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Determination of the Relative Response of Mammalian Cells to Simulated Sunlight & 254 NM Radiation

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DETERMINATION OF THE RELATIVE RESPONSE OF MAMMALIAN CELLS TO SIMULATED SUNLIGHT AND 254 NM RADIATION

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DETERMINATION OF THE RELATIVE RESPONSE OF MAMMALIAN CELLS

TO SIMULATED SUNLIGHT AND 254 nm RADIATION

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DETERMINATION OF THE RELATIVE RESPONSE OF MAMMALIAN CELLS TO SIMULATED SUNLIGHT AND 254 NM RADIATION

Randall F. Gill July, 1983 30 pages

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A comparison between germicidal (254 nm) UV and simulated sunlight (above 300 nm) radiation emitted from a solar simulator has been made using five mammalian cell lines. The cell lines used included normal and photosensitive human skin fibroblasts and one African green monkey kidney cell line. The ratio of 10% survival by exposure to 254 nm radiation divided by 10% survival by simulated sunlight exposure derived from the above comparison was used as a criterion for showing that the above cell lines are statistically significantly different in their relative response to simulated sunlight.

INTRODUCTION AND LITERATURE REVIEW

In mammalian cells ultraviolet (UV) light is known to be cytotoxic (Elkind, Han, and Chang-Liu, 1978), mutagenic (Hsie, Li, and Machanoff, 1977), and oncogenic (Blum, 1959). Human skin cancers have been shown to be closely associated with exposure to sunlight, especially the UV portion of sunlight (Schreiber, et al. 1971). Setlow (1974) has indicated that the most effective wavelengths in producing skin cancer are those below 305 nm. These cancers probably arise from photochemical changes taking place in the DNA of the affected cells. Kantor, Sutherland, and Setlow (1980); Kantor, Warner, and Hull (1977); Rothman and Setlow (1979); Zelle, et al. (1980); Smith and Paterson (1981, 1982); and Kantor and Setlow (1982) have looked at various photochemical changes caused by exposure to ultraviolet light in the DNA with respect to cell lethality and mutagenicity. Similar work has been done using bacterial systems by Tyrrell, Ley, and Webb (1974); Moss and Smith (1981); and Ellison and Childs (1981).

Most of the investigations dealing with the biological effects of ultraviolet light have been made using the radiation emitted from a low vapor pressure mercury "Germicidal" lamp which has 86% of its output at 254 nm (Jagger, 1967). Since this wavelength is very close to the maximum absorption peak of DNA, it is readily absorbed

and is thus capable of producing numerous photochemical changes in the genetic material. The major change is the production of pyrimidine dimers (Rothman and Setlow, 1979). Action spectra by Kantor, Sutherland, and Setlow (1980) and Coohill, Moore, and Drake (1977) indicate that the main target for damage in cells is the nucleic acid. Another reason for using 254 nm radiation is that mammalian cells are about one thousand fold less sensitive to wavelengths above 300 nm (Sutherland and Griffin, 1981) than they are to 254 nm radiation. Thus, a very intense light source would be required for research in this longer wavelength region.

Although useful as a laboratory tool, 254 nm radiation is environmentally irrelevant. This is because sunlight is sufficiently attenuated by the earth's ozone layer such that the surface of this planet receives essentially no radiation below 286 nm. Therefore, the effects produced by 254 nm radiation do not represent naturally occurring phenomena in biological systems. In an effort to determine what is actually happening to cells exposed to "natural" radiation, researchers have begun to use light sources other than the germicidal lamp. The most commonly used sources are certain flourescent lamps, including sunlamps. These lamps produce radiation that is mainly in the region above 300 nm. Work done by Erickson, Bradley, and Kohn (1980) and Ritter and Williams (1981) using cool white flourescent lamps have shown that this light is capable of inducing DNA damage of various types. Others such as Elkind, Han, and Chang-Liu

(1978); Kantor and Setlow (1982); and Suzuki, et al. (1981) have looked at sunlight induced mammalian cell killing using a sunlamp, which is a flourescent-type low vapor pressure mercury discharge source whose peak emission is mainly in the UV region above 290 nm.

Since action on DNA is often implicated, (or at least assumed to be the cause of sunlight-induced effects), it is generally assumed that the effects produced by 254 nm radiation are similar in kind to those produced by wavelengths above 300 nm. However, when comparisons are made between 254 nm radiation and wavelengths above 300 nm the results are conflicting. Some researchers such as Hsie, Li, and Machanoff (1977) and Kantor and Setlow (1982) report no difference in the relative response compared with shorter wavelength studies, while others such as Elkind, Han, and Chang-Liu (1978) and Keyse, Moss, and Davies (1983) report considerable differences.

If it is true that there is no difference between the effects of 254 nm and greater than 300 nm radiation then all cells should have the same relative response to the near UV and should differ only in their sensitivity to it. In this study the effects of simulated sunlight produced by a solar simulator (SS) are compared with the effects produced by 254 nm radiation. The SS was used because its emission is closer to that of natural sunlight than the emission of a flourescent sunlamp. The ratio of 10% survival at 254 nm divided by 10% survival by SS exposure derived from this

comparison will be used as a criterion for determining whether different cultured cell lines differ in their relative response to the near UV.

The solar simulator used in this study is a light source that requires a high pressure xenon lamp and a complex optical system to produce light that is similar to sunlight both in wavelengths produced and, most importantly, in intensity. Since mammalian cells are much less sensitive to wavelengths above 300 nm (Sutherland and Griffin, 1981), this very intense light source was required. The radiation produced by the SS is much more controlled than natural sunlight due to problems of cloud cover, temperature, intensity fluctuations, etc. and thus gives more consistent results. The SS could also be used when needed, this availability is not possible with natural sunlight.

MATERIALS AND METHODS

CELL CULTURES

In these studies four human fibroblast cell lines and one monkey cell line were used. KD cells (ATCC-CRL 1295), a normal human skin cell line, were obtained from Rufus Day III of NIH, Bethesda, MD. The three other skin fibroblast cell lines were from patients suffering from photosensitive diseases. These cell lines were: a line of Bloom's syndrome (BS) cells (GM1492) and two lines of Xeroderma Pigmentosum cells, XP1PW cells (GM0510) complementation group C and XP25RO cells (GM0710) complementation group A. All photosensitive cell lines were obtained from the Human Genetic Mutant Cell Repository, Camden, NJ. All of the above cell lines were maintained in a growth medium that consisted of 1X Eagle's Minimum Essential Medium containing the following components added per liter: 15% fetal bovine serum (K.C. Biological, Inc., Lenexa, KS), 10 ml of 100X non-essential amino acids, 20 ml of 50X essential amino acids, 10 ml of 100X MEM vitamins, 16 ml of 100X antimycotic-antiobiotic mixture (all from GIBCO Laboratories, Grand Island, NY), 0.29 g of L-glutamine (Microbiological Associates, Walkersville, MD), 3.6 g of N-2Hydroxyethyl piperazine-N'-2-ethane sulfonic acid (HEPES), 3.4 g of N-Tris (hydroxymethyl) methyl-2-aminoethanesulfonic acid (TES), 3.1 g of Morpholinopropane

Sulfonic Acid (MOPS) (all from Chemalog, South Plainfield, NJ), and buffered to a pH of 6.8 with 10 N NaOH.

A line of African green monkey kidney cells (CV-1) was obtained from Dr. L.E. Bockstahler of the Bureau of Radiological Health, Rockville, MD. These cells were maintained in a growth medium that consisted of 1X Dulbecco's Modified Eagle's Medium containing the following components added per liter: 10% newborn calf serum (Microbiological Associates, Walkersville, MD), 0.29 g of L-glutamine, 16 ml of 100X antimycotic-antibiotic mixture, 3.6 g of HEPES, 3.4 g of TES, 3.1 g of MOPS, and buffered to a pH of 6.8 with 10 N NaOH. All cell lines were grown and incubated in closed 150 cm^2 flasks or in 21 cm^2 petri dishes (Corning Glass Works, Corning, NY) in closed (approximately 5% CO_2) chambers at 37°C. Cells were passaged by trypsinization of the cells using a solution of 0.025% each of trypsin 1:250 and EGTA dissolved in Mg^{++} and Ca^{++} free phosphate-buffered saline at pH 7.8. The cells were then transferred to an appropriate container.

CAPACITY ASSAY

A macroplaque strain of Herpes simplex virus type 1 was used as a probe for cellular damage to perform viral capacity experiments (Coohill, 1981). The virus was inoculated onto confluent monolayers of CV-1 cells. After plaques became evident, the virus was harvested by centrifugal separation and stored in vials at -70°C until used in experimental viral capacity assays.

For the viral capacity assay, monolayers of various cell lines were inoculated immediately after irradiation with the appropriate viral titer in 2 ml of the appropriate growth medium, as described above. The viral dilution was adjusted so that approximately 100 plaque-forming units (pfu's) were inoculated onto all plates. The cells were incubated with the virus for 60 min at 37^{o}C. The inoculum was then removed and replaced with 4 ml of the appropriate growth medium containing 0.25% immune serum globulin (Cutter Biological, Berkeley, CA) to prevent extracellular viral transfer. Plaques were allowed to develop for 48 to 78 hrs, depending on the cell line used. After plaques became large enough to see and count, the cell monolayers were stained with 0.1% crystal violet. The plaques stained as faint blue or clear areas against a dark violet cellular background. The pfu's could then be counted.

254 nm EXPOSURE

The cells were passaged into 21 cm^{2} petri dishes and allowed to grow for approximately four days to reach confluency. The growth medium was then removed and replaced with 2 ml of phosphate buffered saline (PBS) to prevent the formation of toxic photoproducts (Bradley and Sharkey, 1977). The confluent monolayers of cells were then irradiated in open petri dishes with a 15W germicidal lamp (G15T8, General Electric Co., Schenectady, NY) with 86% of its output at 254 nm (Jagger, 1967). The lamp was mounted in a wooden box

with a sliding shutter to control the exposure (see Fig. 1). The open petri dishes were placed 41 cm from the germicidal UV light source. The exposure rate for this lamp at the above distance has been found to be 2.3 $J/M^2/sec$. The total exposure was equal to the length of time that the plate was exposed multiplied by the exposure rate.

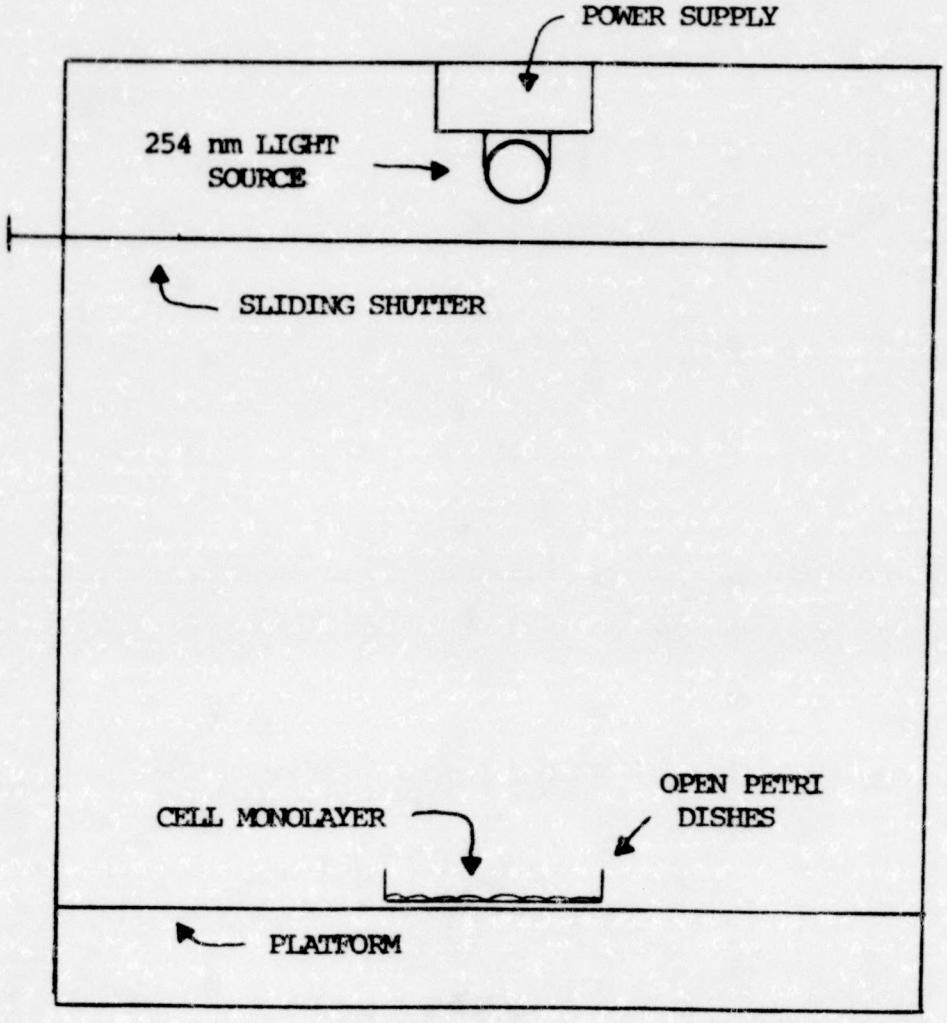
SIMULATED SUNLIGHT EXPOSURE

The cells were passaged into 21 cm^2 petri dishes and allowed to grow for approximately four days to reach confluency. Prior to irradiation, the growth medium was removed, the monolayers were washed once with PBS, and finally 5 ml of PBS was added to each dish. The confluent monolayers of cells were irradiated in closed petri dishes with a solar simulator (Model 302, Aerospace Controls Corporation, Los Angeles, CA) using an Osram 2500W high-pressure xenon lamp (Bulbtronics, Inc., Farmingdale, NY). The beam of light from the solar simulator was reflected from a horizontal direction to a vertical direction using a front surface mirror (see Fig. 2). This experimental arrangement provided a circle of light approximately 30 cm in diameter, in which twelve dishes could be irradiated at once. The cell monolayers were exposed for a minimum of 1 hr to a maximum of 7 hrs. The length of exposure was dependent on the sensitivity of the cells used.

The solar simulator emission spectrum was mainly in the above 300 nm range (see Fig. 3). Figure 4 shows an

expanded version of the aforementioned graph. The exposure rate was found to be approximately 1 X 10^6 $J/M^2/hr$ as compared to 2 X 10^6 $J/M^2/hr$ (an approximation for natural noon sunlight in August at Bowling Green, KY). The majority of the wavelengths below 300 nm would be attenuated by the plastic lids on the petri dishes (Ritter and Williams, 1981).

Figure 1. Diagram of the experimental arrangement for Germicidal (254 nm) exposures.



UV RADIATION CHAMBER

Figure 2. Diagram of the experimental arrangement for simulated sunlight exposures.

SOLAR SIMULATOR

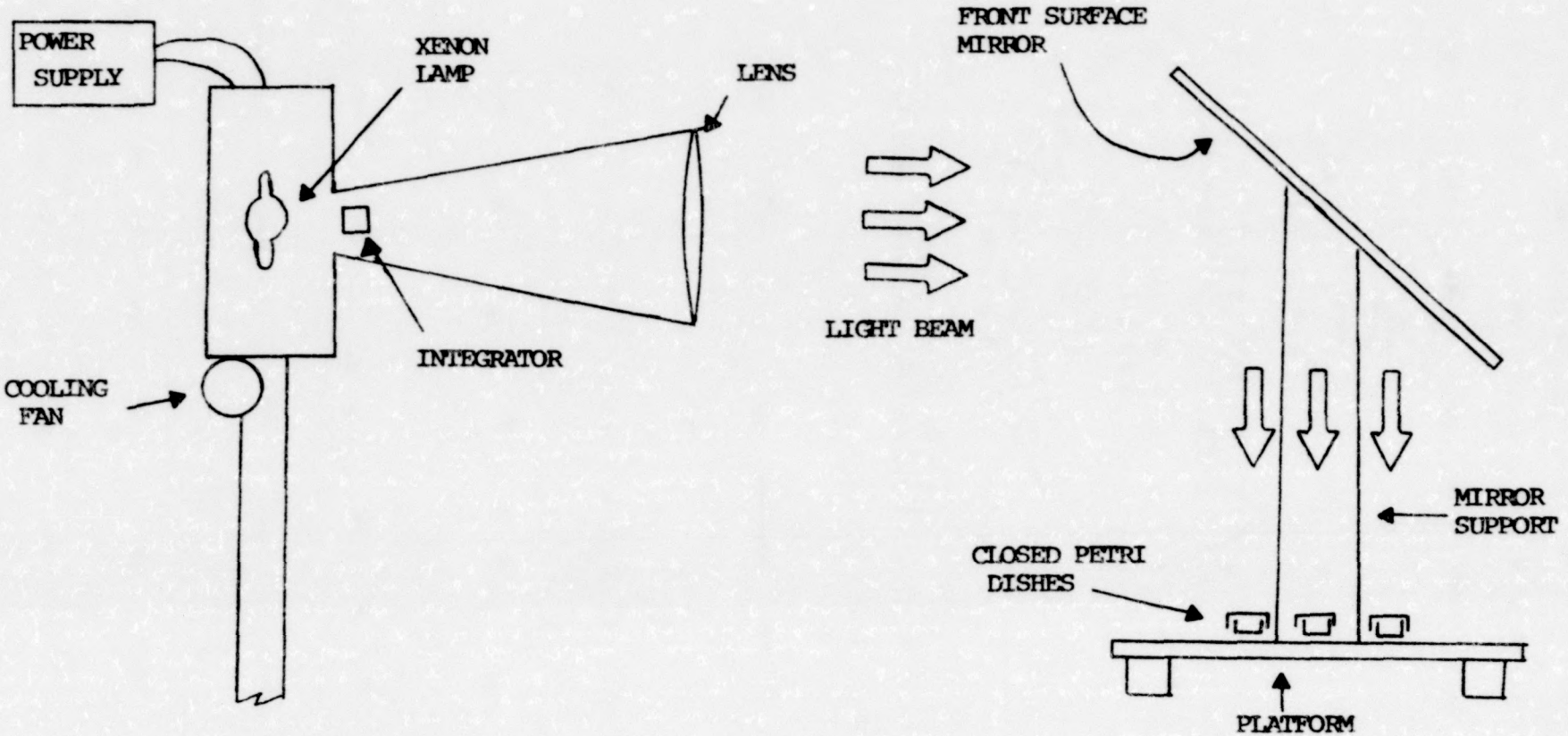


Figure 3. Comparison between the outputs of ACC solar simulator Model 302 (○) and natural sunlight at noon on 21 August 1981 at Oak Ridge, TN (△).

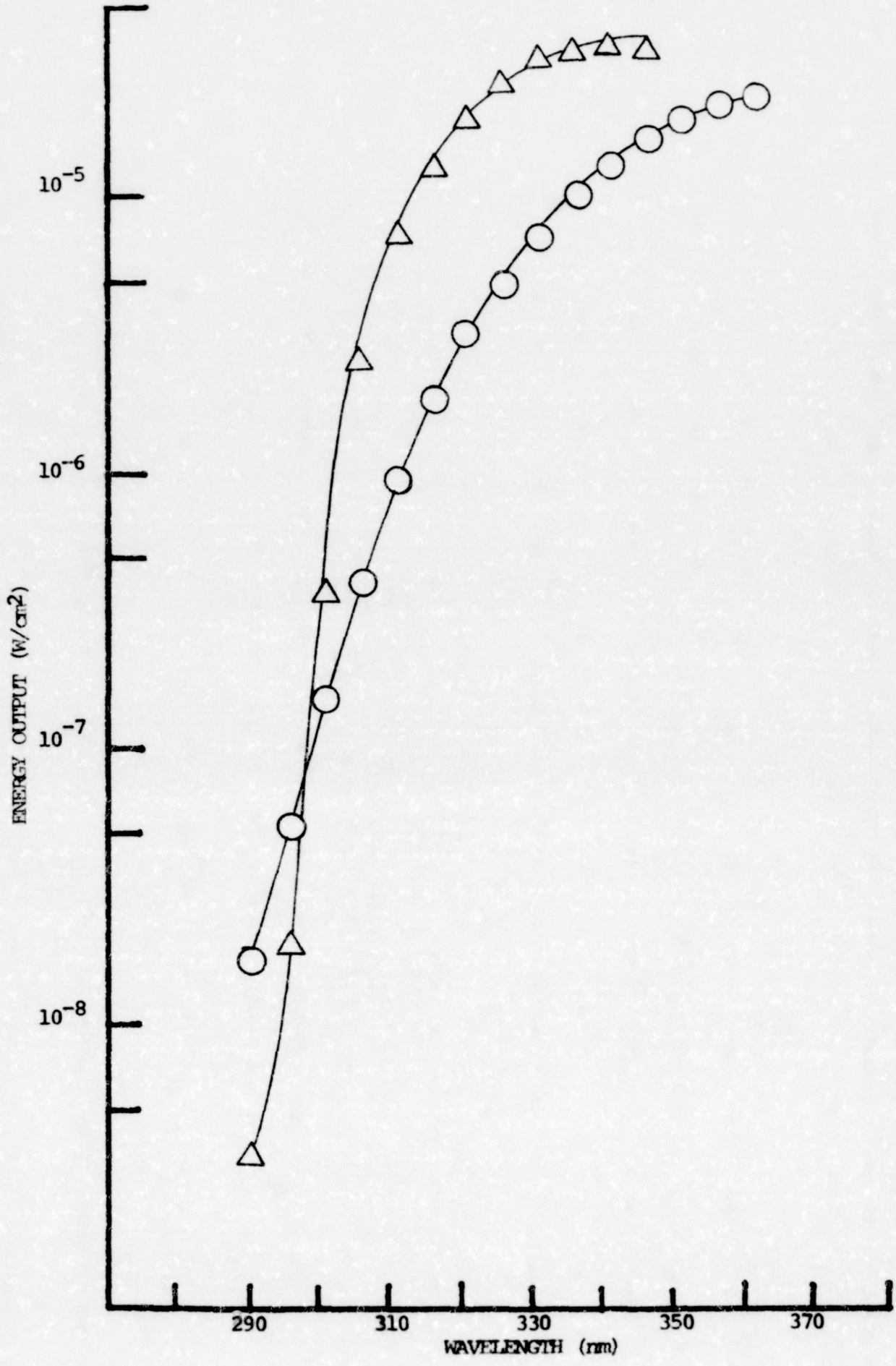
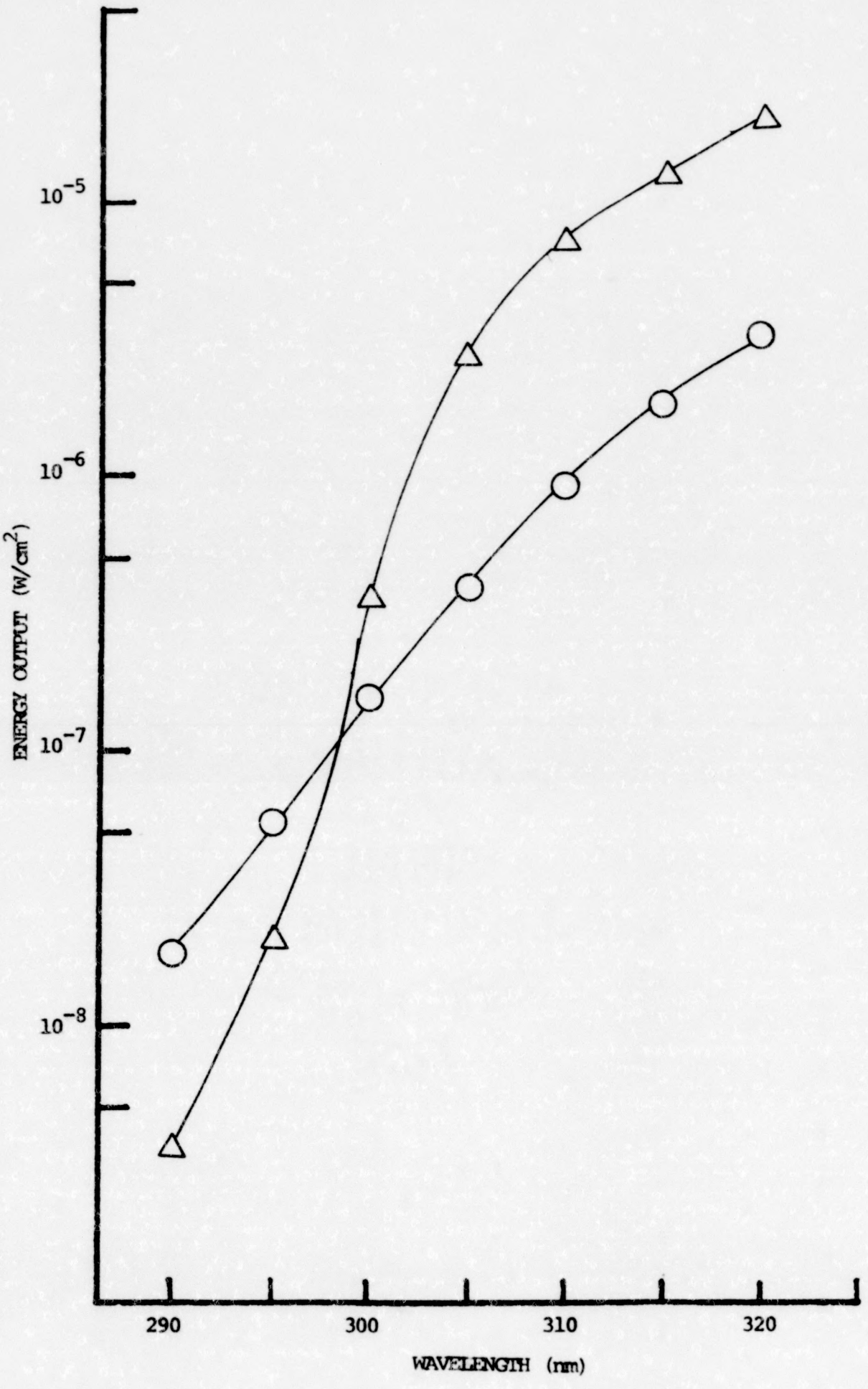

ENERGY OUTPUT (W/cm2)
10-5
10-6
10-7
10-8
290
310
330
350
370
WAVELENGTH (nm)

Figure 4. Expanded wavelength comparison between ACC solar simulator Model 302 (○) and natural noonday sunlight at Oak Ridge, TN (△).


10^{-5}
10^{-6}
10^{-7}
10^{-8}
ENERGY OUTPUT (W/cm^2)
290
300
310
320
WAVELENGTH (nm)

RESULTS

The exposure rate for the solar simulator was found to be approximately 1 X 10^6 J/M^2/hr, about half that of noonday sunlight in August in Bowling Green, KY which was approximately 2 X 10^6 J/M^2/hr. Presented in figure 3 is a comparison of the output of our SS and August noon sunlight at Oak Ridge, TN. Figure 5 shows a comparison between natural sunlight, our SS, Oak Ridge National Laboratory's SS, and the solar simulator at Argonne National Laboratory. All three solar simulators have been calibrated in a similar manner by the same person (Dr. Ronald Ley, Oak Ridge National Laboratory) so that results from one SS can be compared with results from the other two.

Germicidal (254 nm) and simulated sunlight exposures were run on the same day for each cell line. Since the germicidal exposure times were considerably shorter than the exposures made using the SS, the germicidal exposures were run during the last hour of simulated sunlight exposure. By exposing the cells as described they were at the same stage of growth (Griego, Webb, and Matsushita, 1981), thus allowing the same viral solution to be used for both sets of irradiations. Each set had its own unirradiated control.

To determine survival a viral capacity assay was performed. Viral capacity is the cells ability to serve as

the host for the virus. The procedure used is as described by Coohill (1981). The major reason for using capacity is that it is dependent on the cell's DNA and could thus be used to show any changes in the nucleic acid. Also by using this procedure monolayers of cells could be employed. It has been shown that cells are more sensitive to ultraviolet light when they are in the umbonate shape than when they are free cells (Coohill, Knauer, and Fry, 1979). The monolayers are similar in their physiological state to mammalian cells in tissue.

After plaques developed, they were counted and survival was calculated. Survival versus exposure was plotted on semi-log graph paper. Curves for both sets of data were superimposed on the same graph. Exposure was expressed in J/M^2 for cells irradiated with the germicidal lamp and in hours for cells irradiated with the solar simulator. Since time multiplied by exposure rate is equal to total exposure, hours of SS exposure is directly proportional to the total energy. As a matter of convenience this ratio measure could be used in place of total energy for making comparisons. From this graph the exposure that would give 10% survival by either type of radiation could be estimated. These exposures could then be used to derive the ratio used to indicate the relative response of the different cell lines to germicidal radiation and the near UV. This ratio was obtained by dividing the 10% survival exposure for 254 nm by the 10% survival exposure for simulated sunlight.

In figure 6 the survival curves for CV-1 cells are shown. The estimated 10% survival exposures for 254 nm and simulated sunlight are 22.6 J/M^2 and 7.4 hrs respectively. The derived relative response ratio is therefore 3.1. Figure 7 shows the survival curves for the KD cell line. The estimated 10% survival exposures are 33.7 J/M^2 and 4.2 hrs. The derived relative response ratio for this cell line is 8.0. In figures 8, 9, and 10 the survival curves for the BS cell line, the XP1PW cell line, and the XP25RO cell line are shown respectively. The 10% survival exposures for these cell lines are given in Table 1. The relative response ratios are 5.9, 5.5, and 1.6 respectively. The graph for the XP25RO cells show that this cell line is very sensitive to 254 nm radiation, as previously described by Coohill, Moore, and Grider (1983), but shows a normal sensitivity to the simulated sunlight when compared to the other photosensitive cell lines. The data for all the trials run for each cell line and the means for 10% survival exposures and relative response ratios are given in Table 1.

An analysis of variance for the relative response ratios was run using a completely random design. The results of this analysis show that there is a highly significant difference between the means of the relative response ratios for the different cell lines using the F test (Steel and Torrie, 1980).

Figure 5. Comparison between the outputs of ACC solar simulator Model 302 (○), Oak Ridge National Laboratory's solar simulator (□), and the solar simulator at Argonne National Laboratory (■) with natural sunlight (△).

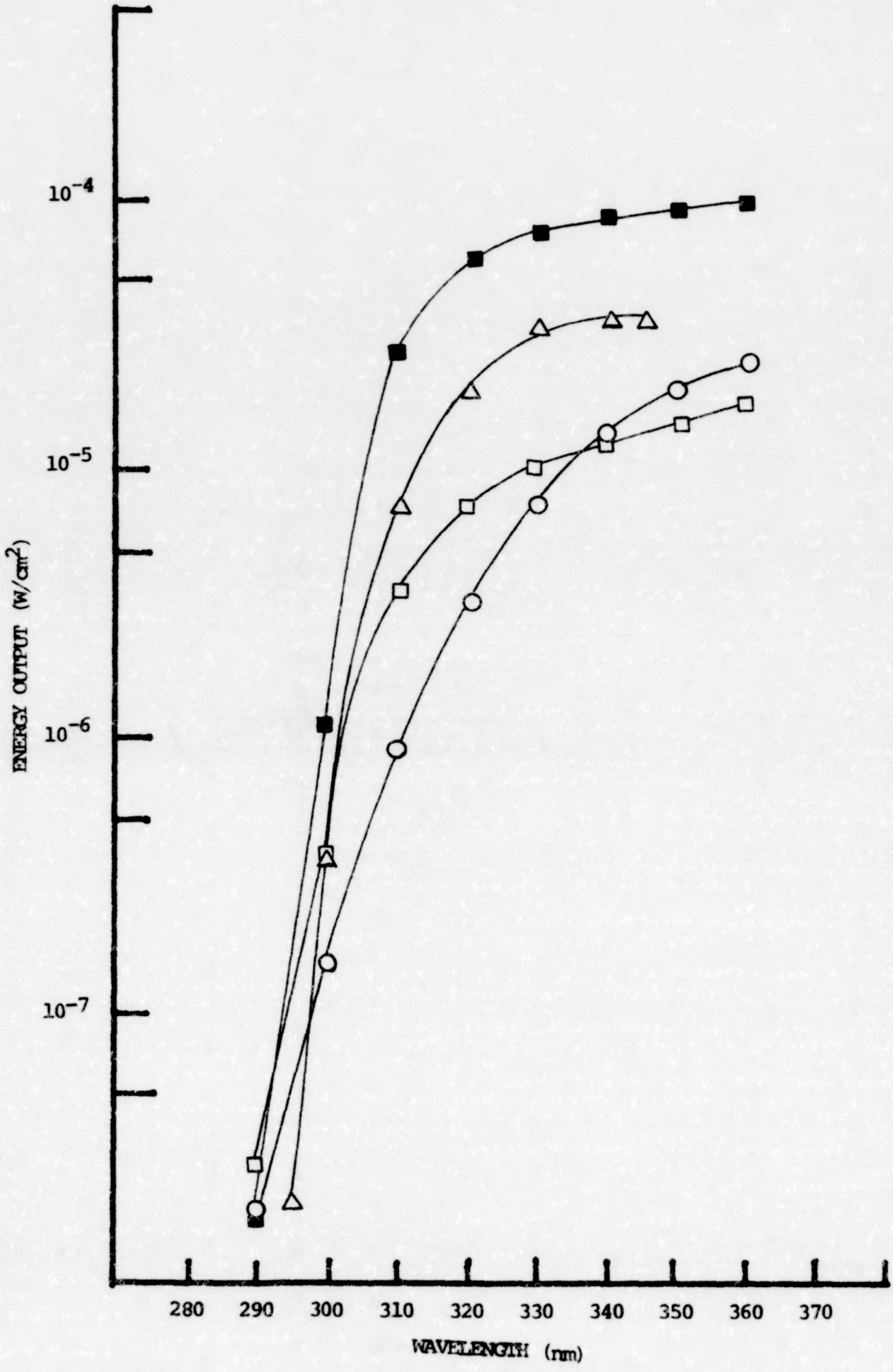

10^{-4}
10^{-5}
10^{-6}
10^{-7}
ENERGY OUTPUT (W/cm^2)
280
290
300
310
320
330
340
350
360
370
WAVELENGTH (nm)

Figure 6. Composite of survival curves for CV-1 cells irradiated with 254 nm radiation (Δ) and simulated sunlight (O).

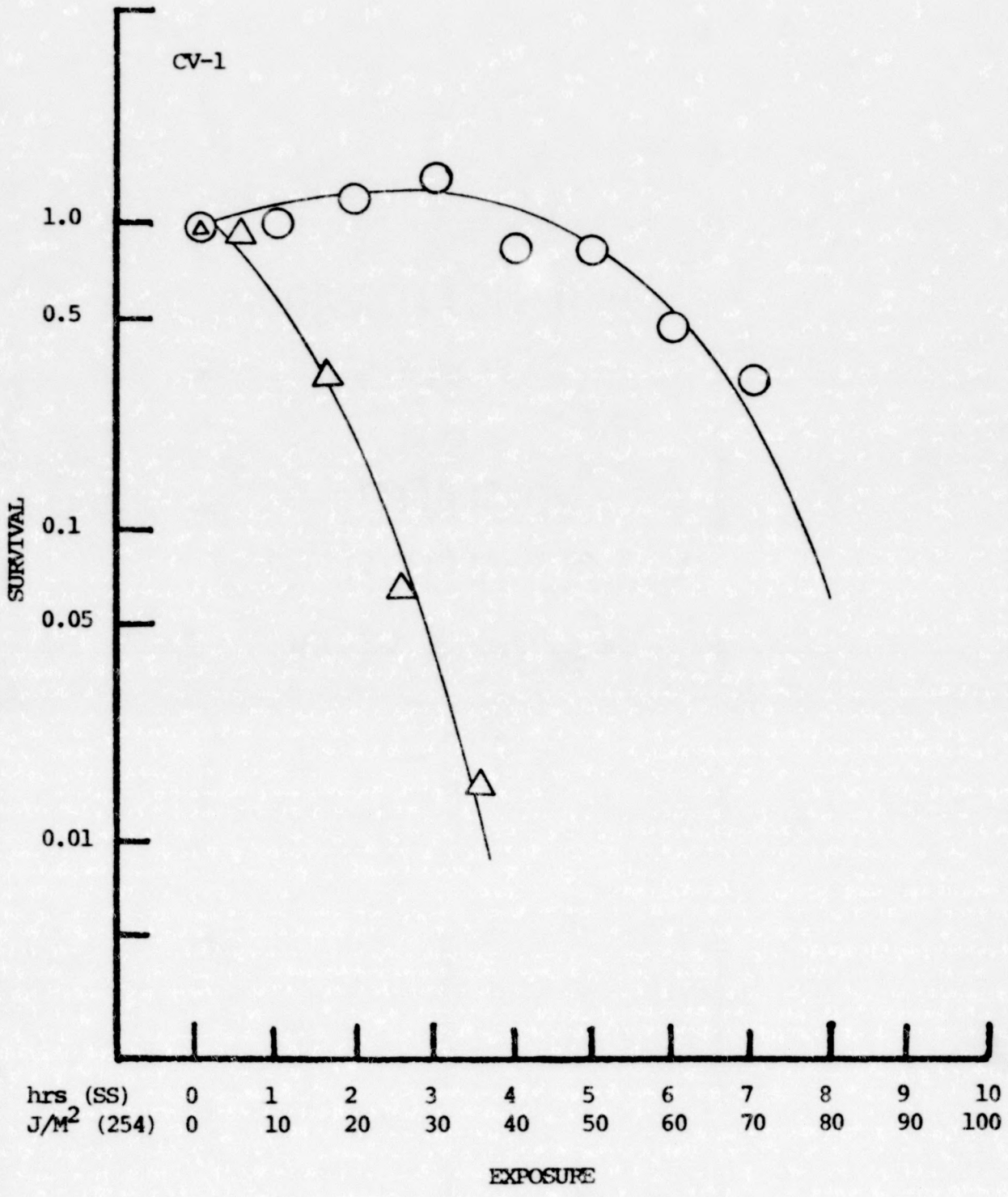

CV-1
1.0
0.5
0.1
0.05
0.01
SURVIVAL
hrs (SS) 0 1 2 3 4 5 6 7 8 9 10
J/M2 (254) 0 10 20 30 40 50 60 70 80 90 100
EXPOSURE

Figure 7. Composite of survival curves for KD cells irradiated with 254 nm radiation (Δ) and simulated sunlight (○).

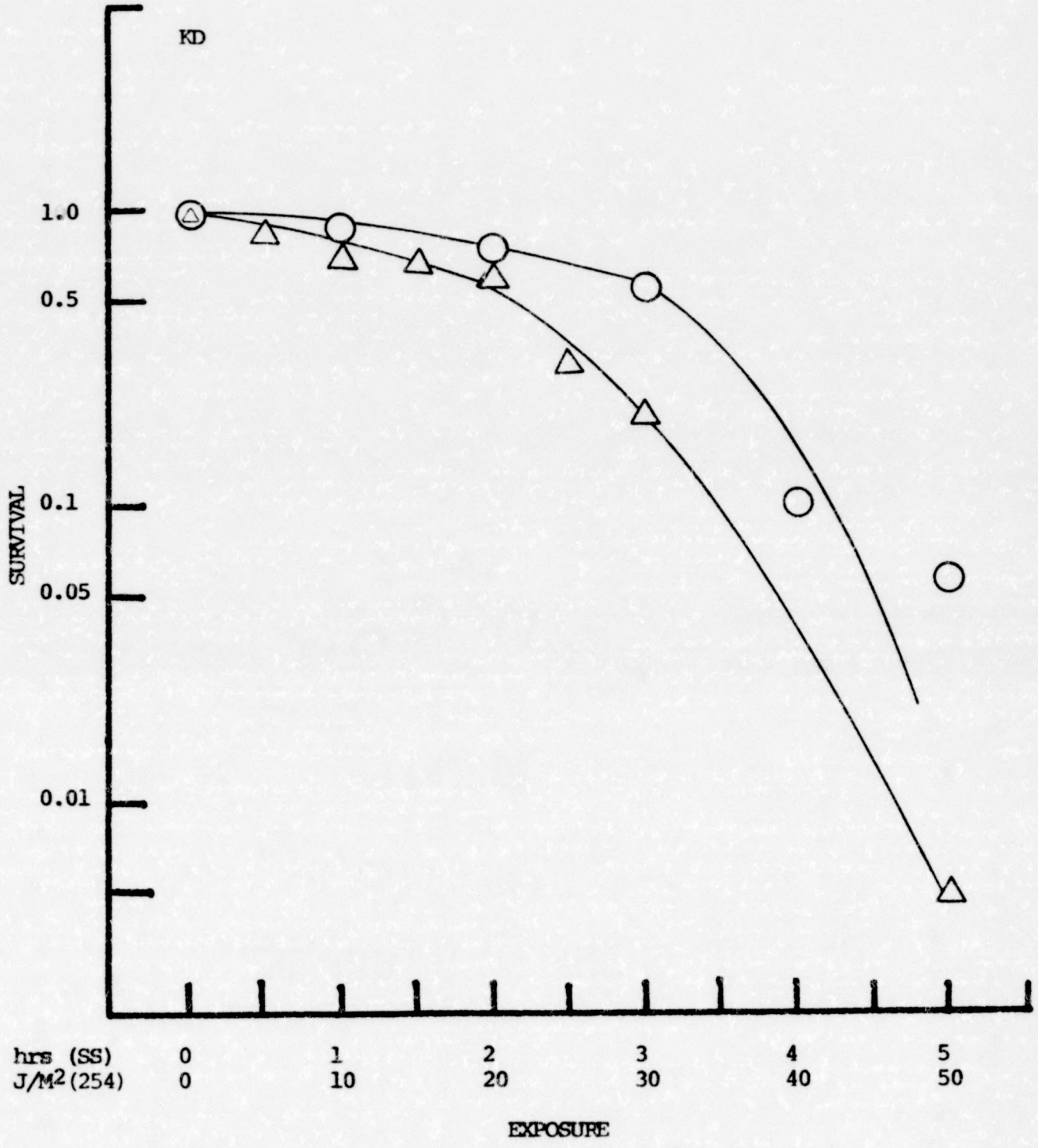

KD
1.0
0.5
0.1
0.05
0.01
SURVIVAL
hrs (SS) 0 1 2 3 4 5
J/M2 (254) 0 10 20 30 40 50
EXPOSURE

Figure 8. Composite of survival curves for BS cells irradiated with 254 nm radiation (△) and simulated sunlight (○).

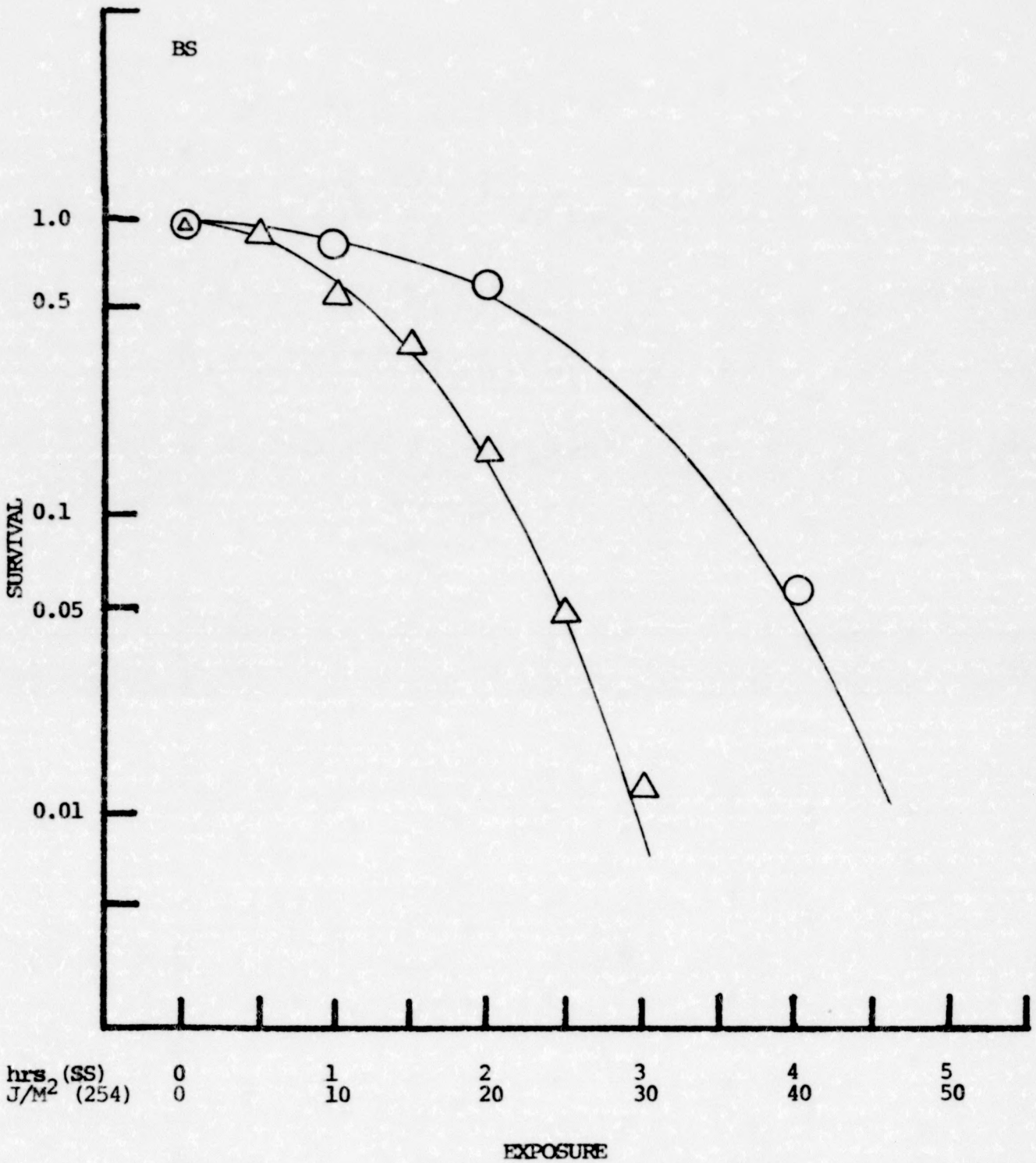

BS
1.0
0.5
0.1
0.05
0.01
SURVIVAL
hrs (SS) 0 1 2 3 4 5
J/M2 (254) 0 10 20 30 40 50
EXPOSURE

Figure 9. Composite of survival curves for XP1PW cells irradiated with 254 nm radiation (Δ) and simulated sunlight (O).

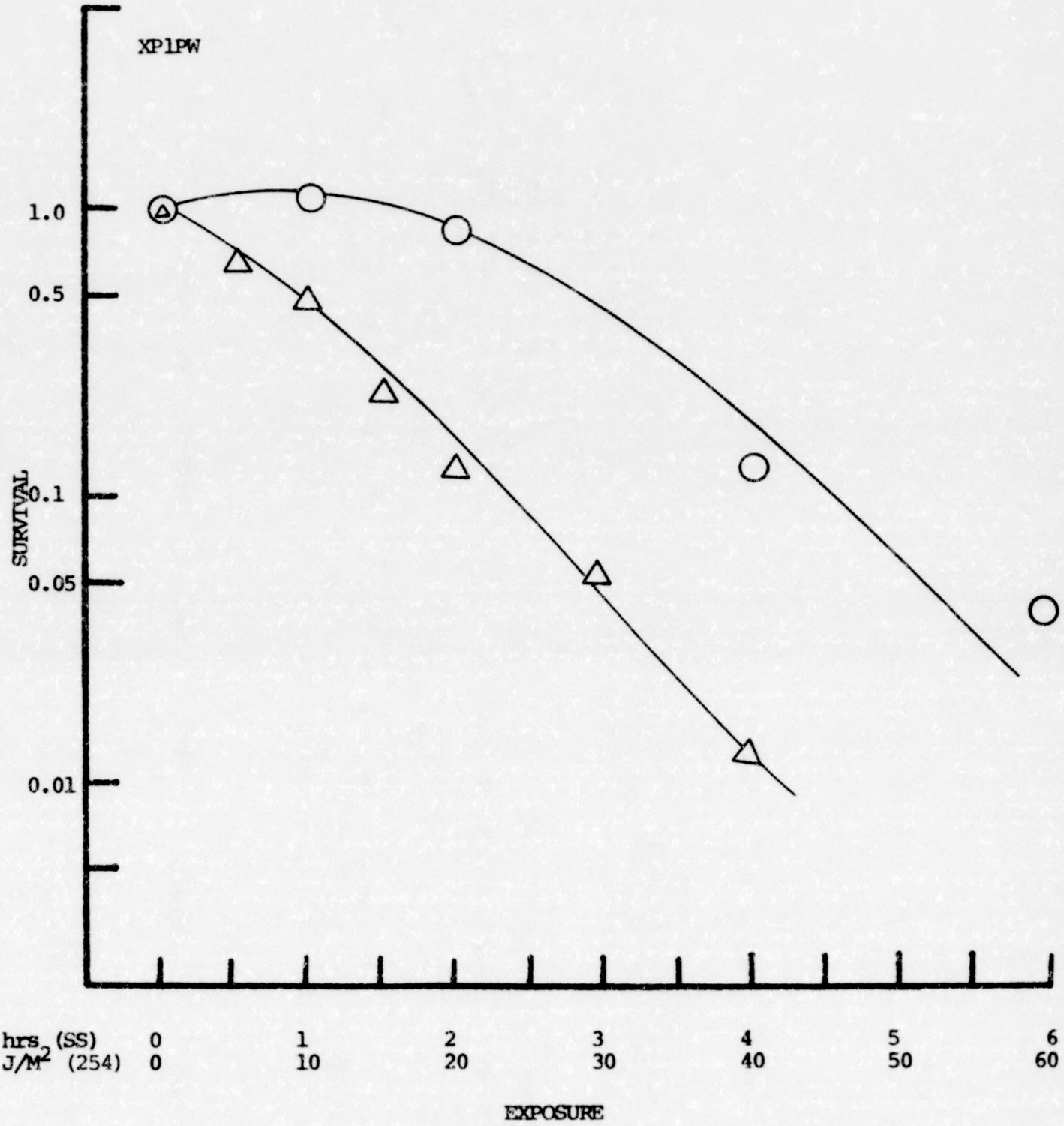

XP1PW
1.0
0.5
0.1
0.05
0.01
SURVIVAL
hrs (SS) 0 1 2 3 4 5 6
J/M2 (254) 0 10 20 30 40 50 60
EXPOSURE

Figure 10. Composite of survival curves for XP25RO cells irradiated with 254 nm radiation (△) and simulated sunlight (○).

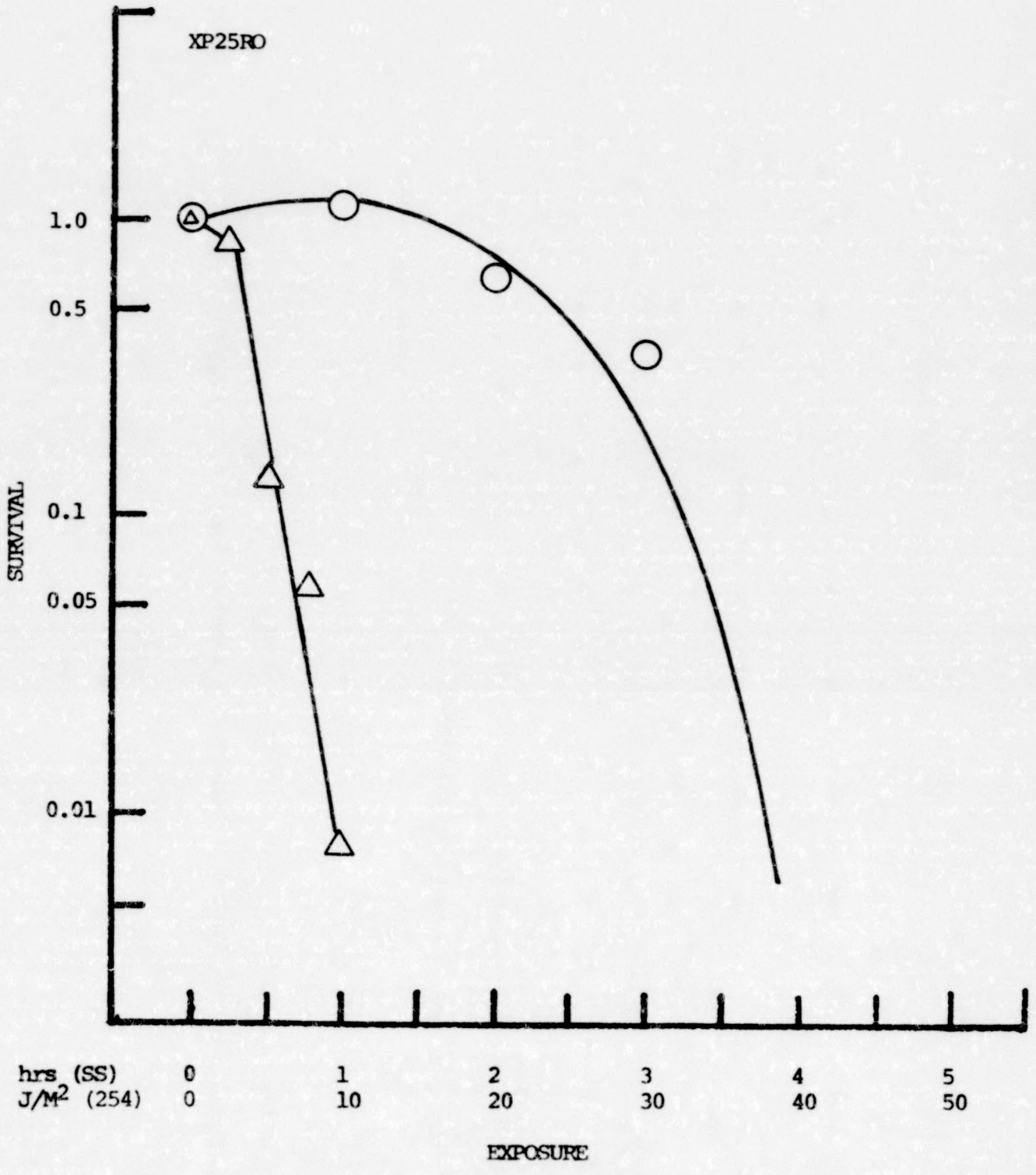

XP25RO
1.0
0.5
0.1
0.05
0.01
SURVIVAL
hrs (SS) 0 1 2 3 4 5
J/M2 (254) 0 10 20 30 40 50
EXPOSURE

TABLE 1

COMPARISON OF 10% SURVIVAL EXPOSURES AT 254 nm AND SIMULATED SUNLIGHT TO GIVE RELATIVE RESPONSE RATIO

CELL LINE	# TRIALS	10% SURVIVAL Germ (J/M^2)	EXPOSURES SS (hrs)	RELATIVE RESPONSE RATIO
CV-1		21	7.0	3.0
		23	8.3	2.8
		22	8.1	2.7
		24	7.6	3.2
		23	6.0	3.8
CV-1 (mean)	5	22.6±1.1	7.2±0.9	3.1±0.4
KD		44	5.0	8.8
		26	3.1	8.3
		31	4.5	6.9
KD (mean)	3	33.7±9.3	4.2±1.0	8.0±1.0
BS		23	3.5	6.6
		18	4.2	4.3
		19	2.8	6.8
BS (mean)	3	20.0±2.6	3.5±0.7	5.9±1.4
XP1PW		28.5	6.1	4.8
		21	3.8	5.5
		22	3.6	6.1
XP1PW (mean)	3	23.8±4.1	4.5±1.4	5.5±0.7
XP25RO		3.4	4.0	0.9
		4.5	2.8	1.6
		7.5	3.1	2.4
XP25RO (mean)	3	5.1±2.1	3.3±0.6	1.6±0.8

DISCUSSION

The results presented here indicate that there is a difference between different cell lines in their relative response to near UV radiation (Table 1). To determine relative response, results from 254 nm irradiation and simulated sunlight irradiation were compared. The data derived from that comparison indicate that the effects of simulated sunlight are different from those caused by 254 nm radiation and that the effects vary from one cell line to another. The difference in relative response between the different cell lines could be due to the formation of different DNA lesions. Keyse, Moss, and Davies (1983) found that both normal and Xeroderma Pigmentosum fibroblast strains exhibit a change in the pattern of lethality when exposed to wavelengths longer than 313 nm. Han and Elkind (1980) showed that there is a difference between the inactivating effects of near UV and 254 nm radiation. Elkind, Han, and Chang-Liu (1978) and Elkind and Han (1978) found that in no case does the sunlight survival curves have the same shape as the far UV survival curves. They conclude that the photolesions caused by these different radiations are at most only partly the same. Smith and Paterson (1981, 1982) suggest that cell killing due to 365 nm radiation is mainly due to non-dimer damage. Results by Zelle, et al. (1980) indicate that lesions other than pyrimidine dimers are

produced by near UV radiation. Erickson, Bradley, and Kohn (1980) suggest that there may be several types of lesions formed in the DNA of cells irradiated with wavelengths greater than 295 nm and are produced by several different mechanisms.

Another factor that could have an effect is repair of DNA damage. Harm (1980) indicates that sunlight greater than 375 nm causes photo-repairable lesions which are fully repairable by the same light. Thus cell inactivation resulting from these solar wavelengths must be due to non-repairable damage. Parsons and Goss (1980) found that repair of solar radiation damage differs considerably from 254 nm UV repair.

The survival curves for simulated sunlight presented in figures 6-10 show a large shoulder, which was also found in work done by Danpure and Tyrrell (1976). They also found that only near UV lethality is strongly oxygen dependent. These findings would indicate a difference in the effects caused by near and far UV radiation.

The results presented here are different from those by Hsie, Li, and Machanoff (1977), who found that survival curves generated by exposure of cells to both sunlamp and sunlight were similar to those obtained by the use of a standard far UV lamp. Also different are the studies by Kantor and Setlow (1982) which suggest that the mechanisms for inactivation of non-dividing human cells by sunlamp radiation are the same as those by 254 nm radiation.

The reason for these differences between the relative

responses of the different cell lines is probably due to damage other than the formation of pyrimidine dimers, which differs from one cell line to another. Smith and Paterson (1981) showed that lethality due to radiation at 254 nm and 310 nm was mainly due to pyrimidine dimer production, but at 365 nm lethality was due to non-dimer damage. Erickson, Bradley, and Kohn (1980) have shown that at wavelengths greater than 295 nm many DNA single-strand breaks occur; they suggest that these breaks may play a role in the lethality of cells exposed to near UV. Keyse, Moss, and Davies (1983) suggest that DNA absorption may not be solely responsible for the induction of damage in cells by near UV radiation. Other components of the affected cells such as proteins, amino acids, etc. may form toxic photoproducts when hit by near UV radiation and thus cause cell death. The complete process of near UV lethality remains to be identified.

The results presented here show differences in the relative response of the cell lines to simulated sunlight, indicating that there are different types of damage occurring in the cell lines. The presence of these different types of damage indicates that the effects caused by 254 nm radiation are not necessarily the same as those caused by wavelengths above 300 nm.

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