrell Ash Division, Fisher Scientific, Waltham, MA) possessing a double mirror setup with gratings blazed at 300 nm and grooved with 1180 grooves per nm, allowing approximately a 5.0-nm bandpass. The linear dispersion equates to a value of 0.82 nm per millimeter. Entrance, intermediate, and exit slits were set to pass a nominal full bandpass of 6.6 nm. The double monochromator system was aligned with a helium-neon laser and the wavelength counter was calibrated with a mercury source.

Exposure durations were set with a Gerbands electronic shutter (Ralph Gerbands Co. Inc., Arlington, MA) controlled by a Hewlett-Packard model 5330B preset counter. The present counter allowed exposure durations of any desired length with millisecond accuracy.

### Source Measurement

An Eppley 16 junction thermopile (Eppley Laboratory Inc., Salem, MA), traceable to a National Bureau of Standards standard source, was used to characterize the spectral irradiance of the UVR source. When taking the spectral irradiance readings, the thermopile was placed in the same position relative to the monochromator exit port as the rabbit's cornea was to be situated during UVR exposure. The irradiance ( $E_e$ ), in watts per square centimeter ( $W \cdot cm^{-2}$ ), incident on the thermopile was determined by the following relation:

$$E_e = kV_t$$

The value "k" represents the thermopile calibration constant in microwatts per square centimeter per microvolt ( $\mu W \cdot cm^{-2} \cdot \mu V^{-1}$ ), whereas the value " $V_t$ " represents the thermopile-voltmeter reading in microvolts ( $\mu V$ ). The calibration constant for the thermopile used in this experiment was  $5.131 \mu W \cdot cm^{-2} \cdot \mu V^{-1}$ . The radiant exposure (H), in Joules per square centimeter, was calculated by the formula  $H$

$= E_e t$ . The value "t" is simply time in seconds; it should be kept in mind that a Joule is a watt-second. Therefore, for a given irradiance ( $E_e$ ), the exposure duration (t) can be varied to obtain different values of radiant exposure (H) as desired. The above means of output characterization and source calibration was estimated to have a  $\pm 10\%$  accuracy.

The variation of t in order to obtain a constant "H," in the context of the wavelengths used in this experiment, creates an outcome that is somewhat dependent upon the validity of the principle of reciprocity (i.e., the biologic effects or endpoints are independent of exposure time and irradiance). Corneal effects of a krypton-ion laser, with simultaneous output at 350.7 and 356.4 nm (3:1 ratio), illustrates that the product of threshold intensity and the pulsewidth is a constant; the thresholds for multi-pulse exposures have been shown to be in agreement with those for single-pulse exposures.<sup>11</sup> A similar corneal damage pattern can be elicited from helium-cadmium laser data at 325 nm.<sup>12</sup> Based on the literature, it is reasonable to assume that reciprocity holds for all four UVR wavelengths used in this experiment.

### Experimental Animals

Healthy, adult, pigmented New Zealand rabbits were used as the experimental animals. All animals were procured from a single source to ensure constant breeding practices. The animals were housed in NIH-approved quarters under normal, controlled (12 h on, 12 h off) lighting conditions. The animals were maintained, and the experiments were conducted in accordance with procedures outlined in the "Guide for Laboratory Animal Facilities and Care" of the National Research Council, National Academy of Sciences. Anesthesia was maintained throughout the course of the experiment with intramuscular injections of Ketalar (ketamine hydrochloride) (10 mg/kg) and Rompun (5 mg/kg).

Before exposure, each eye was examined with a biomicroscope; animals with anomalies of the cornea were rejected. The animals were restrained in a specially designed holder with only one eye per animal being exposed. The cornea was centered normal to the monochromator exit beam while the monochromator was set in the visible range. The eye then was exposed to UVR at one of the four experimental wavelengths (290, 300, 310, or 360 nm) for specific, predetermined radiant exposure durations. All exposure sessions took place at the same time of day for each experimental group, with ambient illuminance kept constant for all  $O_2$  uptake studies.

### Oxygen Electrode

The micropolarographic oxygen probe consisted of a platinum cathode (25  $\mu m$  diameter) and a silver anode embedded in a plastic carrier. A potassium chloride (KCl) solution served as an electrolytic

bridge between the cathode and the anode. An oxygen-permeable polyethylene membrane, 25  $\mu\text{m}$  thick, effectively sealed the entire electrode-KCl assembly into one operating unit. The micropolarographic system was similar to that used by Benjamin and Hill.<sup>13</sup>

The experimental procedure involved applying the probe to the anterior surface of the corneal epithelium of the living anesthetized rabbit. The sensor, when applied to the eye, provided a limited reservoir of oxygen for the underlying tissue. The average rate of oxygen depletion from the sensor reservoir, between recordings of 140 mm Hg and 40 mm Hg, and after correction for the system-specific time constant, became the measure of the corneal oxygen uptake rate. This, in turn, represents only a relative measure of the aerobic requirement of the cornea, because the extent that the epithelium, stroma, and endothelium each contribute to the corneal oxygen uptake rate has not been adequately established. Published estimates for the epithelium range from 55%<sup>14</sup> to 70%,<sup>15</sup> with an unpublished estimate ranging as high as 93% (WJ Benjamin and M Zagrod, personal communication, 1988).

#### Micropolarographic Application

The eyes of 16 rabbits were exposed *in vivo* to specific exposure levels of UVR. There were four rabbits in each experimental group. Before UVR exposure, five baseline oxygen uptake recordings were made for each eye in the fashion previously described. Oxygen uptake recordings were made again, 2 min after UVR exposure was discontinued, enabling the experimenter to compare the change in oxygen uptake rate resulting from the UVR exposure. The uptake rate values were subjected to a paired-difference analysis. Because the postexposure reading was a "one-time" reading, the standard error of the mean baseline reading was used as an estimate of the postexposure error. The unexposed eyes were also monitored pre- and postexposure to assess the stability of the readings. A two-way analysis of variance was performed in order to estimate differences both within and among experimental groups, and to determine the presence or absence of an overall effect of UVR on the measured oxygen uptake rates.

#### RESULTS

The radiant exposure for all experimental wavelengths was varied from 0.10 to 0.25  $\text{J}\cdot\text{cm}^{-2}$  in 0.05  $\text{J}\cdot\text{cm}^{-2}$  steps. The mean exposure levels were selected from a larger data-set that examined dose issues. The corneal oxygen uptake rate was measured 2 min after the UVR exposure was discontinued. A difference comparison between the pre-exposure baseline and the postexposure oxygen uptake rate demonstrated a wavelength- and dose-specific effect; see Table 1 for a summary data chart.

By plotting the UVR-altered corneal oxygen up-

TABLE 1. Corneal oxygen uptake rate data.\*

Wavelength (nm)	Radiant Exposure ( $\text{J}\cdot\text{cm}^{-2}$ )	Decreased Corneal Oxygen Uptake Rate ( $\text{mm Hg O}_2\cdot\text{sec}^{-1}$ )	SE (of Baseline)
290	0.10	-2.67	0.22
290	0.15	-3.47	0.21
290	0.20	-4.17	0.21
290	0.25	-4.81	0.23
300	0.10	-1.08	0.22
300	0.15	-1.43	0.20
300	0.20	-1.75	0.21
300	0.25	-2.05	0.21
310	0.10	-0.57	0.21
310	0.15	-0.76	0.20
310	0.20	-0.95	0.21
310	0.25	-1.12	0.23
360	0.10	-0.10	0.23
360	0.15	-0.16	0.20
360	0.20	-0.21	0.22
360	0.25	-0.26	0.22

\* Summary data chart outlining the four wavelengths and four radiant exposures that were used, plus the resultant paired decrease in the oxygen uptake rate. The SE is from the pre-exposure baseline data and is reported in an attempt to portray at least an estimate of the experimental error. This same comment applies to the error bars seen in both Fig. 1 and Fig. 2.

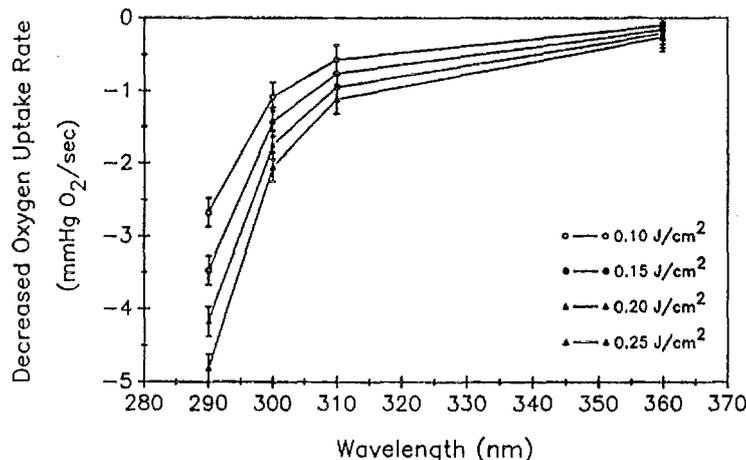
take rate data as a function of wavelength, and by making separate data-sets for each radiant exposure, a "family" of plots is obtained (Fig. 1). A two-way analysis of variance demonstrated an overall significant between-groups difference ( $p < 0.0001$ ), as well as revealed an interactive effect between wavelength and dose ( $p < 0.005$ ). Unexposed eyes exhibited no significant change in corneal oxygen uptake rates over the course of the experiment.

#### DISCUSSION

Fig. 1 presents the decrease in corneal oxygen uptake rate as a function of wavelength with separate plots for each level of radiant exposure. The alteration in corneal oxygen uptake is both wavelength- and dose-dependent, suggesting the presence of at least two different mechanisms of action, based on the differentiation of the three regions of the UV spectrum as discussed in the introduction. The importance here is that different proposed damage mechanisms, unique to the different regions of the UV spectrum, appear to have the common effect of decreasing the corneal oxygen uptake rate and, presumably, metabolic activity. Speculation regarding the possible mechanism(s) responsible for this alteration in oxygen uptake would have to take into account the fact that the change was registered 2 min after the exposure was discontinued.

Current damage mechanism theories involve DNA structural alteration,<sup>16-18</sup> generalized changes in enzymatic activity,<sup>19-23</sup> and/or changes in mitochondrial activity.<sup>24-28</sup> Because the metabolic alteration suggested by the decrease in the corneal oxygen uptake rate is essentially immediate, it would

## Wavelength- and Dose-Dependency Effects of UVR on the Corneal Oxygen Uptake Rate



**Figure 1.** The 16 data points depict four "families" of curves ascending toward normal levels of corneal oxygen uptake as the UVR dose decreases and as the UVR wavelength increases. The error bars represent the SE of the pre-exposure baseline mean before the difference analysis.

be unlikely that DNA structural alteration is responsible. A change in overall enzymatic activity, or a change in mitochondrial activity, or both mechanisms acting "in concert" could be responsible for this UVR-induced decrease in the measured corneal oxygen uptake rate.

The demonstrated UVR-alteration of the corneal oxygen uptake rate implies an alteration in the relative metabolic activity that is graded in nature, suggesting the absence of a true threshold effect. Therefore, even a minimal dose could have some detrimental effect on corneal tissue function. When an already metabolically stressed cornea is exposed to a radiation source for a prolonged period of time, the adverse metabolic effect may be compounded. This has potential clinical significance when applied to contact lens wearers; extended periods of outdoor activity could be subjecting the cornea to a doubly stressful situation: decreased oxygen availability as a result of contact lens wear, and decreased oxygen utilization as a result of the sunlight's radiant energy. Although the conclusion that UVR is capable of causing a decrease in metabolic activity is specific to the cornea, it might be more generally extended to other tissues.

UV-A has been clearly linked with cataract development associated with certain phototoxic pharmaceutical compounds.<sup>29-33</sup> Evidence also has been presented for the noninteractive induction of cataracts by both UV-B<sup>34</sup> and UV-A.<sup>35</sup> Although epidemiologic studies have sought to establish a possible relation between sunlight exposure and cataract prevalence,<sup>36-42</sup> some investigators have suggested the presence of a specific link between sunlight exposure and individual cataract development.<sup>35,43</sup> The retina, as well, has been shown to be

subject to damage as a result of exposure to radiant energy; by UV-B exposure,<sup>44,46</sup> as well as by UV-A exposure.<sup>47</sup>

In fact, some of these experimental UVR exposures have induced cataracts or caused retinal damage at levels close to those available from midday solar exposure.<sup>48</sup> In addition, visible radiation has been implicated in retinal damage processes.<sup>49-58</sup> Further research along this line might provide significant steps toward understanding the mechanism of blue light damage to the retina.<sup>49,51,53,58</sup>

The fact that computerized extrapolations of the data plots illustrated in Fig. 1 intersect the pre-exposure, normalized baseline at a mean wavelength of 447 nm (Fig. 2) suggests that the cornea could be vulnerable to a decrease in metabolic activity when exposed to radiation extending into the visible spectrum. The results of this study highlight the issue of adequate visual protection. At one time 320 nm was considered to be an adequate protection cut-off value for the entire eye.<sup>6</sup> Later studies revealed 340 to 360 nm radiation to be potentially harmful to the eye in general.<sup>7,59,60</sup> Now it is intimated that short wavelength, visible radiation might be stressful to the cornea, and perhaps similarly affect other ocular tissues. In conclusion, all UVR sources (including some recently publicized diagnostic systems),<sup>61-64</sup> and perhaps visible short wavelength sources as well, regardless of the energy output or the waveband, should be regarded with greater caution and used in a more prudent fashion.

### ACKNOWLEDGMENTS

I thank William J. Benjamin, Jr., O.D., Ph.D. and Donald G. Pitts, O.D., Ph.D.

Extrapolated Projection to Baseline  
of UVR—Altered Corneal Oxygen Uptake Rates

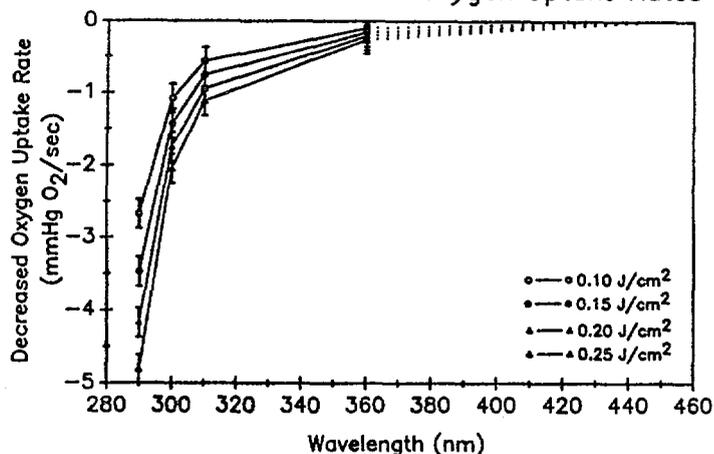


Figure 2. An extrapolated regression analysis of the four UVR wavelength groups reveals a mean return to baseline at 447 nm, suggesting a metabolic efficacy of short wavelength, visible radiation. Again, the error bars represent the SE of the pre-exposure baseline mean before the difference analysis.

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