An Action Spectrum for UV-B Radiation and the Rat Lens

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Purpose. To determine an action spectrum for UV-B radiation and the rat lens and to show the effect of the atmosphere and the cornea on the action spectrum.

Methods. One eye of young female rats was exposed to 5-nm bandwidths of UV-B radiation (290, 295, 300, 305, 310, and 315 nm). Light scattering of exposed and nonexposed lenses was measured 1 week after irradiation. A quadratic polynomial was fit to the dose–response curve for each wave band. The dose at each wave band that produced a level of light scattering greater than 95% of the nonexposed lenses was defined as the maximum acceptable dose (MAD). Transmittance of the rat cornea was measured with a fiberoptic spectrophotometer. The times to be exposed to the MAD in Stockholm (59.3° N) and La Palma (28° N) were compared.

Results. Significant light scattering was detected after UV-B at 295, 300, 305, 310, and 315 nm. The lens was most sensitive to UV-B at 300 nm. Correcting for corneal transmittance showed that the rat lens is at least as sensitive to UV radiation at 295 nm as at 300 nm. The times to be exposed to the MAD at each wave band were greater in Stockholm than in La Palma, and in both locations the theoretical time to be exposed to the MAD was least at 305 nm.

Conclusions. After correcting for corneal transmittance, the biological sensitivity of the rat lens to UV-B is at least as great at 295 nm as at 300 nm. After correcting for transmittance by the atmosphere, UV-B at 305 nm is the most likely wave band to injure the rat lens in both Stockholm and La Palma. (*Invest Ophthalmol Vis Sci.* 2000;41:2642–2647)

In the late nineteenth century careful observers noted that cataract was more common in equatorial regions than in Europe.[1,2] Why cataract prevalence varies with location is not fully understood, but exposure to ultraviolet radiation (UVR) is thought to be an important factor. The English physicist Tyndall proved in 1876 that the atmosphere absorbs UVR,[1] and it is now known that stratospheric ozone is the principal filter of UVR, especially ultraviolet B (UV-B includes wavelengths between 280 and 315 or 320 nm). UVR exposure at the earth's surface decreases with increasing path length through the atmosphere and, thus, decreases with increasing distance from the equator. In 1889 Magnus reported that one type of cataract, presumably cortical, began in the inferior lens[3]; and in 1909 Handmann proved that cortical cataract was most prevalent in the inferior lens.[4]

More recent work has confirmed that cataract prevalence varies with location[2,5] and that cortical cataract begins most often in the inferonasal lens,[6,7] where sunlight is concentrated.[2,8–10] In 1988 the watermen study established an association between cortical cataract and UV-B radiation.[11] The relation of UV-B to other types of cataract or of UV-A to cataract remains uncertain.[11–13]

Determination of the relative contribution of UV-A and UV-B to cataract is important both for public health and understanding the mechanism of UVR injury to the lens.[14–21] This article presents an action spectrum for the rat lens in vivo to acute injury from 5-nm bandwidths of UV-B from 290 to 315 nm and shows how corneal transmittance and the atmosphere affect the relative toxicity of these wavelengths.

Methods

All animals were treated in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Action Spectrum

Experimental Design. Female Sprague–Dawley rats (n = 120, age 6 weeks), divided randomly into 6 groups of 20, were anesthetized with an intraperitoneal injection of 1.0 ml of a mixture of ketamine (12.5 mg/ml; Parke–Davis Scandinavia AB) and xylazine (2 mg/ml; Bayer Sverige AB) for UV-B exposure. Both pupils were dilated with topical 0.5% tropicamide (Alcon Laboratories, Fort Worth, TX). Four animals in each wavelength group were anesthetized but not exposed to UVR, and one eye of each of these animals was randomly designated as the exposed eye for statistical analysis. One eye of the other 16 animals in each group was exposed to UV-B. Treatment of

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TABLE 1. Exposure Parameters

	290 nm	295 nm	300 nm	305 nm	310 nm	315 nm
Dose, kJ/m^2	2.25–19.1	1.0–8.2	0.75–6.6	1.0–8.8	4.9–40.7	10.5–98.5
Exposure, min	20–80	15–31	15	15–28	15–121	15–124

the animals was randomized by wavelength, dose, and left or right eye for exposure, and forward light scattering of each lens was measured three times.

Exposure. Collimated radiation from a mercury lamp (350 W; Oriel Instruments, Stratford, CT), filtered through water to eliminate infrared radiation, passed through a double monochromator (model 77250; Oriel) set to the appropriate wavelength. The entrance and output slits were adjusted to achieve a full width at half maximum of 5 nm. Irradiance at the plane of the cornea was measured with a thermopile (model 7104; Oriel) before and after each exposure; dose was calculated from the mean of these readings. Total dose was adjusted with time of exposure and distance from the source (Table 1). Minimum distance from the source was 3 cm, and minimum exposure time was 15 minutes. At wavelengths 290 and 315 nm only, increasing exposure time could increase the dose. At wavelengths 295, 300, 305, and 310 nm, distance was varied to maintain a minimum exposure time of 15 minutes. A bland lubricating ointment (Oculentum simplex ATL; Apoteksbolaget, Sweden) was applied to both corneas after exposure.

Forward Light Scattering. One week after UV-B exposure rats were euthanatized by carbon dioxide inhalation and cervical dislocation. After enucleation, the lens was removed through a scleral incision and placed in Ringer-acetate solution (Pharmacia & Upjohn, Sweden). Adherent ciliary body and vitreous were peeled from the lens before measuring forward light scattering of each lens three times with the light dissemination meter developed by Söderberg et al.[22] This instrument uses the principle of dark field illumination (Fig. 1). The light below transilluminates the rat lens at 45° from the horizontal. At this angle light does not enter the objective aperture unless the lens scatters light in the forward direction. A photodiode at the film plane in a camera body captures forward scattered light and converts light energy to current, which in turn is converted to a standardized unit (transformed equivalent Diazemuls concentration, or tEDC), based on the light scattering of known concentrations of diazepam (Diazemuls; KabiVitrum, Sweden). Typical forward light scattering values in these units are a little greater than 0.1 tEDC for a normal rat lens and 1.0 tEDC for an opaque lens.

Data Analysis. Light scattering after acute UV-B injury rises continuously to a maximum, after which increasing opacification results in decreasing forward light scattering.[23] Therefore, the measurement of forward light scattering in this system is most sensitive when the lens is not densely opaque. Pilot exposures based on the Pitts et al. rabbit study estimated the minimum dose (D) to produce significant light scattering at each wavelength.[24] The initial part of the dose–response curve was determined by using small, regular increments between doses (0, 0.25 D, 0.5 D, D, and twice D). The initial part of the dose–response curve is well described by a quadratic polynomial: $y = m_1 + m_2x^2$ (where y is light scattering, in tEDC units, and x is dose, in kilojoules per square meter). Variance increases with dose, so estimates of the parameters and confidence intervals were calculated with weighted curvilinear regression (Origin 6.0; Microcal, Northampton, MA). Because a clear lens scatters some light, the minimum forward light scattering with no UV-B dose is not zero. When m_2 is zero, the function reduces to $y = m_1$, and m_1 thus defines the forward light scattering, in tEDC units, of the clear lenses in each wavelength group. The 95% confidence intervals were calculated to show the reliability of m_1 and m_2.[25]

Maximum Acceptable Dose. As light scattering rises continuously after UV-B exposure, no threshold separates minimally detectable cataract from a clear lens. To compare different wave bands of UV-B, we defined the "maximum acceptable dose," or MAD, as the dose that produces light scattering greater than 95% of the nonexposed lenses (Fig. 2). The levels of light scattering (in tEDC units) of nonexposed lenses were plotted to be sure that their distribution was normal. With the mean and SD of light scattering of the nonexposed lenses, the level of light scattering (in tEDC units) corresponding to any probability of the normal distribution may be calculated.[25] In this article a significant lens opacity is defined as any opacity that produces a level of light scattering greater than 95% of the nonexposed lenses.

Light Transmission of the Rat Cornea

The rat cornea is small and thin, and it may wrinkle after removal. Fluid on both surfaces of the cornea can scatter light,

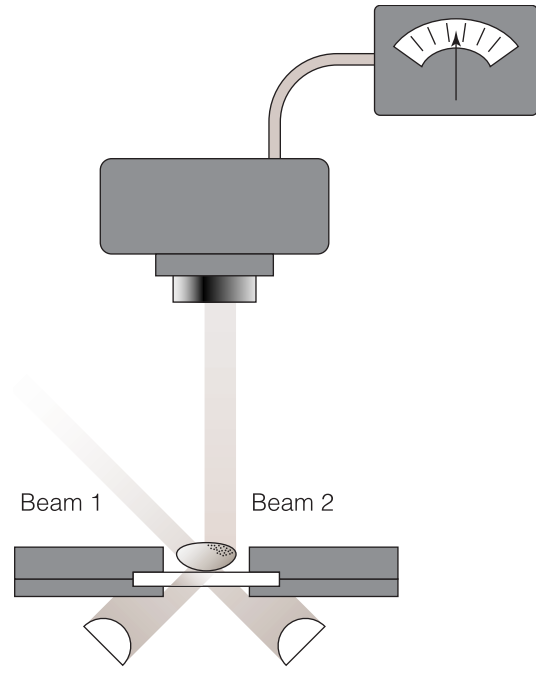

FIGURE 1. Principle of forward light scattering. Light below the sample strikes the lens at a 45° angle. If the lens is perfectly clear, no light is scattered (Beam 1). Opacities within the lens scatter light in a forward direction (Beam 2), which is collected and measured by the photodiode in the camera body.

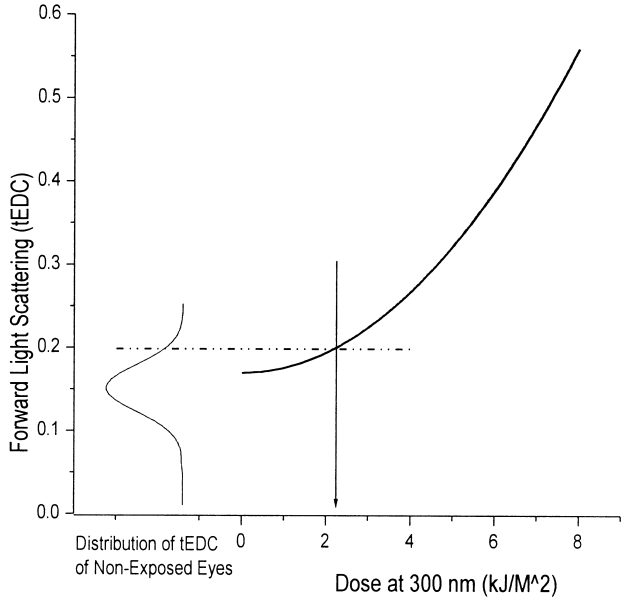

FIGURE 2. Definition of the MAD. On the *left* side is the distribution of light scattering of nonexposed eyes. The *curve* shown on the *right* side is the response to 300 nm UV-B radiation. The *horizontal dashed line* from the 0.95 level of the distribution of nonexposed eyes intersects the dose–response curve (*arrow*) at the MAD for this wave band.

and the cornea can swell quickly when exposed to air after surgical removal. To minimize these problems, the entire cornea of Sprague–Dawley rats (n = 6), excised at the limbus, was placed in a quartz cuvette filled with balanced salt solution (BSS). The refractive index of BSS (1.33) is very close to that of the cornea, helping to eliminate scatter from the liquid/cornea interface and irregularities of the corneal surface and reducing the focusing of light by the cornea. The Cuvette Sample Holder (Ocean Optics, Dunedin, FL) has collimating lenses (f/2) for both the light source and transmitted light; both were focused to optimize the result. Covering the cuvette with Parafilm permitted the holder to be turned on its side, allowing the cornea to settle on the cuvette wall. Only the light transmitted by a small area of the cornea was collected because a black plastic sheet with a 0.2-mm hole was placed on the backside of the cuvette and transmitted light was focused to a 0.2-mm fiberoptic cable. The CCD array detector on a PC card collected full wavelength spectra from 200 to 1000 nm (PC 1000 Fiber Optic Spectrometer, Ocean Optics).[26]

Comparing a Northern and Southern Location. The Swedish Radiation Protection Institute provided irradiance by wavelength at solar noon (solar elevation of 50°) on a clear July day at sea level in Stockholm (59° 20′ N, 18° 3′ W) and at solar noon (solar elevation of 85°) at an elevation of 2350 meters in the Canary Islands (28° N, 17° 36′ W).[27,28] To estimate the time for a rat to be exposed to the MAD, it is assumed that a rat in each location stared continuously at the sun with dilated pupils and that the sun's position remained constant. The product of time and irradiance is dose. The time to be exposed to the MAD at each location was calculated by substituting the MAD for dose and the integrated irradiance for each 5-nm bandwidth.

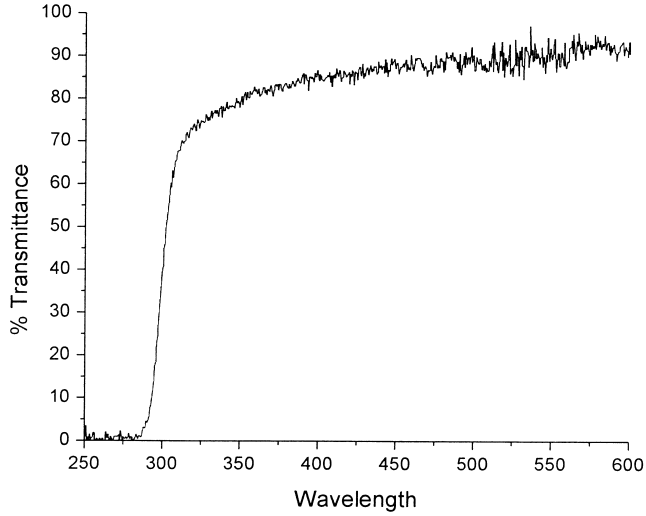

FIGURE 3. Transmittance of the rat cornea from 285 to 600 nm.

RESULTS

Transmission of the Rat Cornea

Transmission of UVR by the rat cornea begins at approximately 285 nm and is only approximately 5% at 290 nm (Figs. 3, 4).

Effects of UV-B Radiation

Clinical Observations. The corneas of some animals in each group were examined with the slit lamp immediately after exposure and 1 week after treatment, and all animals were examined with the dissecting microscope 1 week after exposure. Immediately after UVR exposure all corneas had a punctate keratitis, including the nonexposed eyes and the eyes of the control animals. However, the reaction was noticeably more severe after any dose at 290 nm; most of these corneas were opaque at the end of the treatment. Hyphema was an unexpected complication of UV-B, and the presence of hyphema was recorded only for the last 72 animals enucleated. Because the animals were randomized to dose and wavelength,

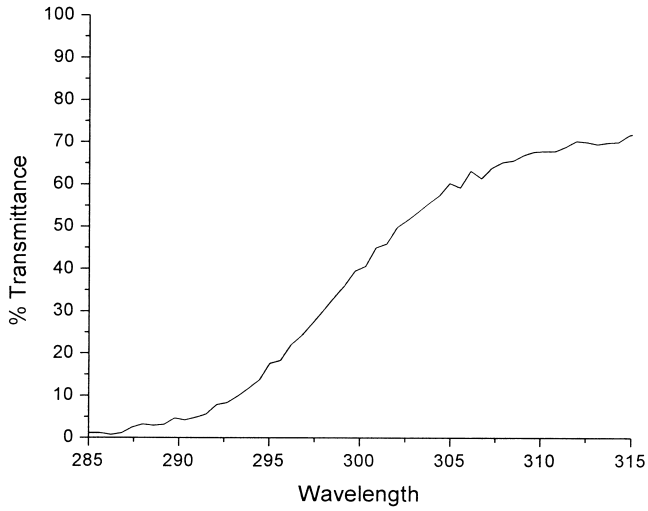

FIGURE 4. Transmittance of the rat cornea from 285 to 315 nm.

TABLE 2. Light Scattering (y) as Function of Dose (x) at Various Wave Bands

Wavelength, nm	Function: $y = m_1 + m_2x^2$	
	m_1 ± 95% CI*	m_2 ± 95% CI*
290	0.17 ± 0.0185	$(6.38 \pm 12)\ 10^{-5}$†
295	0.13 ± 0.014	$(3.3 \pm 1.8)\ 10^{-3}$
300	0.16 ± 0.02	$(6.6 \pm 5.4)\ 10^{-3}$
305	0.16 ± 0.02	$(1.3 \pm 0.97)\ 10^{-3}$
310	0.14 ± 0.008	$(9.54 \pm 3.53)\ 10^{-5}$
315	0.145 ± 0.01	$(4.67 \pm 3.37)\ 10^{-6}$

* 95% Confidence interval.
† Not significantly different than zero.

the number in each wavelength group in the final 72 animals is not the same. One week after exposure, 5 of 13 of the rats exposed to UV-B at 290 nm had hemorrhage in the anterior chamber, and hyphema was found at all doses at 290 nm. Four other animals had hemorrhage in the anterior chamber, all exposed to the highest dose of UV-B in the group: 2 of 8 at 305 nm, 1 of 12 at 300 nm, and 1 of 11 at 310 nm. None of the nonexposed eyes had hyphema at enucleation.

Nonexposed Eyes. The values of light scattering of the nonexposed lenses ($n = 120$) were distributed normally (mean, 0.152; SD, 0.028). Forward light scattering greater than 95% of the nonexposed lenses was 0.199 tEDC unit. ANOVA for three variables (doses, animals, measurements) confirmed that light scattering of the nonexposed lenses did not vary with dose in each wavelength group ($P < 0.05$). A second ANOVA for three variables (wavelength, animals, measurements) confirmed that light scattering of the nonexposed lenses did not vary with wavelength ($P < 0.05$).

Exposed Eyes. Light scattering of clear lenses is not zero; and, hence, the term m_1 describes the y intercept at no dose for each group. The values of m_1 are close but not identical, as expected (Table 2). None of the confidence intervals for m_1 include zero. However, the confidence interval for m_2 for the 290-nm group does include zero. Therefore, with 95% confidence the possibility that m_2 is zero cannot be excluded. When m_2 is zero, the function reduces to $y = m_1$; and, therefore, the only detected forward light scattering is that due to a clear lens. Light scattering after UV-B at 295, 300, 305, 310, and 315 nm is greater than that of nonexposed lenses (Table 2, Fig. 5). However, the slope of the dose–response curve at 315 nm suggests that light scattering of this group is only slightly greater than that of clear lenses.

Maximum Acceptable Dose. Light scattering greater than 95% of the nonexposed lenses in these experiments is 0.199 tEDC unit. The dose (MAD) for each 5-nm bandwidth corresponding to 0.199 tEDC unit, calculated with the quadratic function that describes the data for each group (Table 2), is least at a wavelength of 300 nm (Table 3). To estimate the actual dose received by the lens, it is assumed that corneal transmittance for each 5-nm bandwidth is the transmittance at the center of the bandwidth. The product of the transmittance at each bandwidth and the MAD yields the dose passing through the cornea to the lens that produces a level of light scattering greater than 95% of normal lenses. The MAD corrected for corneal transmittance was slightly lower at 295 nm than 300 nm (Table 3).

Effect of Location. Although the rat lens is more sensitive to shorter wavelengths, UV-B at 305 nm is potentially more harmful than either 295 or 300 nm UV-B (Table 4). Exposure to UV-B is less in Stockholm than in La Palma, especially at the shortest wavelengths.

DISCUSSION

In 1916 Verhoef and Bell found that 295 nm UV-B produced keratitis and hyphema in the rabbit,[29] and in 1956 Bachem confirmed that UV-B produced keratitis and iris hemorrhages in the rabbit and guinea pig.[30] Verhoef and Bell attributed hy-

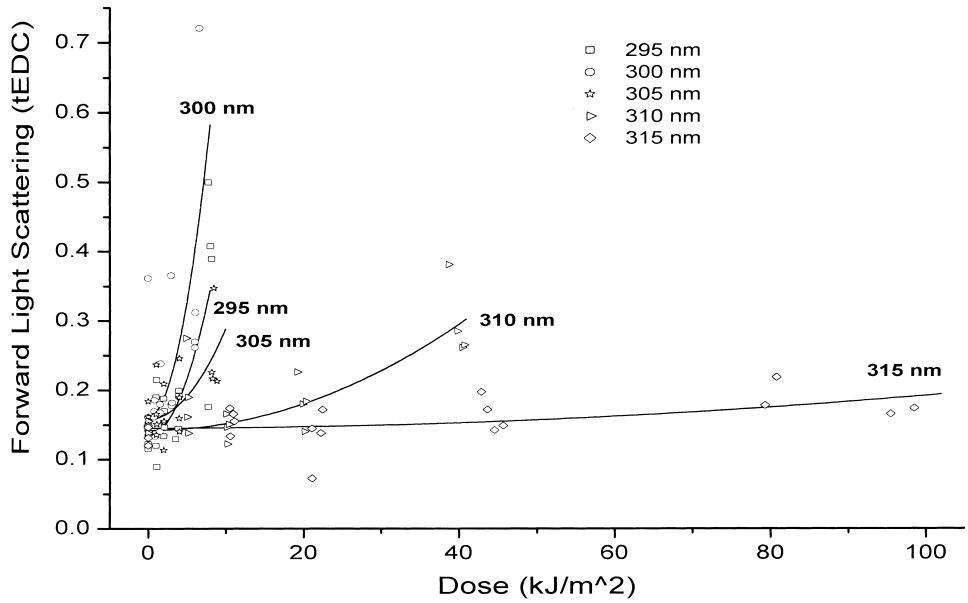

FIGURE 5. Dose–response curves for 5-nm bandwidths of UV-B centered at 295, 300, 305, 310, and 315 nm.

TABLE 3. Wavelength Dependence of MAD

Wavelength, nm	MAD, kJ/m²	Cornea Transmittance	Corrected MAD,* kJ/m²
295	4.44	0.17	0.75
300	2.38	0.4	0.95
305	5.57	0.61	3.40
310	24.35	0.68	16.56
315	106.91	0.72	76.98

* MAD corrected for corneal transmittance.

phema after UV-B to loss of vascular endothelium,[29] but the corneas of both the rabbit and guinea pig transmit so little energy below 295 nm that the iris vessels must be particularly sensitive to short wavelength UV-B, or hyphema is an indirect effect of keratitis.

Based on slit-lamp and pathologic evaluation, Verhoef and Bell concluded that wavelengths between 295 and 305 were most likely to produce cataract in the rabbit.[29] Bachem suggested that the action spectrum for cataract in the rabbit and guinea pig peaked at 297 nm, fell to 313 nm, and had "a long tail through the near ultraviolet."[30]

The action spectrum that Pitts et al.[24] reported in 1977 is more comparable to this study. They exposed pigmented rabbits to single doses of UV-B at 5-nm bandwidths from 290 to 320 nm and to 335 and 365 nm UV-A. Two observers graded transient and permanent lens opacities with the slit lamp. As in the present study, radiation at 290 nm damaged the cornea but had no visible effect on the lens. The effective action spectrum for the adult rabbit lens began at 295 nm and extended to 315 nm. They were unable to establish a threshold dose for the lens at 320, 335, and 365 nm.

In the study by Pitts et al.[24] the rabbit lens, like the rat lens, was most sensitive to UV-B at 300 nm, but the dose to produce permanent lens opacity in the rabbit was 5 kJ/m² at 300 nm, roughly twice the MAD at 300 nm for the rat lens. Differences between the action spectra of the rabbit and rat may be due in part to method. Even the most careful observer cannot detect subtle differences between lens opacities with the slit lamp; and the ordinal grading of cataract, such as 1+, can only be analyzed with nonparametric methods. Quantification of light scattering of lens opacities solves these problems, and an action spectrum based on the measurement of light scattering should be more sensitive to the effect of UV-B radiation than one based on slit-lamp grading. However, the MAD for the rat at both 310 and 315 nm is nearly twice the threshold for permanent cataract in the rabbit, despite the fact that measurement of light scattering is more sensitive than slit-lamp evaluation.

Biological differences must be considered when one compares the action spectra of different species. The rat lens is exposed to more short wavelength UV-B than the rabbit lens because the rat cornea is thinner. The lenses of the young rat and mouse absorb very little radiation between 320 and 360 nm and essentially none from 360 to 400 nm.[26] The adult rabbit lens absorbs at least 75% of transmitted light to 375 nm, but absorbance then falls rapidly to nearly zero at 400 nm.[26] Thus, the rabbit lens may be more sensitive than that of the rat to 310 and 315 nm UV-B because the rabbit lens absorbs more UVR.

The human lens absorbs more UVR than the rabbit lens, and the absorbance increases with age. The young human and monkey lenses have a small window of transmission centered at approximately 320 nm but absorb virtually all UV-A above 340 nm; absorbance falls to near zero by 425 nm.[1,31–33] In youth absorbance of UVR from 295 to 400 nm is due to 3-hydroxykynurenine (3-HKG).[33] With age the concentration of 3-HKG in the human lens decreases, but the lens becomes more yellow, especially in the nucleus, increasing the absorption of light across the entire UVR spectrum and in the visible to approximately 550 nm.[26,31–33] Thus, the complex effects of UVR on the primate lens vary both with age and with location within the lens.

Although in the laboratory the rat and rabbit are most sensitive to 300 nm UV-B, solar radiation at 305 nm is potentially more toxic (Table 4). As distance from the equator increases, the effect of path length through the atmosphere becomes more apparent, especially at short wavelengths. The time to the MAD at each UV-B wave band is less in La Palma than in Stockholm, but the relative difference in the time to be exposed to the MAD at each wave band decreases with increasing wavelength. UV-B at 315 nm had little effect on forward light scattering of the rat lens, yet in Stockholm the theoretical time to the MAD at 315 nm is nearly the same as at 300 nm.

One must be cautious when extrapolating from animal studies to human cataract. The effect of combinations of wavelengths, the length and intensity of exposures, the time between exposures, and the species and age of the animal are some of the variables that may be important. The human lens is exposed to relatively low levels of UVR for many years, and the effect of chronic UVR exposure may be different from acute UVR injury. For epidemiologic studies it is convenient to divide human cataract into cortical, nuclear, and posterior subcapsular types, but mixed types are very common.[34] Electron microscopy has revealed junctions between lens cells,[35] and it is possible that injury to one part of the lens also affects other parts of the lens.

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TABLE 4. Time Exposed to the MAD in Stockholm and La Palma

Wavelength, nm	MAD 0.95, kJ/m²	La Palma, min	Stockholm, min	Time to MAD Stockholm/La Palma
295	4.44	2741	113199	41.3
300	2.38	189	2613	13.8
305	5.57	141	736	5.2
310	24.35	307	1065	3.5
315	106.91	979	2522	2.6

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