FINAL

Report on Carcinogens
Background Document for

Broad-Spectrum Ultraviolet (UV) Radiation and UVA, and UVB, and UVC

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Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

U.S. Department of Health and Human Services
National Toxicology Program

Known to be Human Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated to be Human Carcinogens:

There is limited evidence of carcinogenicity from studies in humans which indicates that causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded; or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species, or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a *known to be human carcinogen, or reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Summary Statement

Broad-Spectrum Ultraviolet (UV) Radiation and UVA, and UVB, and UVC

Carcinogenicity

Broad-spectrum ultraviolet radiation (UVR) is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans. Epidemiology studies clearly demonstrate that exposure to broad spectrum UVR increases both melanocytic and non-melanocytic skin cancer. Studies of humans exposed to solar radiation, artificial devices emitting broad-spectrum UVR, and devices emitting predominantly ultraviolet A radiation (UVA) or ultraviolet B radiation (UVB) all contribute to this conclusion. Exposure to solar radiation is associated with an increased risk of malignant melanoma of the skin, non-melanoma skin cancer, malignant melanoma of the eye, and cancer of the lip (IARC 1992, NTP 2000). Evidence for the role of the UVR component of solar radiation in carcinogenicity comes from studies of human cancers associated with exposure to artificial UVR-emitting devices, tumor site-concordance between humans exposed to sunlight and animals exposed to UVR from artificial sources and human mechanistic studies using artificial sources of UVR. Exposure to sunlamps or sunbeds has been associated with malignant melanoma of the skin (Autier *et al*. 1994, Swerdlow *et al*. 1988, Walter *et al.* 1990, 1999, Westerdahl *et al*. 1994, 2000, Chen *et al.* 1998). Mechanistic studies using human tissue demonstrate that UVR is absorbed by DNA and causes direct and indirect DNA damage with mutagenic potential. Mutations found in the p53 tumor suppressor gene of human skin cancer are specific for UVR-induced damage (see below).

The findings in humans are supported by evidence in experimental animals. Exposure to broad spectrum UVR induced skin tumors (papilloma and squamous cell carcinoma) and eye tumors (spindle cell sarcoma) in albino rats and skin tumors (fibrosarcoma and/or squamous cell carcinoma) in mice, hamsters and opossum.

The epidemiological literature does not provide a basis for subdividing the effects of sunlight or artificial UVR into components attributable specifically to UVA, UVB, or ultraviolet C radiation (UVC). However, information regarding the specific effects of UVA, UVB, and UVC can be inferred from the results of human epidemiology studies of mixed UVR exposure together with the results of studies on the effects of specific UVR components in experimental animals and human tissues.

UVA is *reasonably anticipated to be a human carcinogen* based on limited evidence from studies in humans and evidence from studies in experimental animals. Studies in which UVA has contributed substantially to human exposure (solar radiation and UVA emitting sunbeds) have demonstrated an excess of skin cancer. Westerdahl *et al.* (2000) reported an association of melanoma with exposure to sunbeds when the majority of the exposure was considered to be from sunbeds emitting mainly UVA (source reported to emit 0.1% to 2.1% UVB). The finding in humans is supported by evidence in experimental animals. UVA exposure induced skin tumors in mice (squamous cell carcinoma and papilloma) and fish (melanoma).

UVB is *reasonably anticipated to be a human carcinogen* based on limited evidence from studies in humans and evidence from studies in experimental animals. Mechanistic studies in humans have demonstrated that the UVB component in solar radiation is responsible for the mutagenic photoproducts that lead to the signature p53 mutations observed in human skin cancer. However, epidemiologic studies are limited by lack of information identifying exposure wavelength specificity. Although exposure to UVB, as a component of solar radiation or from sunlamps used before the early 1970s, is clearly associated with excess skin cancer, these human exposures are not solely to UVB but are confounded by exposures to other components of the UVR spectrum. In one study, exposure to sunlamps used in the early 1970s, which produced significant amounts of UVB (22% to 40%), was associated with cutaneous malignant melanoma (CMM) (Chen *et al*. 1998). The finding in humans is supported by evidence in experimental animals. Prolonged exposure to devices emitting primarily UVB caused the development of skin tumors in rats (papilloma), mice (squamous cell carcinoma, fibrosarcoma, papilloma, keratoacanthoma), guinea pigs (fibroma and trichofolliculoma), and opossums (melanocytic hyperplasia and melanoma).

UVC is *reasonably anticipated to be a human carcinogen* based on limited evidence from human mechanistic studies and evidence from studies in experimental animals. Studies of human tissue have demonstrated that both *in vivo* and *in vitro* exposure to UVC causes DNA damage. UVC is absorbed by DNA and induces mutagenic photoproducts similar to the types of damage caused by UVB. However, there are no epidemiologic studies adequate for evaluation of UVC carcinogenicity in humans. UVC is absorbed by the ozone layer and does not contribute to solar exposure, and studies using artificial devices emitting UVC are not specific for UVC radiation. Exposure of experimental animals to high doses of radiation from devices emitting primarily UVC caused skin tumors in rats (keratoacanthoma-like skin tumors) and mice (squamous cell carcinoma and fibrosarcoma).

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

Broad-spectrum UVR causes skin cancers via mechanisms that include DNA damage, immunosuppression, tumor promotion, and mutations in the p53 tumor suppressor gene. Broad-spectrum UVR induces mutations in cultured human cells, the type of damage depends upon the specific wavelength applied and the competence of an affected cell to repair the damage without error. DNA is a major cellular chromophore absorbing UVR (mainly UVB and UVC) and responds to irradiation by yielding free radical reactive intermediates and various photoproducts with mutagenic potential. UVB photons cause the following four major DNA base modifications in humans: (i) cyclobutane-type pyrimidine dimers, (ii) (6-4) photoproducts, (iii) the corresponding Dewar isomers, and (iv) thymine glycols. Both UVA and UVB induced 8- hydroxydeoxyguanosine produced from guanosine by the action of singlet oxygen.

UVA, UVB, and UVC as individual components of UVR are genotoxic in prokaryotes, lower eukaryotes, non-human mammalian cells, and human cells. Moreover, *in vivo* exposure from all three components of UVR results in DNA damage in humans. UVA's

biological effects are indirect and largely the result of energy transferred through active oxygen intermediates, whereas UVB and UVC photons are absorbed by DNA and direct damage occurs through DNA base modifications. Based on the number of positive genotoxic studies, UVC is the most potent and UVA is the least potent genotoxin of the components of broad spectrum UVR

More than 90% of human squamous-cell carcinomas contain mutations of the p53 tumor suppressor gene. These mutations were found in 74% of sun-exposed normal human skin, compared with 5% of unexposed skin, indicating a strong association with sun exposure. Observed p53 gene mutations were most frequently C to T or CC to TT transitions at pyrimidine-pyrimidine sequences. These specific 53 mutations are now considered a signature of UVR carcinogenesis.

Exposure to solar radiation and UVR has been found to alter immune function in humans and experimental animals. Evidence that immunosuppression is related to skin cancer incidence comes from the following observations that: (i) immunosuppressed organ transplant recipients showed a marked increase in skin cancer, particularly squamous-cell carcinoma, (ii) UVR decreased the ability to mount a delayed type hypersensitivity response, and (iii) mice exposed to low levels of UVR failed to reject highly immunogenic tumor cell lines.

Human skin grafts on mice also yielded human skin tumors (squamous cell carcinomas, actinic keratoses, melanocytic hyperplasia and melanoma) following irradiation with UVB after pretreatment with the carcinogen dimethylbenz(*a*)anthracene. Precancerous lesions (melanocytic hyperplasia) were found in human skin grafts on mice treated with UVB alone.

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1 Introduction

Ultraviolet radiation (UVR) was nominated for listing in the Report on Carcinogens by Dr. Hiroshi Yamasaki, of the International Agency for Research on Cancer (IARC), on the basis of the IARC's classification of UVR as *carcinogenic to humans* (Group 1) (IARC 1992). In 1997, the National Toxicology Program (NTP) reviewed the effects of solar radiation, which includes most of the electromagnetic spectrum, and exposure to sunlamps and sunbeds, which provide exposure to radiation primarily in the ultraviolet A (UVA) and ultraviolet B (UVB) portions of the spectrum (NTP 1997). The NTP recommended that solar radiation and exposure to sunlamps and sunbeds be listed in the Ninth Report on Carcinogens (RoC), where they are listed as *known to be human carcinogens,* based on studies in humans that (1) clearly indicate a causal relationship between exposure to solar radiation and cutaneous malignant melanoma and nonmelanocytic skin cancer and (2) have shown that exposure to sunlamps or sunbeds is associated with cutaneous malignant melanoma (NTP 2000). Malignant melanoma of the eye also is associated with use of sunlamps. In contrast, there is little support for association of exposure to sunlamps or sunbeds with nonmelanocytic skin cancer (IARC 1992). The 1997 NTP review recommended that broad-spectrum UVR, including UVA, UVB, and ultraviolet C (UVC), be reviewed for possible separate listings in the Tenth RoC.

The sun is the major source of UVR. UVR is a small portion of the solar spectrum outside the visible range. The bandwidths within the optical radiation spectrum are listed in Table 1-1.

Table 1-1 Optical radiation spectrum

Region	Wavelength range
UV	100 to 400 nm
UVC[a]	100 to 280 nm
UVB[a]	280 to 315 nm
UVA[a]	315 to 400 nm
Visible	400 to 780 nm
Infrared (IR)	780 nm to 1 mm
IRA	780 nm to 1.4 μm
IRB	1.4 to 3.0 μm
IRC	3.0 μm to 1 mm

Source: Adapted from ACGIH 1996
[a]Photobiological designations of the *Commission Internationale de l'Eclairage* (International Commission on Illumination), cited in IARC 1992.

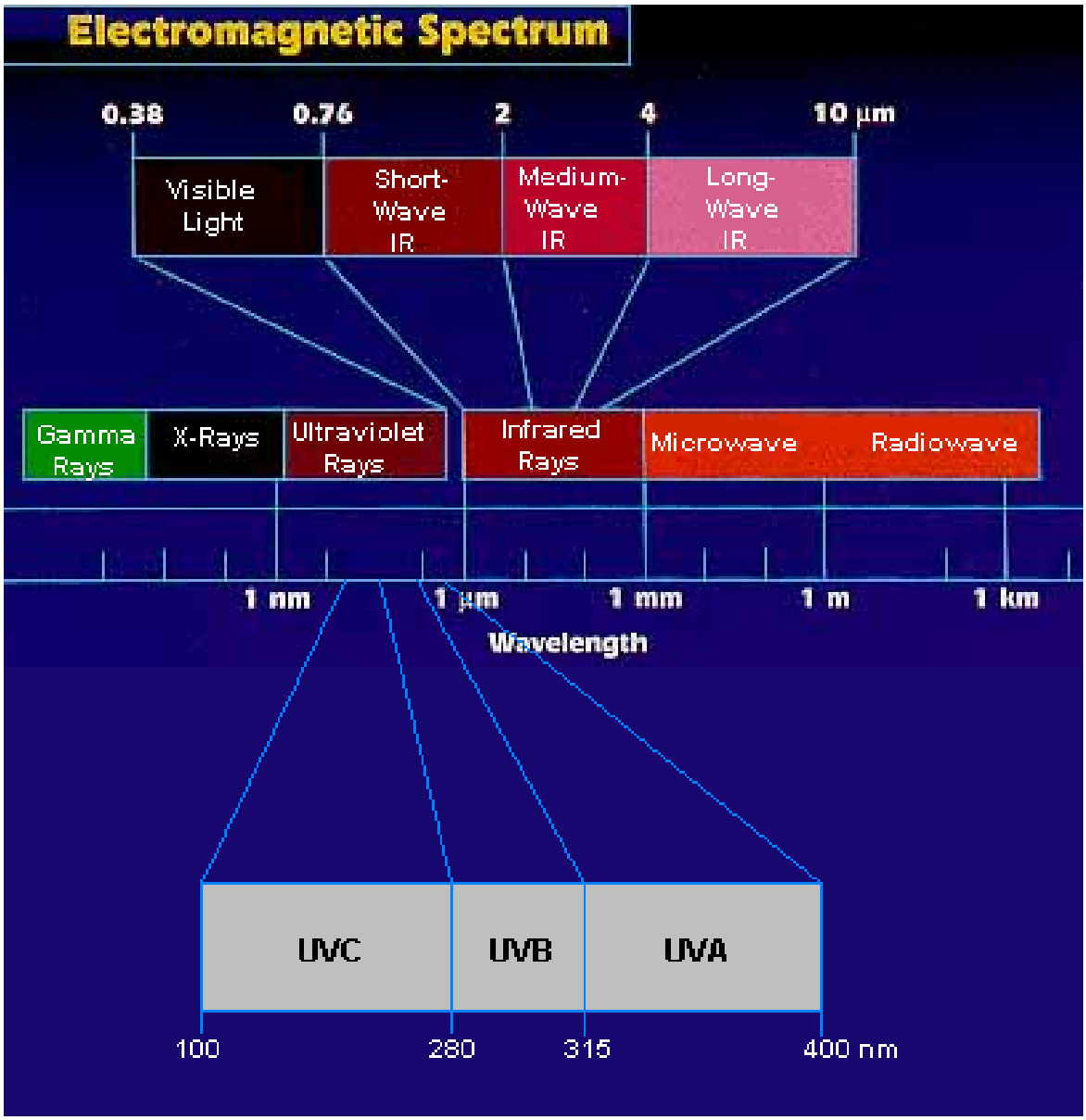
Various conventions are used to classify the optical radiation spectrum into separate bands (e.g., on the basis of transmission and absorption properties). These spectral-band categories are used to identify approximate wavelengths; they do not designate fine dividing lines below which an effect is present and above which it does not occur.

1.1 Identification of UVR by type

UVR contains wavelengths from 100 to 400 nm and is classified as follows: UVA, 315 to 400 nm; UVB, 280 to 315 nm; and UVC, 100 to 280 nm. This nomenclature is not always rigorously followed, as different researchers use slight variations in these ranges. The relative position of UVR in the electromagnetic spectrum is shown in Figure 1-1.

1.2 Physical properties

The atmosphere does not absorb UVA, which is the most abundant of the three UVR bands and accounts for 95% of the UV energy reaching the earth's surface at the equator. UVB normally is absorbed by the ozone layer; it constitutes 5% of solar UVR and is the most biologically critical part of solar UVR (Farmer and Naylor 1996, cited in NTP 2000). Naturally occurring UVC, the shortest UV wavelength produced by the sun, is the type of UVR most harmful to the genome; however, it is totally absorbed by the earth's atmosphere (Daya-Grosjean *et al.* 1995, cited in NTP 2000).



Adapted from NASA 2000

Figure 1-1. Electromagnetic spectrum

1.3 Photochemical and photobiological activities

Photochemical and photobiological interactions occur when a photon reacts with a molecule of matter, producing either a photochemically altered species or two dissociated molecules (Phillips 1983, Smith 1989, both cited in IARC 1992). For this reaction to be effective, the amount of photon energy must be sufficient to alter molecular bonds. Photon energy typically is expressed in electronvolts (the photon energy of light of wavelength 300 nm = 4.1 eV) (WHO 1979, cited in IARC 1992). The number of altered molecules produced relative to the number of absorbed photons is referred to as

"quantum yield" (Phillips 1983, cited in IARC 1992). The efficiency of a photochemical interaction per incident quantum and the photobiological effects per unit radiant exposure vary widely with wavelength (Jagger 1985, cited in IARC 1992).

2 Human Exposure

2.1 Use

UVR has many uses as a natural source of energy and is important in various biological processes. Artificial sources of UVR are used for tanning, medical diagnosis and treatment, and promoting polymerization reactions. Exposure to UVR usually is expressed as a dose rate in watts per square meter (the power striking a unit surface area of an irradiated object). The commonly used unit of effective dose is the minimal erythema dose (MED), which is defined as the lowest radiant exposure to UVR sufficient to produce erythema of the skin with sharp margins within 24 hours of exposure. Though imprecise, MEDs are useful, because they are related to the biological consequences of the exposure (IARC 1992).

2.1.1 Cosmetic use

Tanning beds use artificial light to allow individuals to develop "suntan" for cosmetic reasons. Originally, tanning beds were built with mercury arc lamps, which emitted large quantities of UVB and UVC. Now, sunbeds and solaria emit mostly UVA (IARC 1992). Table 2-5 summarizes the characteristics of various light sources used for tanning.

Lamp	Radiation emission (%)			Contribution to tanning (%)		
	UVA	UVB	UVC	UVA	UVB	UVC
Mercury arc sunlamp	40	40	20	0	35	65
Simulated sunlight lamp	95	5	0	20	80	0
Type I UVA lamp	99	1	0	60	40	0
Type II UVA lamp	> 99.9	< 0.1	0	> 90	< 10	0
Optically filtered high-pressure lamp	100	0	0	100	0	0
Summer UV sunlight	95	5	0	20	80	0

Source: IARC 1992

2.1.2 Medical and dental applications

UVR has both diagnostic and therapeutic uses in medicine and dentistry. More than 30 disorders can now be treated through UVA exposure with psoralens (PUVA). Psoriasis and eczema are the skin diseases most frequently treated with PUVA therapy. PUVA can also be used with UVB exposure to treat psoriasis patients who are not good candidates for systemic therapy with methotrexate or etretinate (Morison 1992). UVR (most commonly UVB) and coal-tar creams also are used to treat psoriasis (FDA 1996). In addition, UVB is used to convert 7-dehydrocholesterol (provitamin D3) to vitamin D in the skin of vitamin D–deficient patients.

UVA has been used to treat neonatal jaundice or hyperbilirubinemia. Although treatment usually involves irradiating the infant with visible light for several hours a day, for up to one week, one commercial neonatal phototherapy unit was found also to emit UVA and radiation at wavelengths down to 265 nm (in the UVC range) (IARC 1992). UVA has been found to alter the molecular structure of melatonin, a hormone that helps regulate

sleep-wake cycles, to unidentified photoproducts; moderate phototoxicity of melatonin has been predicted (Kim *et al.* 1999). UVR also has been used to detect various dental disorders, such as early dental caries, dental plaque, and calculus (IARC 1992).

2.1.3 Industrial applications

UVR has many industrial applications. One of the major industrial uses involves photopolymerization, which includes curing of protective coatings and inks. UVR also is used to simulate weathering of various materials, such as polymers. It is used to sterilize and disinfect, usually in the range of 260 to 265 nm (UVC). Other uses include UV photography and use of UV lasers. UVR is a byproduct of electric-arc welding (IARC 1992).

2.2 Production

In the broadest sense, UVR is formed when a body is heated (through incandescence) or when electrons that have been raised to an excited state return to a lower energy level. UVR is naturally emitted from the sun. Around two-thirds of the energy emitted by the sun penetrates the atmosphere. UVR comprises approximately 5% of the solar radiation that reaches the earth's surface. Artificial sources of UVR include tungsten/halogen, gas discharge, arc, fluorescent, metal halide, and electrodeless lamps (IARC 1992).

2.3 Analysis

UVR can be measured with chemical or physical detectors, often in conjunction with a monochromator or band-pass filter for wavelength selection. Chemical detectors include photographic emulsions, actinometric solutions, and UV-sensitive plastic films. Physical detectors include radiometric devices and photoelectric devices (IARC 1992).

2.3.1 Spectroradiometry

Spectroradiometry is generally considered the best way to characterize a source of UVR and is based on measurement of its spectral power distribution (radiated power as a function of wavelength). Spectral measurements are used to calculate biologically weighted radiometric quantities. A spectroradiometer consists of three parts. (1) Input optics collect the incident radiation and conduct it to (2) the entrance slit of a monochromator, which disperses the radiation with one or two dispersion devices (diffraction grating or prism). The monochromator then guides the radiation to the exit slit by way of mirrors, where it enters (3) the radiation detector, normally a photodiode, or a photomultiplier tube for higher sensitivity. The accuracy of UVR measurements is affected by various parameters, including wavelength calibration, bandwidth, stray radiation, polarization, angular dependence, linearity, and calibration sources. Double monochromators are used to provide accurate UVR readings.

2.3.2 Wavelength-independent (thermal) detectors

Thermal detectors usually are used to measure the total radiant power of a source, rather than just the UV component. Thermal detectors operate on the principle that UVR absorbed by a receiving element will cause a temperature rise in the element. This rise is measured, usually with a thermopile or pyroelectric detector. Thermopiles must have a window made of fused silica for measuring UVR at wavelengths as low as 250 nm.

Pyroelectric detectors rely on voltage generated by temperature changes in a lithium tantalate crystal.

2.3.3 Wavelength-dependent detectors

The accuracy of wavelength-dependent detectors varies depending upon the types of detectors and filters used. The most common is the Robertson-Berger meter, which incorporates optical filters, a phosphor, and a vacuum phototube or photovoltaic cell. The meter measures wavelengths < 330 nm in the global spectrum. The spectral response rises sharply with decreasing wavelength.

Detectors incorporating a photodiode or vacuum photocell in conjunction with optical filters and suitable input optics (such as a quartz hemispherical detector) have been used to match a number of different action spectra. The American Conference of Governmental Industrial Hygienists (ACGIH) uses one of these detectors, the International Light Model 730 UV Radiometer, to evaluate the health hazards of exposure to UVR.

A complementary approach to evaluating UVR is the use of photosensitive films. By relating the degree of deterioration of the films, usually measured as changes in their optical properties, the user can determine the dose of incident UVR. The most widely used photosensitive film is polymer polysulfone.

It is difficult to achieve a prescribed UVR spectral dose with wavelength-dependent detectors. Accurate results require detectors that are calibrated against the appropriate source spectrum with a spectroradiometer. If this is not done, dosimetric errors will arise. Measuring UVB radiation also is difficult, as only 0.3% of the sun's total radiant energy is UVB.

2.4 Environmental occurrence

Solar radiation is scattered by various components of the atmosphere, and about two-thirds of it penetrates to the earth's surface. UVC exists in the extraterrestrial solar spectrum, but is completely filtered out by the ozone layer. Most UVB is absorbed by ozone in the stratosphere, and only a small fraction (around 5%) of the total radiation penetrating to the earth's surface is UVB (IARC 1992).

2.5 Environmental exposure

2.5.1 Solar UVR

Information on global UVR levels has been compiled from data gathered for epidemiological studies of skin cancer and other health effects, such as premature aging of the skin, cataracts, and suppression of the immune response. Despite the large number of measurements, estimating human exposure is complex. UVR spectral irradiance varies considerably with latitude, altitude, time of day, and season. People also vary in their length of outdoor exposure and parts of the body exposed. In addition, individual exposure geometry complicates efforts to estimate human exposure. Although UVR levels were estimated for many studies, few were able to differentiate among UVA, UVB, and UVC (IARC 1992).

2.5.1.1 UVA

Various factors influence terrestrial levels of UVA. UVA levels decrease with increasing distance from the equator and increase with increasing altitude (decreasing with distance below sea level). Terrestrial UVA levels also are decreased by stratospheric ozone, which varies with latitude and season. When there is less ozone, more UVA will reach the earth's surface. Time of day also influences daily UVA levels (IARC 1992). Table 2-1 shows the proportion of UVA radiation received during two periods on a summer day at three latitudes (altitude not specified).

Table 2-1. Percentage of daily UVA radiation received during two periods on a clear summer day

Latitude (°N)	UVA (% of daily total)	
	11:00 AM – 1:00 PM	9:00 AM – 3:00 PM
20	27	73
40	25	68
60	21	60

Source: IARC 1992

Clouds reduce the amount of UVA reaching ground level. Air pollution, including tropospheric ozone, can decrease UVA exposure, especially in urban areas (IARC 1992). Surface reflection also contributes to personal exposures to UVA.

2.5.1.2 UVB

Terrestrial UVB levels are affected by the same factors that influence terrestrial UVA levels. However, because UVB is absorbed more by stratospheric ozone than is UVA, differences in latitude and altitude affect UVB exposure more than UVA exposure. Seasonal changes affect UVB levels, mostly in temperate regions. Table 2-2 gives UVB exposure levels for various latitudes and seasons (altitude not specified).

Table 2-2. Typical values for ambient daily and annual UVB radiation expressed as minimal erythema dose

Latitude (°N)	Diurnal UVB (MED)			
	Winter	Spring/Autumn	Summer	Annual
20, Hawaii	14	20	25	6,000
30, Florida	5	12	15	4,000
40, New Jersey	2	7	12	2,500
50, Washington	0.4	3	10	1,500

Source: IARC 1992

Time of day at a given latitude also affects UVB levels, as shown in Table 2-3 (altitude not specified).

Table 2-3. Percentage of daily UVB radiation received during two periods on a clear summer day

Latitude (°N)	UVB (% of daily total)	
	11:00 AM – 1:00 PM	9:00 AM – 3:00 PM
20	30	78
40	28	75
60	26	69

Source: IARC 1992

Variation in stratospheric ozone with latitude and season affects UVB levels. Air pollution decreases UVB exposure, and clouds also affect UVB levels. Generally, cloud cover scatters less than 10% of the UVB under a clear sky. However, very heavy cloud cover virtually eliminates UVB, even in the summer. Surface reflection contributes to human UVB exposure. Exposure due to reflection is important, as body parts normally shaded are exposed to reflected radiation (IARC 1992). Table 2-4 summarizes reflectance for various types of terrain.

Table 2-4. Representative terrain reflectance factors for horizontal surfaces measured with a UVB radiometer at 12:00 PM at various U.S. locations

Material	Reflectance (%)
Lawn grass, summer, Maryland, California, and Utah	2.0–3.7
Lawn grass, winter, Maryland	3.0–5.0
Wild grasslands, Vail Mountain, Colorado	0.8–1.6
Lawn grass, Vail, Colorado	1.0–1.6
Flower garden, pansies	1.6
Soil, clay and humus	4.0–6.0
Sidewalk, light concrete	10–12
Sidewalk, aged concrete	7.0–8.2
Asphalt roadway, freshly laid (black)	4.0–5.0
Asphalt roadway, two years old (gray)	5.0–8.9
House paint, white, metal oxide	22
Boat dock, weathered wood	6.4
Aluminum, dull, weathered	13
Boat deck, wood, urethane coating	6.6
Boat deck, white fiberglass	9.1
Boat canvas, weathered, plasticized	6.1
Chesapeake bay, Maryland, open water	3.3
Atlantic Ocean, New Jersey coastline	8.0
Sea surf, white foam	25–30
Atlantic beach sand, wet barely submerged	7.1
Atlantic beach sand, dry, light	15–18
Snow, fresh	88
Snow, two days old	50

Source: IARC 1992

2.5.1.3 UVC

No data on environmental exposure to UVC were found in the published literature.

2.5.2 Artificial sources

Six artificial sources of UVR have been identified. (1) Incandescent sources provide optical radiation that appears as a continuous spectrum. A "color temperature" usually describes incandescent sources. UVR emission occurs when the color temperature exceeds 2,500°K (2,227°C). (2) Gas discharge lamps produce optical radiation by passing an electrical current through a gas. The type of gas present in the lamp determines emission wavelengths. At low pressures, fine lines are produced, while higher pressures create broad bands. Low-pressure discharge lamps filled with mercury, argon, xenon, krypton, or neon are used to create specific bands for spectral calibrations. (3) Arc lamps are intense sources of UVR. They are operated under extreme pressures and have color

temperatures of 6,000°K (5,727°C). Arc lamps often are used to simulate solar radiation. (4) Fluorescent lamps create radiation from a low-pressure mercury discharge, which produces a strong emission at 254 nm. This in turn excites the phosphor-coated lamp to produce fluorescence. Various emission spectra can be obtained by alteration of the composition and thickness of the phosphor and the glass envelope. (5) Metal halide lamps add metal to a mercury discharge lamp, allowing for lines in addition to the mercury emission spectrum. (6) Electrodeless lamps use magnetrons to generate microwave energy, which then is absorbed by the discharge tube (IARC 1992).

2.6 Occupational exposure

2.6.1 Solar UVR

Occupational exposure to solar UVR occurs for anyone working outside. For a group of more than 800 outdoor workers in the United States at 40° N latitude, personal annual facial exposure doses were estimated at 30 to 200 MED (Rosenthal ***et al.*** 1991, cited by IARC 1992). This unusually low estimate may be due to the fact that Rosenthal assumed facial exposure to be about 5% to 10% of ambient exposure. Other data suggest that facial exposure is around 30% of ambient exposure. By the latter estimate, the annual facial exposure doses for these outdoor workers would be 80 to 500 MED.

2.6.2 Artificial UVR

Electric arc welders are the largest occupational group with exposure to artificial UVR. It has been estimated that over half a million welders in the United States have been occupationally exposed to UVR. Levels of effective UV irradiance (relative to the action spectrum of the ACGIH) around electric arc welding equipment at 1 m with an arc current of 400 A ranged from 1 to 50 W/m^2, and the unweighted UVA irradiance ranged from 3 to 70 W/m^2, depending upon the type of welding and the metal being welded. Other occupational exposures to artificial UVR are low, ranging from 10 W/m^2 (offices and discotheques) to 20 W/m^2 (sunbed shop with 20 or more tanning appliances). Occupational exposure to artificial UVR depends upon both the source and the protective methods used to decrease exposure. Some artificial UVR sources are self-contained, such as germicidal lamps in some uses, and present no risk to workers. Other occupational uses, such as use of UVR in laboratories, UV photography, and UV lasers, inevitably lead to UVR exposure where short-term and intense exposures may occur (IARC 1992).

2.7 Biological indices of exposure

The common biological indices of exposure to UVR are erythema and photokeratitis. Erythemas, or “sunburns,” are used as a simple indicator of the biological consequences of UVR exposure. One study determined the action spectra for DNA photodamage in different human epidermal layers *in situ*. Overall, the action spectrum for erythema is 280 to 340 nm (UVB and part of UVA) (Young ***et al.*** 1998).

2.8 Regulations

The U.S. Food and Drug Administration (FDA) regulates UVR, establishing safe uses for irradiation in the production, processing, and handling of food. The FDA also sets forth labeling requirements for drugs containing coal tars for use with UVR. The FDA

regulates various devices that emit UVR, such as sunlamps, sunbeds, medical lamps, and purifiers. The Occupational Safety and Health Administration (OSHA) regulates UVR exposure among welders and cutters; regulations cover safety precautions, guidelines, and treatment. Table 2-5 summarizes FDA regulations that affect UVR, and Table 2-6 summarizes OSHA regulations that affect UVR.

Table 2-5. FDA regulations

Regulatory action	Effect of regulation and other comments
21 CFR 101.70ff—SUBPART E—Specific Requirements for Health Claims. Promulgated: 58 FR 2801, 01/06/93. Health claims: dietary lipids and cancer.	Labels on dietary food low in fat may identify one or more of the following risk factors for development of cancer: family history of a specific type of cancer, cigarette smoking, alcohol consumption, overweight and obesity, ultraviolet or ionizing radiation, exposure to cancer-causing chemicals, and dietary factors.
21 CFR 179—PART 179—IRRADIATION IN THE PRODUCTION, PROCESSING AND HANDLING OF FOOD. Promulgated: 42 FR 14635, 03/15/77. U.S. Codes: 21 U.S.C. 321, 342, 343, 348, 373, 374.	Subparts A through C govern the radiation, radiation sources, and packing materials for irradiated foods in the production, processing, and handling of food.
21 CFR 179.39—Ultraviolet radiation for the processing and treatment of food. Promulgated: 61 FR 42383, 08/15/96.	Ultraviolet radiation for the processing and treatment of food may be safely used under the following conditions: (1) The radiation sources consist of ultraviolet emission tubes designed to emit wavelengths within the range of 2200–3000 Δ units with 90% of the emission being the wavelength 2537 Δ units. (2) The ultraviolet radiation is used or intended for use as follows: surface microorganism control for food and food products and the sterilization of potable water used in food production.
21 CFR 358—PART 358—MISCELLANEOUS EXTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE. Promulgated: 55 FR 33255, 08/14/90. U.S. Codes: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371. Labeling of drug products for the control of dandruff, seborrheic dermatitis, or psoriasis.	For labeling of products containing coal tar identified in 358.710(c) for the control of psoriasis, under the heading "Indications," the labeling of the product will state: "Do not use this product with other forms of psoriasis therapy such as ultraviolet radiation or prescription drugs unless directed to do so by a doctor."
21 CFR 872.6010ff.--Miscellaneous Devices. Promulgated: 52 FR 30097, 08/12/87. U.S. Codes: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371. Ultraviolet activator for polymerization.	An ultraviolet activator for polymerization is a device that produces ultraviolet radiation intended to polymerize (set) resinous dental pit and fissure sealants or restorative materials by transmission of light through a rod. It is classified as a Class II product.
21 CFR 878—PART 878—GENERAL AND PLASTIC SURGERY DEVICES. Promulgated: 53 FR 23872, 06/24/88. U.S. Codes: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.	This part sets forth the classification of general and plastic surgery devices intended for human use that are in commercial distribution.

Regulatory action	Effect of regulation and other comments
21 CFR 878.4630—Ultraviolet lamp for dermatologic disorders. Promulgated: 53 FR 23872, 06/24/88. U.S. Codes: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.	An ultraviolet lamp for dermatologic disorders is a device (including a fixture) intended to provide ultraviolet radiation of the body to photoactivate a drug in the treatment of a dermatologic disorder if the labeling of the drug intended for use with the device bears adequate directions for the device's use with that drug. It is classified as a Class II product.
21 CFR 878.4635—Ultraviolet lamp for tanning. Promulgated: 55 FR 48440, 11/20/90. U.S. Codes: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.	An ultraviolet lamp for tanning is a device that is a lamp (including a fixture) intended to provide ultraviolet radiation to tan the skin. This device is classified as a Class I product and therefore is exempt from the premarket notification procedures in subpart E of part 807 of this chapter.
21 CFR 880—PART 880—GENERAL HOSPITAL AND PERSONAL USE DEVICES. Promulgated: 45 FR 69682-69737, 10/21/80. U.S. Codes: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.	This part sets forth the classification of general hospital and personal use devices intended for human use that are in commercial distribution.
21 CFR 880.6500—Medical ultraviolet air purifier. Promulgated: 45 FR 69682-69737, 10/21/80. U.S. Codes: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.	A medical ultraviolet air purifier is a device intended for medical purposes that is used to destroy bacteria in the air by exposure to ultraviolet radiation. This device is classified as a Class II product (performance standards).
21 CFR 880.6710—Medical ultraviolet water purifier. Promulgated: 45 FR 69682-69737, 10/21/80. U.S. Codes: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.	Identification. A medical ultraviolet water purifier is a device intended for medical purposes that is used to destroy bacteria in water by exposure to ultraviolet radiation. This device is classified as a Class II product (performance standards).
21 CFR 1000—PART 1000—GENERAL. Promulgated: 38 FR 28624, 10/15/73. U.S. Codes: 21 U.S.C. 360hh-360ss. Examples of electronic products subject to the Radiation Control for Health and Safety Act of 1968.	Examples of electronic products that may emit ultraviolet radiation are biochemical and medical analyzers, tanning and therapeutic lamps, sanitizing and sterilizing devices, black-light sources, and welding equipment.

Regulatory action	Effect of regulation and other comments
21 CFR 1040—PART 1040—PERFORMANCE STANDARDS FOR LIGHT-EMITTING PRODUCTS. Promulgated: 50 FR 36550, 09/06/85. U.S. Codes: 21 U.S.C. 351, 352, 360, 360e-360j, 371, 381; 42 U.S.C. 263b-263n. Sunlamp products and ultraviolet lamps intended for use in sunlamp products.	Sunlamp products and ultraviolet lamps manufactured on or after May 7, 1980, but before September 8, 1986, are subject to the provisions of this section. Sunlamp product means any electronic product designed to incorporate one or more ultraviolet lamps and intended for irradiation of any part of the living human body, by ultraviolet radiation with wavelengths in air between 200 and 400 nm, to induce skin tanning. Timer systems, control for termination of radiation emission, protective eyewear requirements, and labeling requirements are described. A warning statement with the words "DANGER—Ultraviolet radiation. Follow instructions. Avoid overexposure. As with natural sunlight, overexposure can cause eye and skin injury and allergic reactions. Repeated exposure may cause premature aging of the skin and skin cancer. WEAR PROTECTIVE EYEWEAR; FAILURE TO MAY RESULT IN SEVERE BURNS OR LONG-TERM INJURY TO THE EYES. Medications or cosmetics may increase your sensitivity to the ultraviolet radiation. Consult physician before using sunlamp if you are using medications or have a history of skin problems or believe yourself especially sensitive to sunlight. If you do not tan in the sun, you are unlikely to tan from the use of this product" must be placed on each sunlamp product. Each ultraviolet lamp shall have a label which contains the words "Sunlamp—DANGER—Ultraviolet radiation. Follow instructions."

Source: The regulations in this table have been updated through the 1999 Code of Federal Regulations 21 CFR, 1 April 1999.

Table 2-6. OSHA Regulations

Regulatory action	Effect of regulation and other comments
29 CFR 1910.250—SUBPART Q—Welding, Cutting and Brazing. Promulgated: 55 FR 13696, 04/11/90. U.S. Codes: 29 U.S.C. 653, 655, 657.	Where the work permits, the welder should be enclosed in an individual booth painted with a finish of low reflectivity, such as zinc oxide (an important factor for absorbing UVR) and lamp black, or shall be enclosed with noncombustible screens similarly painted. Booths and screens shall permit circulation of air at floor level. Workers or other persons adjacent to the welding areas shall be protected from UVR by noncombustible or flameproof screens or shields or shall be required to wear appropriate goggles.
29 CFR 1926.350—SUBPART J—Welding and Cutting. Promulgated: 58 FR 35179, 06/30/93. U.S. Codes: 29 U.S.C. 653, 655, 657, 40 U.S.C. 333. Inert-gas metal-arc welding.	Since the inert-gas metal-arc welding process involves the production of ultraviolet radiation of intensities of 5 to 30 times those produced during shielded metal-arc welding, employees shall not be permitted to engage in or be exposed to the process until the following special precautions have been taken: (1) The use of chlorinated solvents shall be kept at least 200 feet, unless shielded, from the exposed arc, and surfaces prepared with chlorinated solvents shall be thoroughly dry before welding is permitted on such surfaces. (2) Employees in the area not protected from the arc by screening shall be protected by filter lenses. When two or more welders are exposed to each other's arc, filter lens goggles of a suitable type shall be worn under welding helmets. Hand shields to protect the welder against flashes and radiant energy shall be used when either the helmet is lifted or the shield is removed. (3) Welders and other employees who are exposed to radiation shall be suitably protected so that the skin is covered completely to prevent burns and other damage by ultraviolet rays. Welding helmets and hand shields shall be free of leaks and openings, and free of highly reflective surfaces.

Source: The regulations in this table have been updated through the 1999 Code of Federal Regulations 29 CFR, 1 July 1999.

3 Human Cancer Studies

Humans can be exposed to UVR from natural (solar) and artificial sources (see Sections 1 and 2). The IARC (1992) and the National Toxicology Program (NTP 2000) reviewed the evidence for human carcinogenicity of solar radiation and exposure to sunlamps or sunbeds. Both reports concluded there was sufficient evidence in humans that solar radiation was carcinogenic, causing malignant melanoma of the skin and non-melanoma skin cancer. Solar radiation is classified by the IARC (1992) as *carcinogenic to humans* (Group 1) and is listed in the Ninth RoC (2000) as *known to be a human carcinogen.*

The 1992 IARC review also considered artificial sources of UVR. The IARC Working Group characterized the human evidence concerning the carcinogenicity of artificial sources of UVR as limited, and classified exposures associated with the use of sunlamps and tanning beds as *probably carcinogenic to humans* (Group 2A). The NTP (2000) review concluded that there was sufficient evidence from human studies to list exposure to sunlamps or sunbeds as *known to be a human carcinogen*, based on epidemiological studies evaluated by the IARC and studies published after the 1992 IARC review. The NTP (2000) conclusions about the carcinogenicity of solar radiation and exposure to sunlamps and sunbeds were based on the NTP background document (1997) prepared to evaluate these exposures.

The purpose of this section is to review evidence in humans regarding the potential carcinogenicity of broad-spectrum UVR and its components (UVA, UVB, and UVC). The most extensive literature comes from studies on sunlight and cancer; however, these studies are not specific for UVR. Evidence for the role of the UVR component of solar radiation in carcinogenicity comes from studies with artificial sources of UVR, tumor-site concordance between humans exposed to solar radiation and animals exposed to UVR from artificial sources (see Section 4), and human mechanistic studies using artificial sources of UVR (see Sections 5 and 6). Epidemiologic studies evaluating exposure to artificial sources of UVR are valuable for assessing the effects of UVR itself and the role of the UVR component in solar radiation. Human epidemiologic evidence on the carcinogenicity of specific components of the UVR spectrum, including UVA, UVB, and UVC, is limited. The IARC Working Group noted that none of the studies reviewed had assessed the emission spectra of artificial UV sources, and little additional information from human studies has been produced since the 1992 IARC evaluation. This section summarizes the 1992 IARC review, the 1997 NTP review, and post-1992 reviews of the extensive literature on solar radiation, and reviews human studies evaluating carcinogenic effects of exposure to UVR from artificial sources (including broad-spectrum UVR and specific UVR components), concentrating on exposure to sunlamps or sunbeds.

3.1 Solar radiation

3.1.1 Evaluations by the IARC (1992) and the NTP (2000)

The IARC (1992) evaluation provides extensive information on the evidence for the carcinogenicity of solar radiation in humans. The studies reviewed examined malignant melanoma of the skin, non-melanoma skin cancer, malignant melanoma of the eye, and cancer of the lip, with the majority of the evidence pertaining to the first two cancers. The results of descriptive epidemiologic studies suggest that exposure to sunlight increases the risk of nonmelanocytic cancer. Nonmelanocytic tumors occur predominantly on regions of the body exposed to sunlight. Evidence to suggest that these cancers are associated with the UVR component of sunlight comes from latitude studies. There is a strong inverse relationship between latitude of residence and cancer incidence or mortality and, conversely, a positive relationship between measured or estimated ambient UVR and cancer incidence or mortality. Three case-control studies found a significantly increased risk of cancer of the lip associated with outdoor work (a proxy for UVR exposure).

The analytic epidemiologic literature on the relationship between malignant melanoma of the skin and exposure to sunlight is extensive. Population-based case-control studies in western Australia, Queensland, western Canada, and Denmark showed consistent positive associations of malignant melanoma with residence in sunny environments throughout life, in early life, and for short periods in early adult life, and with measures of cumulative sun damage, such as microtopographical changes or history of keratosis or nonmelanocytic skin cancer. Most studies showed positive associations with measures of intermittent sun exposure, but associations with total (lifetime) sun exposure or occupational sun exposure were inconsistent.

Only one study reviewed by the IARC referred to a specific component of the UVR spectrum. A cross-sectional study of Maryland fishermen included estimates of annual and lifetime exposure to UVB obtained through a combination of self-reported history and measurements with film dosimeters (Vitasa *et al.* 1990, cited in IARC 1992). After adjustment for age, eye color, childhood freckling, and skin reaction to sunlight, squamous-cell carcinoma was associated with cumulative UVB exposure above the 75th percentile (odds ratio [OR] = 2.53, 95% CI = 1.18 to 5.01), but basal-cell carcinoma was not associated with exposure to UVB. Basal-cell carcinoma is more strongly associated with nonoccupational than occupational sun exposure and with intermittent than total exposure (English *et al.* 1997). No other study providing information about the association of specific UV wavelengths with skin cancer was identified.

The relationship between solar radiation and non-Hodgkin's lymphoma is less clear. The NTP background document on solar radiation and exposure to sunlamps or sunbeds evaluated four studies (Bentham and Aase 1996, Newton *et al.* 1996, Hartge *et al*. 1996, McMichael and Giles 1996) that provided limited support for an association of solar radiation with non-Hodgkin's lymphoma. Two of these studies evaluated the relationship of cancer with levels of solar UVB. In a U.S. study, Hartge *et al.* (1996) reported that state annual average estimated solar UVB levels (adjusted for latitude,

altitude, and cloud cover) were positively correlated with state mortality rates for melanoma and non-melanoma skin cancer in white males, but negatively correlated with mortality rates for non-Hodgkin's lymphoma ($P < 0.0001$ for all coefficients). In contrast, in a worldwide study, McMichael and Giles (1996) reported that the incidences of non-Hodgkin's lymphoma and cutaneous malignant melanoma in white Caucasoid populations (from 49 registries in 19 countries) were positively correlated with estimated average annual UVB exposure (as MED, based on latitude and adjusted for cloud cover). The correlation coefficients were 0.50 in males and 0.51 in females for non-Hodgkin's lymphoma and 0.75 in males and 0.67 in females for melanoma ($P < 0.001$ for all coefficients). Neither of these studies was specific for UVB radiation, because they were based on estimates of UVB levels as a portion of total solar UVR, which also includes a UVA component.

3.1.2 Recent epidemiologic studies

Epidemiologic studies of sun exposure and skin cancer published after the 1992 IARC evaluation were reviewed by Elwood (1996) and Armstrong and Kricker (1996). Elwood (1996) provided a comprehensive review of studies on melanoma and sun exposure published through 1995, including eight case-control studies published after the IARC review, and Armstrong and Kricker (1996) reviewed studies of malignant melanoma and non-melanoma skin cancer. These reviews reinforced the IARC's fundamental conclusions, but presented no new information relating specifically to UVA or UVB.

The importance of the conditions of sunlight exposure with respect to melanoma has been further evaluated in recent studies. Elwood and Jopson (1997) reported an overall analysis of 35 case-control studies that evaluated the relationship between cutaneous malignant melanoma and sun exposure (intermittent, occupational, and total) and age-specific history of sunburn. Overall, risk was significantly increased by intermittent exposure (OR = 1.71, 95% CI = 1.54 to 1.90) and significantly reduced by high occupational exposure (OR = 0.86, 95% CI = 0.77 to 0.96); a small excess risk associated with total exposure was marginally significant (OR = 1.18, 95% CI = 1.02 to 1.38). The estimates of risk with respect to sun exposure showed considerable heterogeneity ($P < 0.001$). For intermittent exposure, 21 of 23 studies with relevant exposure information found a positive association with melanoma, which was statistically significant in 16 studies. Sunburn at all ages or as an adult significantly increased the risk of melanoma (OR = 1.91, 95% CI = 1.6 to 2.17), as did sunburn in adolescence or in childhood. The authors suggested that the association with sunburn also reflected the effect of intermittent exposure.

Recent studies evaluating the relationship between sunlight and non-Hodgkin's lymphoma provided little additional information bearing on the conclusions of the Ninth RoC (2000). Adami *et al.* (1999) conducted a population-based cohort study in Sweden, which assessed UVR exposure by occupation (using job titles obtained from the census) and latitude (based on classification of each individual's home and work addresses). Data for incidences of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, malignant melanoma, and squamous-cell carcinoma were obtained from the Swedish Cancer Registry. Adami *et al.* (1996) reported a positive association between

latitude of residence and sex-specific age-adjusted relative risks of non-Hodgkin's lymphoma but did not find an association with occupation, where job title and industry served as a surrogate for exposure (indoor versus outdoor occupations). In a population-based case-control study in the United States, Freedman *et al.* (1997) reported an inverse association between non-Hodgkin's lymphoma mortality and sunlight exposure, as assessed from occupational and residential information on death certificates. Two separate case-report studies reported positive associations with residential and occupational surrogates for sunlight exposure, for skin cancer mortality in one study and for melanoma in the other (Freedman *et al.* 1997).

3.2 UVR from artificial sources

Humans are exposed to artificial sources of UVR for cosmetic purposes (sunlamps or sunbeds), for medical treatment (PUVA and UVB treatment of psoriasis), and through occupational exposure (e.g., fluorescent lights or welding) (see Section 2). In most of these studies, with the possible exception of medical exposure, exposure was to broad-spectrum UVR, or the type of UVR was unknown (see Tables 3-1, 3-2, and 3-3).

3.2.1 Cosmetically related UVR exposure

As mentioned above, the most extensive epidemiological evidence for evaluation of the relationship between human cancer and exposure to artificial UVR comes from studies where the exposure was to sunlamps or sunbeds. This section reevaluates the literature on cutaneous malignant melanoma and exposure to sunlamps or sunbeds, because of the importance of these human studies in evaluation of the carcinogenicity of UVR radiation, their relevance in elucidating the role of UVR in the carcinogenicity of solar radiation and to address a recent epidemiologic review and assessment of exposure to tanning lamps and malignant melanoma that was published since the 1997 NTP background document (Swerdlow and Weinstock 1998).

The IARC (1992) classified exposure to sunlamps or sunbeds as *probably carcinogenic to humans*. Two case-control studies published between the 1992 IARC review and the 1997 NTP assessment (Autier *et al.* 1994, Westerdahl *et al*. 1994) provided evidence that exposure to sunlamps or sunbeds increased the risk of melanoma. The Ninth RoC listed exposure to sunlamps or sunbeds as *known to be a human carcinogen* (NTP 2000), based on these two studies and the studies reviewed by the IARC (1992). Since the 1997 NTP assessment, a review article and three additional studies have been published. Swerdlow and Weinstock (1998) reviewed 19 case-control studies evaluating the relationship of exposure to sunlamps and sunbeds with cutaneous malignant melanoma, including the nine studies reported in the 1997 NTP background document. The authors concluded that "although several investigations have found a positive relation between tanning lamp use and melanoma, in some instances including dose-response or duration-response effects, the methodologic limitations preclude any firm conclusions regarding a causative relation".

Since Swerdlow and Weinstock's review, there have been three additional publications evaluating the relationship of exposure to sunlamps or sunbeds to melanoma; one study provided positive evidence (Westerdahl *et al.* 2000) and another provided limited

evidence (Chen *et al.* 1998). In addition, Walter *et al.* (1999) reanalyzed the case-control study (Walter *et al* 1990) discussed in the NTP background document (1997), providing further support for an elevated risk of melanoma with sunlamp or sunbed exposure. The following sections evaluate the case-control studies on exposure to sunlamps or sunbeds and cutaneous malignant melanoma and address the methodologic concerns raised by Swerdlow and Weinstock (1998).

3.2.1.1 Epidemiologic studies of melanoma and sunlamp or sunbed exposure

The 22 publications evaluating the association between exposure to sunlamps or sunbeds and malignant melanoma (19 reviewed by Swerdlow and Weinstock and three more recent) relate to 21 case-control studies, because two of these publications analyzed the same population (Walter *et al*. 1990, 1999); these reports were considered as one study for the purpose of this evaluation. Two other case-control studies cited by Swerdlow and Weinstock were not evaluated, because one study (Autier *et al.* 1991) was descriptive rather than analytical, and exposure in the second study (Dubin *et al.* 1989) was not specific for sunlamp or sunbed use, but was characterized only as medical and occupational. The remaining 19 case-control studies were reviewed.

Because these studies varied greatly in quality, including power to detect an effect, characterization of exposure, and analysis of the effect, they did not contribute equal information to the assessment of causality. The power of some studies was limited by small numbers of exposed cases or because cases were accrued at an earlier time period and so were inadequate to detect exposures that occurred in the 1980s (when tanning salons became more popular). Some studies included "ever-use" of sunlamps or sunbeds as part of larger studies focusing primarily on other risk factors for melanoma, and provided little information about frequency or duration of exposure, age at exposure, location of exposure, or body sites exposed. Also, several studies did not report a risk estimate or reported little subgroup analysis with respect to such factors as exposure, histologic type of cancer, or patient characteristics. Stratified analyses can increase the sensitivity to detect an effect and provide other pertinent information concerning sensitive subgroups.

Studies lacking sufficient power, detailed exposure assessment, or detailed analyses were difficult to evaluate and provided little information about cancer effects due to exposure to sunlamps or sunbeds. On the other hand, a few studies provided relatively detailed exposure assessment and analyses. Thus, in an effort to evaluate causality, the case-control studies were grouped into four tiers with respect to the quality of the information concerning the exposure to sunlamps or sunbeds and its relationship to cancer. Some studies differ in the ranking criteria according to analysis, exposure or power; priority generally was given to the quality of exposure information. The case-control studies are summarized in Table 3-1.

3.2.1.2 Criteria for the four tiers and ranking of the studies

Tier 1. *Exposure assessment:* limited information; exposure was reported only as ever-use. *Analyses:* a quantitative risk estimate was not calculated or reported; percentages of

exposed cases and controls were not reported, so risk estimates could not be calculated. *Power:* limited by small numbers of exposed cases.

Studies: Klepp and Magnus 1979, Holly *et al.* 1987, Beitner *et al.* 1990.

Tier 2. *Exposure assessment:* limited information; exposure was reported only as ever-use. *Analyses:* no detailed analyses, but information was provided (e.g., percentages of exposed cases and controls) allowing a risk estimate to be calculated. *Power:* limited by small numbers of exposed cases.

Studies: Adam *et al.* 1981, Gallagher *et al.* 1986, Holman *et al.* 1986, Zanetti *et al.* 1988, MacKie *et al.* 1989, Dunn-Lane *et al.* 1993, Garbe *et al.* 1993.
(Note: Gallagher *et al.* reported that they had queried more detailed information on frequency of exposure; however, they did not described the frequency of use, the number of individuals exposed, or a risk estimate, thus this study was grouped in Tier 2.)

Tier 3. *Exposure assessment:* some information with respect to duration or frequency. *Analyses:* more information with respect to risk calculation; some subgroup analysis. *Power:* larger sample sizes; higher percentages of exposed individuals, but duration or lifetime usage was low, so the numbers of highly exposed cases were small.

Studies: Elwood *et al.* 1986, Osterlind *et al.* 1988, Holly *et al.* 1995.

Tier 4: *Exposure assessment:* detailed information with respect to duration, frequency, and other factors, such as age when exposure occurred or location of exposure. *Analyses:* detailed subgroup analyses with respect to exposure characteristics, patient characteristics, or histologic type of melanoma. *Power:* larger study populations, higher percentages of individuals exposed to sunlamps or sunbeds, and/or longer durations of usage. Exposure to sunlamps or sunbeds generally was the major focus of these studies.

Studies: Swerdlow *et al.* 1988, Walter *et al.* 1990 (reanalyzed in Walter *et al.* 1999), Autier *et al.* 1994, Westerdahl *et al.* 1994, Chen *et al.* 1998, Westerdahl *et al.* 2000.

3.2.1.3 Evaluation of the evidence for association of malignant melanoma with exposure to sunlamps or sunbeds

The three Tier 1 studies (Klepp and Magnus 1979, Holly *et al.* 1987, Beitner *et al.* 1990) and five of the seven Tier 2 studies (Gallagher *et al.* 1986, Holman *et al*. 1986, Zanetti *et al*. 1988, Dunn-Lane *et al*. 1993, Garbe *et al*. 1993) found no association between malignant melanoma and exposure to sunlamps or sunbeds. The other two Tier 2 studies (Adam *et al.* 1981, MacKie *et al*. 1989) reported that a larger percentage of cases than controls had used sunbed or sunlamps. Because the studies in Tiers 1 and 2 were limited in their ability to detect an effect or did not report information needed in order to evaluate an effect, they provided little or no information for assessing causality.

None of the studies in Tier 3 found a positive association between exposure to sunlamps and malignant melanoma (Elwood *et al*. 1986, Osterlind *et al*. 1988, Holly *et al*. 1995). Elwood *et al*. (1986) reported information on the duration of exposure;

however, this study was limited in power by the relatively small number of exposed cases (15) resulting from the small number of malignant melanoma cases (83), and a low level of exposure (average duration was 2.3 hours). Both Osterlind *et al*. (1988) and Holly *et al*. (1995) evaluated malignant melanoma risk in relation to number of sunlamp or sunbed uses. Holly *et al*. (1995) found no association between melanoma and either low or high categories of sunlamp exposure but did not define the exposure levels in each category, making it difficult to compare the exposures with those in other studies. Osterlind *et al.* (1998) found no relationship between melanoma and number of sunlamp uses, but did not report an OR for each exposure category. Exposures to sunlamps were for both medical and cosmetic reasons. Melanoma risk in this study also was not related to sunbed usage. The Tier 3 studies contributed some information to the evaluation of causality.

The studies in Tier 4 provided the most information concerning causality, because they contained detailed exposure assessments and analyses. Moreover, most of these studies were better able to detect an effect, because of adequate study populations (mostly > 400 cases), a higher proportion of exposed cases (> 20%), and a higher level of lifetime exposure (total number of uses). Five of the six studies reported increased risk of malignant melanoma associated with exposure to sunlamps or sunbeds (Swerdlow *et al.* 1988, Walter *et al.* 1990, 1999, Autier *et al*. 1994, Westerdahl *et al*. 1994, 2000). The sixth study (Chen *et al.* 1998) provided limited support, because elevated risks were observed only after subgroup analysis (e.g., stratification by the number of types of lamps used and location and timing of exposure), but not for ever-use of sunlamps or sunbeds (crude OR = 1.3; adjusted OR = 1.1).

In the Tier 4 studies, odds ratios for ever-use of sunlamps or sunbeds ranged from 1.1 to 2.9. Higher odds ratios were found for the higher exposure strata and in subgroup analyses by patient characteristics (younger patients), exposure characteristics (younger age of exposure), body site of cancer (mostly trunk and legs), and histologic type of melanoma (superficial spreading and lentigo maligna). Four of the five studies that tested for an exposure-response relationship reported a positive association (Swerdlow *et al*. 1998, Walter *et al.* 1990, Westerdahl *et al*. 1994, 2000), though Westerdahl *et al.* (2000) reported an exposure-response relationship only up to a total of 250 uses. Chen *et al.* (1998) reported no relationship between the total number of sunlamp uses and melanoma risk.

Few of these studies provided information on the types of sunlamps or sunbeds used. This factor is important, because exposure in the 1970s was more likely to take place at home with devices that emitted greater amounts of UVB and UVC radiation, whereas exposure in the 1980s increasingly occurred in commercial salons using devices that emitted mainly UVA.

Chen *et al.* (1998) was the only study that obtained information concerning the type of sunbed or sunlamp used (e.g., desktop models, floor models, beds, or walk-in booths). This information was obtained by showing subjects pictures of various types of sunlamps and sunbeds. The study found a nonsignificant elevated risk of malignant melanoma associated with the use of desktop sunlamps and heavyweight floor-model

sunbeds and a statistically significant tripled risk associated with use of more than two types of sunlamps, compared with no use of sunlamps. Increased risk of melanoma also was associated with first use of sunlamps before 1971 and with sunlamp use at home. However, the study had insufficient power to detect an association between melanoma and use of sunlamps in the late 1970s and 1980s, because of insufficient follow-up time for cases accrued between 1987 and 1989. Walter *et al.* (1990) also found a greater risk for exposures that occurred at home than at commercial sites.

In contrast, Westerdahl *et al*. (2000) reported a greater risk associated with commercial than with home use of sunbeds. This was the first population-based case-control study to accrue cases in the late 1990s; thus, it had greater power to detect the effects of exposure in the 1980s. Most (80%) of the exposure to sunbeds in this study took place in the 1980s, probably from predominantly UVA-emitting sunbeds. This contrasts with the exposures reported by Chen *et al.* (1998), in which only 59 of the subjects (25% of the exposed subjects) had used sunlamps in a commercial setting after 1970, and in which the follow-up for exposures that occurred in the 1980s was shorter.

3.2.1.4 Methodologic concerns

Swerdlow and Weinstock (1998) discussed seven biases or methodologic limitations present in many of case-control studies listed in Table 3-1; however, many of these limitations were not specific for exposure to sunlamps or sunbeds, but are inherent to most retrospective case-control studies. Three of the limitations concerned exposure assessment: inadequate information on the types of sunlamps used (discussed above), inadequate classification according to the level of exposure, and misclassification of exposure through inclusion of both medical and cosmetic exposure. The fourth limitation related to the limited power to detect an association because only a small proportion of subjects had ever used sunlamps or sunbeds or had used tanning devices at an exposure level sufficient for an effect to be detected. Both exposure misclassification and limited power would diminish the strength of an association with melanoma. These issues were addressed by ranking of the studies in the four tiers described above. The studies in Tier 4, which largely overcame these limitations, showed positive associations of melanoma with exposure.

The other three biases, confounding due to sun exposure, recall bias, and publication bias, may induce an artifactual association. Regarding confounding, several studies (Autier *et al.* 1994, Swerdlow *et al.* 1988, Westerdahl *et al.* 1994) reported an association between exposure to sunlamps or sunbeds and increased risk of melanoma after adjusting for recreational sun exposure or indicators of sun exposure (raised nevi and number of sunburns) (Westerdahl *et al*. 2000). However, the control of recreational sun exposure may not be appropriate in this situation, because UVR presumably is the relevant exposure underlying both exposures, solar radiation and sunlamps or sunbeds; thus, the two exposures may have an additive effect on the risk of melanoma. Thus, controlling for sun exposure may lead to an underestimation of the effect of exposure to sunlamps or sunbeds. All studies reporting a positive association between sunlamp or sunbed exposure and malignant melanoma adjusted for phenotypic indicators of sun sensitivity.

Several studies (Autier *et al.* 1994, Walter *et al.* 1990, Westerdahl *et al.* 2000, 1994) used measures to control for recall bias. Autier *et al.* (1994) focused on recall bias in the training of the interviewers; neither interviewers nor subjects were informed of the study's objective. Westerdahl *et al*. (1994) used a questionnaire with many variables and stated that at the time of the interview (1988 to 1990), the population was unaware of the relationship between sunlamps or sunbeds and malignant melanoma. Westerdahl *et al.* (2000) used identical procedures of data collection for cases and controls and collected information from melanoma patients shortly after diagnosis. Walter *et al*. (1990) reported that rates of sunbed use were similar in patients interviewed before and after the diagnosis of melanoma, suggesting that recall bias was not important. The fact that studies with negative results and methodological limitations (small sample sizes and low exposure) were published suggests that publication bias probably was not a major factor.

3.2.2 Medically related UVR exposure

As discussed in Section 2, UVR has been used to treat psoriasis, alone or in combination with chemical agents; e.g., PUVA (UVA plus methoxsalen), UVB, or UVB plus coal tar. Most human studies evaluating health effects of medically related exposure to UVR have been compromised by exposure of subjects to another potential carcinogen; coal tar, for instance, is a *known to be human carcinogen* (NTP 2000).

3.2.2.1 IARC and NTP evaluations

Methoxsalen (methoxypsoralen) with UVA therapy (PUVA) is *known to be a human carcinogen* based on sufficient evidence in humans (IARC 1982, 1987, NTP 2000). Squamous-cell carcinoma was reported in patients treated with PUVA therapy. UVB therapy, either alone or in combination with other treatments, has not previously been reviewed for carcinogenic risk by either the IARC or the NTP.

3.2.2.2 Recent epidemiologic studies

The studies with PUVA provided only limited information concerning the carcinogenicity of UVR exposure, because of the co-exposure with psoralens, which may be photocarcinogens (see Section 5 for discussion of the genotoxicity of PUVA therapy). A wealth of literature has been published on PUVA treatment and cancer. In a review of the literature published after 1992, Studniberg and Weller (1993) concluded that a long-term multicenter prospective study following psoriasis patients treated with PUVA (Stern *et al.* 1979, 1984, Stern and Lange 1988) provided evidence that PUVA was an independent carcinogen in humans, capable of initiating and promoting the formation of squamous-cell carcinoma. These findings were supported by several long-term retrospective studies (Forman *et al*. 1989, Lindelof *et al.* 1991, Bruynzeel *et al.* 1991). At the time of the review, the relationship of basal-cell carcinoma to PUVA alone was not well established.

Since this review, Stern *et al.* (1997, 1998) reported the results of a 15-year follow-up of the PUVA cohort with respect to both non-melanoma skin cancer and melanoma. Risk of basal-cell carcinoma was elevated only in psoriasis patients exposed to high levels of PUVA (Stern *et al.* 1998). An excess risk of malignant melanoma, relative to

the age- and sex-specific rates for the U.S. population, also was reported (Stern *et al.* 1997). This risk did not become evident until the period from 1991 to 1996, suggesting that a long follow-up time was needed to detect melanoma. The risk of melanoma was higher among patients receiving at least 250 PUVA treatments. This study was criticized by Whitmore and Morison (1997) for (1) inaccurate statistics, as the use of cancer statistics from the National Cancer Institute's Surveillance, Epidemiology, and End Results data may underestimate the true incidence of melanoma, (2) confounding variables, as the cohort study lacked a control group of patients with psoriasis who never received PUVA, and (3) surveillance bias, as cohort members were aware that they were being followed for adverse effects of PUVA therapy.

A Swedish prospective study that followed a cohort of PUVA-treated patients did not find an increased risk of malignant melanoma (Lindelof *et al.* 1999). However, the treatment regimen was different in this study; one-fifth of the cohort received PUVA bath therapy, in which the UVA dose is 15 to 20 times lower than in oral therapy. Moreover, both the mean and cumulative UVA doses for PUVA treatment generally are much lower in Europe than in the United States (Studniberg and Weller 1993).

Pasker-de Jong *et al.* (1999) conducted a systematic review of nine human studies evaluating the relationship between UVB psoriasis treatment and non-melanoma skin cancer. All studies followed cohorts of psoriasis patients, some of whom had received UVB treatment. Three studies evaluating the effects of UVB therapy without coal tar found no excess of cancer in UVB-exposed individuals (Larko and Swanback 1982, Bhate *et al*. 1993, Maier *et al*. 1996). Two studies evaluated the effect of exposure to UVB and coal tar in the same PUVA cohort used in Stern *et al.* (1997, 1998) discussed above. Elevated risks of genital SCC (RR = 4.6 [Stern 1990]) and non-melanoma skin cancer (OR = 2.4, 95% CI = 2.2, 10.0 [Stern *et al*. 1980]) were reported in patients exposed to over 300 treatments with UVB and/or over 90 months of treatment with coal tar compared with members of the PUVA cohort without high exposure to UVB or coal tar. However, a later follow-up of the cohort no longer found a significant association between non-melanoma skin cancer and long-term exposure to UVB or coal tar after controlling for PUVA exposure and other confounders (Stern and Laird 1994). Pittelkow *et al.* (1981) also did not find an increase in the cumulative incidence of non-melanoma skin cancer in psoriasis patients treated with UVB and coal tar, compared with the age-specific incidence of non-melanoma skin cancer for that geographical area.

A cohort study (Hannuksela-Svahn *et al*. 2000) published after the Pasker-de Jong *et al.* (1999) review, studied a population of psoriasis patients diagnosed between 1973 and 1984 and treated with different UVR therapies (30 cases and 137 controls for squamous-cell carcinoma and 19 cases and 110 controls for non-Hodgkin's lymphoma). The mean length of follow-up was 14 years. Because increased incidences of squamous-cell carcinoma (30), non-Hodgkin's lymphoma (19), and laryngeal cancer (11) were observed for the cohort as a whole, a nested case-control study was used to evaluate the role of prior exposures to different psoriasis treatments. An elevated but nonsignificant risk of squamous-cell carcinoma (RR = 1.6, 95% CI = 0.4 to 6.4) from prior UVB treatment was reported. Risk of non-Hodgkin's lymphoma was not

increased by any treatment, including UVB, and results for laryngeal cancer were not reported.

3.2.3 Occupationally related UVR exposure

3.2.3.1 IARC evaluation

The IARC commented that epidemiological studies evaluating effects of exposure to artificial UVR had not measured actual doses of UVR nor considered the emission spectrum, and that subjects were exposed to sources of varying intensity and emission spectra. The IARC reviewed eight case-control studies evaluating the relationship between fluorescent lighting and melanoma. Most of these studies provided limited information. Two studies reported an increased risk of melanoma from exposure to fluorescent lamps (Beral *et al.* 1982, Elwood *et al*. 1986), but the measurement of exposure was crude in one of the studies (Beral *et al*. 1982) and the effects were inconsistent depending on the method of ascertainment of information in the other study (Elwood *et al*. 1986). Exposure to UVR from arc welding and other occupational sources was not associated with malignant melanoma. However, exposure to arc welding torches increased the risk for melanoma of the eye (OR = 8.3, 90% CI = 2.5 to 27.10) in a Canadian study (Siemiatycki *et al*. 1991), though not in an U.S. study (Seddon *et al*. 1990).

3.2.3.2 Recent epidemiologic studies

Studies evaluating the effects of occupational UVR exposure and cancer published since the IARC evaluation include three analytic studies and one case report. The case report was of five cases of non-melanoma skin cancer in welders, reported from the Skin Cancer Clinic in Bedford, England (Currie and Monk 2000).

Bajdik *et al*. (1996) evaluated the risk of non-melanoma skin cancer from nonsolar radiation in a population-based case-control study of 226 basal-cell carcinoma and 180 squamous-cell carcinoma cases and 406 age-matched controls. Subjects were asked about job history and exposure to fluorescent lighting, sunlamps, welding torches, mercury-vapor lamps, ultraviolet or black lights, printing or photocopying lights, UV lamp treatments, or horticultural growth-inducing lights. Slightly elevated but nonsignificant risks of basal-cell carcinoma were observed for exposure to sunlamps, mercury-vapor lamps, and horticultural growth-inducing lights, and similar nonsignificant elevated risks of squamous-cell carcinoma were observed for exposure to sunlamps and welding torches. However, the authors noted that the statistical power was low because of the limited number of exposed individuals (except for exposure to fluorescent lighting or welding torches).

Holly *et al.* (1996) reported that welding exposure was a risk factor for uveal (intraocular) melanoma (OR = 2.2, 95% CI = 1.3 to 3.5) in a population-based case-control study (221 patients and 447 controls) in the western United States. Other occupational groups that were also exposed to UVR also had an increased risk of uveal melanoma (OR = 3.0, 95% CI = 1.2 to 7.8) for sailors, ship officers or fisherman and (OR = 1.2, 95% CI = 0.74 to 1.9) for agricultural occupations. For these occupations, the source of UVR exposure was sunlight.

The relationship between fluorescent light exposure and cutaneous malignant melanoma was evaluated in a population-based case-control study (583 cases and 608 controls) in Ontario, Canada (Walter *et al*. 1992). In males, significantly increased risk of melanoma was associated with cumulative years of occupational exposure (with an exposure-response relationship) and with various indices of exposure to domestic fluorescent light. In females, results were inconsistent. The observed increased risk remained after adjustment for other major risk factors, including time spent outdoors for occupation.

3.3 DNA repair

Xeroderma pigmentosum is a rare autosomal recessive genetic disease characterized by an excision repair defect, as observed in cultured skin fibroblasts damaged by UVR. Patients display cellular and clinical hypersensitivity to UVR and have a > 200-fold excess of sunlight-related skin cancer (IARC 1992, Cleaver and Kraemer 1989, cited in Wei *et al*. 1994). Xeroderma pigmentosum is a rare disease, resulting in exceptionally low DNA repair capacity.

DNA repair capacity may also vary in the general population and thus may be a hereditary susceptibility factor for skin cancer. Wei *et al.* (1994, 1995) provided evidence that DNA repair capacity may be the underlying cause of sunlight-induced basal-cell carcinoma resulting from certain known risk factors (susceptible skin type, poor tanning ability, history of multiple sunburns, frequent sunbathing, exposure to chemicals, or multiple medical irradiations) (see Section 5 for discussion of DNA repair assays).

3.4 Discussion

The studies reviewed by the IARC (1992) and the substantial number of studies published since provide strong evidence that exposure to solar radiation causes malignant melanoma and basal- and squamous-cell carcinoma of the skin. Terrestrial sunlight is a mixture of UVR, visible, and infrared light, so it can be deduced that one or more of these components is carcinogenic. Studies using artificial sources of UVR, mainly sunlamps and sunbeds, suggest that UVR is the carcinogenic component of solar radiation. Positive associations between exposure and skin cancer have been reported both for early models of sunlamps emitting high percentages of UVB and for later models of sunbeds emitting mainly UVA.

The epidemiological literature, while extensive, does not provide a basis for subdividing the effects of solar radiation or UVR from artificial sources into components attributable specifically to UVA, UVB, or UVC. However, some information with respect to the specific effects of UVA, UVB, and UVC can be inferred from the results of studies in which the predominant exposure was to a specific UVR component.

3.4.1 UVA

Evidence for carcinogenic effects of UVA exposure comes from studies on solar radiation and melanoma, sunscreen usage, sunlamps and sunbeds, and PUVA treatment. It has been suggested that UVA is important in the development of melanoma. Solar radiation contains varying amounts of UVA and UVB, depending on latitude. In

descriptive epidemiological studies of worldwide incidence of cutaneous malignant melanoma, cancer incidence correlated better with latitude changes in UVA intensity than latitude changes in UVB intensity; correlations of latitude with melanoma incidence and correlations of latitude with UVA intensity had similar slopes (Moan *et al*. 1999). Several, but not all, studies showed sunscreen use to be a risk factor for melanoma, possibly as a result of longer exposure to sunlight (because of protection from sunburn) or inadequate blocking of UVA radiation (early sunscreens blocked mainly UVB radiation) (Gasparro 2000). Westerdahl *et al.* (2000) reported an association between malignant melanoma and exposure to sunbeds, the majority of which probably emitted mainly UVA (0.1% to 2.1% UVB). PUVA therapy is a known human carcinogen. Most studies showed an association between PUVA therapy and non-melanoma skin cancer, and a recent study reported an association with melanoma (Stern *et al.* 1997). However, these studies are compromised by co-exposure to psoralens and the use of psoriasis patients as study populations.

3.4.2 UVB

Individuals are exposed to UVB radiation from the sun and from artificial sources, such as sunlamps and sunbeds, medical therapies, fluorescent lighting, and welding. The strongest evidence for UVB carcinogenicity comes from the importance of the UVB component to the association of cancer with solar radiation and exposure to sunlamps and sunbeds. There is a strong inverse relationship between latitude and both the incidence of nonmelanocytic skin cancer and measured or estimated ambient UVR. The yearly average intensity of all wavelengths in sunlight increases with decreasing latitude; however, the greatest increase is in UVB exposure, because the stratospheric ozone layer is thicker at higher latitudes and absorbs much more UVB than UVA. In fact, several studies have used estimated solar UVB as an indicator of exposure to solar radiation (e.g., Hartge *et al.* 1996, McMichael and Giles 1996).

In one study, exposure to sunlamps used in the early 1970s, which produced significant amounts of UVB (22% to 40%), was associated with malignant melanoma (Chen *et al*. 1998). Other studies using artificial sources of UVB radiation gave mainly negative or inconsistent results or were limited by confounding with exposure to other potential carcinogens. UVB therapy does not appear to be a risk factor for psoriasis patients. Fluorescent lighting devices generate light by emitting UV radiation, which strikes a phosphor on the interior lining of the tube. The glass tubes absorb most of the radiation below 290 nm, but longer wavelengths, particularly above 297 nm, are more readily transmitted. There is some evidence that fluorescent lighting may increase the risk of skin cancer (Walter *et al.* 1992); however, results of earlier studies were inconsistent (IARC 1992). Other occupational exposures also appear to involve mainly UVB-emitting devices. Welding used to join metal components produces ultraviolet light (250 to 297 nm). Some evidence suggests that welding may increase the risk of uveal melanoma; however, confirmatory studies are needed, and the effects of welding fumes are unknown (Holly *et al.* 1996).

3.4.3 UVC

The effects of UVC are harder to evaluate. Solar UVC is filtered by the ozone layer, and few studies have examined the effects of exposure to artificial sources of UVC. Desktop sunlamps used before the 1970s may have emitted UVC (see Section 2), as may welding torches.

3.5 Summary

Epidemiologic studies have clearly demonstrated that exposure to broad-spectrum UVR increases both melanocytic and nonmelanocytic cancer. Studies of solar radiation, artificial devices emitting broad-spectrum UVR, and devices emitting predominantly UVA or UVB all have contributed to this conclusion. Both UVA and UVB components of solar radiation appear to be important, and they may contribute differently to risks of different types of cancer. Some evidence suggests that UVA or UVB alone also may increase the risk of skin cancer or melanoma of the eye, but it is not conclusive. Little information from human studies was available to evaluate UVC.

Table 3-1. Epidemiologic studies of the relationship between cutaneous malignant melanoma and exposure to sunlamps or sunbeds (listed in chronological order by publication date)

Reference Study location Years cases accrued	Study design	Population	Exposure Percent exposed (case/controls)	Effects	Comments Ranking tier
Klepp and Magnus 1979 Norway 1974–1975	hospital-based case-control	cases: 89 melanoma controls: 227 hospital controls with malignant lymphoma, testicular cancer, or bone or soft-tissue sarcoma The study was restricted to 78 cases and 131 controls from Oslo and surrounding areas because of differences in geographical distribution between cases and controls.	exposure to UV lamps (not clear whether sunbeds or sunlamps) assessed by questionnaire use of artificial light very rare % exposed not given	no difference between cases and controls	sunlamps not a major focus; no subgroup analysis poor exposure assessment, little exposure information, and sources of exposure not clear limited power due to rare use of lamps and small sample size possible selection bias because controls were cancer patients Tier 1
Adam *et al.* 1981 England 1971–1976	case-control	cases: 169 women with malignant melanoma controls: 503 women matched by age and marital status randomly selected from general practitioners response to questionnaire: 111 cases and 342 controls	sunlamp used assessed by postal questionnaire; other information assessed from medical records 8/3	use of sunlamps was low, but significantly higher in cases than controls ($P < 0.05$) calculated (not reported) crude OR = 2.9	sunlamps not a major focus; no subgroup analysis little exposure information limited power due to small sample size and low exposure rate Tier 2

Reference Study location Years cases accrued	Study design	Population	Exposure Percent exposed (case/controls)	Effects	Comments Ranking tier
Gallagher *et al*. 1986 Canada 1979–1981	population-based case-control	cases: 595 newly confirmed controls: 595 age- and sex-matched controls from insurance subscribers	exposure to sunlamps including frequency and duration; assessed by interview with a standardized questionnaire exposure characterized as moderate and relatively limited % exposed not given	no association between sunlamp use and melanoma (χ^2, NS) no association by gender or body site	sunlamps not a major focus; subgroup analysis by sex and body site, but nos. used for risk estimates not reported, and OR not calculated excluded lentigo maligna cases Tier 2
Holman *et al.* 1986 Australia 1980–1982	population-based case-control	cases: 511 preinvasive or invasive melanoma controls: 511 sex- and age-matched controls from electoral rolls or student rolls of public schools	exposure to sun and sunlamps assessed by structured questionnaire administered by nurse interviewers 9 overall	crude OR = 1.1 (0.6–1.8)	sunlamps not a major focus; no subgroup analysis because of small no. of exposed subjects Tier 2
Elwood *et al*. 1986 England 1981–1984	hospital-based case-control	cases: 83 malignant melanoma identified from pathology services of 2 hospitals controls: 83 age-, sex-, and residence-matched hospital controls (in or out)	home exposure to fluorescent lighting and the use of sunlamps average exposure = 2.3 h 18/14	no association with risk calculated (not reported) crude OR = 1.3	sunlamps not a major focus; no subgroup analysis little information on assessment of association; no risk estimate given limited power due to small sample size and short duration of exposure lentigo maligna melanoma excluded Tier 3

Reference Study location Years cases accrued	Study design	Population	Exposure Percent exposed (case/controls)	Effects	Comments Ranking tier
Holly *et al*. 1987 U.S. 1984–1985	case-control	cases: 121 consecutive melanoma patients at clinic controls: 139 sex- and age-matched patients at same clinic (not dermatology)	exposure to use of tanning salon assessed by questionnaire % exposed not given	melanoma patients similar to controls with respect to use of tanning salons	sunlamp use not a major focus; no subgroup analysis; no information on risk estimate (none given) very little exposure information. lentigo maligna melanoma excluded small sample size Tier 1
Zanetti *et al*. 1988 Italy 1984–1986	population-based case-control	cases: 208 histologically confirmed malignant melanoma from the regional tumor registry controls: 416 from National Social Service Registry	exposure to UVA lamps assessed by questionnaire 7/5	crude OR = 1.5 adjusted OR = 0.9 (0.4–2.0)	sunlamp use not a major focus; no subgroup analysis adjusted for age, hair color, skin reaction to the sun, sunburn in childhood, and education Tier 2

Reference Study location Years cases accrued	Study design	Population	Exposure Percent exposed (case/controls)	Effects	Comments Ranking tier
Osterlind *et al.* 1988 Denmark 1982–1985	population-based case-control	cases: 474 melanoma controls: 926 sex- and age-matched randomly selected from population registrar	exposure to sunlamps and sunbeds, including no. of uses (< or > 10), assessed with structured questionnaire at home interview sunbeds: 14/18 50% used < 10 times sunlamps: 45/42	sunbeds: crude OR = 0.7 (0.5–1.0) sunlamps: use not related to risk and risk not related to no. of uses	risk estimate for sunbeds given, but analysis by dose not stated sunlamp use evaluated by dose, but information on analysis and risk estimates not given somewhat limited power for sunbeds due to low percentage of individuals exposed in the higher exposure group (~7%–8% used sunbeds > 10 times) excluded lentigo maligna melanoma Tier 3
Swerdlow *et al.* 1988 Scotland 1979–1984	hospital-based case-control stratum	cases: 180 malignant melanoma from university depts. of dermatology and plastic surgery controls: 197 hospital in- and out-patients with various nonmalignant diseases, stratum-matched for age, sex, and city where treated	exposure to UV lamps and sunbeds, including ever use, duration, age at first exposure, and when exposure occurred (5 yr. before presentation) assessed by interview 21/8	ever use OR = 2.9 (1.3–6.4) exposure response for increasing duration ($P < 0.05$) greater risk for first use before age 30 (OR = 3.8) greater risk for use > 5 years before presentation (OR = 9.1) elevated risk for cancer on legs and trunk elevated risk for superficial spreading melanoma and nodular melanoma	sunlamps a major focus detailed exposure information and subtype analyses adj. for nevi, skin type, hair and eye color, and sun exposure cells small after stratification by duration or exposure characteristics Tier 4

Reference Study location Years cases accrued	Study design	Population	Exposure Percent exposed (case/controls)	Effects	Comments Ranking tier
MacKie *et al.* 1989 Scotland 1989–1987	hospital-based case-control	cases: 280 (181 women and 99 men) identified from registry controls: 280 age- and sex- matched hospital patients with non-dermatological illness	exposure to artificial sources of UV (classed as modern sunbeds or older sunlamps); exposure to sunbeds 1 or 2 times/wk for at least 12 wk artificial UV sources: 12/3 sunbed: M: 8/1 F: 10/3	artificial sources of UV: M: crude OR = 2.6 (0.9–7.3), adj. OR = 1.3 (0.2–7.9) F: crude OR = 1.5 sunbeds: calculated ORs (by 2 x 2 table) from nos. of exposed cases and controls M: crude OR = 8.6 F: crude OR = 3.8	sunlamps not a major focus; no subgroup analysis conditional regression method reported but details relating to matching not described limited power due to small no. of exposed cases adjusted ORs for nevi (total, atypical), freckling tendency, skin type, severe sunburn, tropical residence Tier 2
Beitner *et al*. 1990 Sweden 1978–1983	population-based case-control	cases: 523 incident malignant melanoma controls: 505 age- and sex-matched controls selected from population registry	exposure in solariums assessed by questionnaire % exposed not given	no increased risk with frequent exposure to solariums	sunlamps not a major focus; no subgroup analysis no information given with respect to risk estimate or no. of individuals exposed poor exposure assessment Tier 1

Reference Study location Years cases accrued	Study design	Population	Exposure Percent exposed (case/controls)	Effects	Comments Ranking tier
Walter *et al.* 1990 Ontario, Canada 1984–1986	population-based case-control	cases: 583 histologically confirmed controls: 608 randomly selected from tax rolls, matched for sex, age, and municipality	exposure, including ever use, year began, months of use, no. uses/wk, length of exposure, location, and parts of body exposed, assessed by interview with questionnaire M: 24/14 F: 28/21	ever use (crude OR): M: 1.9 (1.2–3.0) F: 1.5 (0.2–2.1) adj. did not change OR for either sex exposure-response for cumulative min. of use ($P < 0.01$) slightly greater risk for face, head, or neck than trunk; little risk for legs; greater risk for trunk in M than F ORs for histol. type: lentigo maligna and Hutchison's melanotic freckle: M = 2.4, F = 3.1 superficial spreading and *in situ*: M = 1.90, F = 1.4 nodular: M = 1.7, F = 1.4 greater risk for home use greater risk for first use before age 30 greater risk for 5 yr. since last use	detailed exposure information and subgroup analysis adj. for age, nevus density, skin color, skin reaction to sun, and socioeconomic status; adjusted analyses gave same effect as unadjusted analysis recreational sun exposure a possible confounder Tier 4

Reference Study location Years cases accrued	Study design	Population	Exposure Percent exposed (case/controls)	Effects	Comments Ranking tier
Dunn-Lane 1993 Ireland 1985–1986	hospital-based case-control	cases: 100 consecutive patients at 7 hospitals controls: 100 sex- and age-matched orthopedic hospital controls with limb injuries excluding sports injuries	exposure to sunlamps and sunbeds assessed by standard pre-coded questionnaire 17/15	17% cases and 15% controls used sunbeds; duration of use similar calculated (not reported) crude OR = 1.2	sunbeds not a major focus; some indication that duration was considered, but risk estimates not given and details on duration of use not described little exposure information limited power due to small sample size Tier 2
Garbe *et al.* 1993 Germany 1983–1990	case-control	cases: 1,079 melanoma patients from Central Malignant Melanoma Registry controls: 778 outpatients from dermatology clinics excluding patients with previous UV treatment for skin disorders, skin cancer, or nevi	exposure to sunbeds assessed by questionnaire and interview 8/7	adj. OR = 1.5 (0.9–2.4) for 885 cases and 705 controls with known information	sunlamps not a major focus; no subgroup analysis little exposure information low percentages with exposure (7.7, 7.1) adj. for no. of nevi, hair color, skin type, age, and participating center Tier 2

Reference Study location Years cases accrued	Study design	Population	Exposure Percent exposed (case/controls)	Effects	Comments Ranking tier
Autier *et al*. 1994 Europe 1991	population-based case-control	cases: 420 consecutive malignant melanoma patients controls: 447 controls in the same municipality, randomly chosen by a quota sampling method, with no skin cancer history	exposure assessed with respect to ever use, location of exposure, type of machine, duration of exposure session, year first used, no. of sessions, reason for use by interview and questionnaire 26/27	ever use: crude OR = 1.0 (0.7–1.3) for tanning purposes: crude OR for sunlamps = 1.8 (1.0–3.3) OR for 10+ h exposure for tanning purposes: first exposure before 1980: 2.1 (0.8–5.34) experience of sunburn: 7.4 (1.7–32.3)	detailed exposure information and subgroup analysis; adj. for age, sex, hair color, and no. of holidays wk spent in sunny resort; overall OR given only as crude insufficient follow-up for exposure occurring after 1980 Tier 4
Westerdahl *et al*. 1994 Sweden 1988–1990	population-based case-control	cases: 400 patients from South Swedish Health Care Region controls: 640 randomly selected from population registry matched by sex, age, and parish	exposure to sunbeds or sunlamps, including ever use and how often, assessed by comprehensive questionnaire 30/25	adj. OR: ever use: 1.3 (0.9–1.8) >10 uses: 1.8 (1.0–3.2) exposure response ($P < 0.06$) greater risk age < 30 yr: ever use: OR = 2.7 (0.7–9.8) use >10 times: OR = 7.7 (1–64) for use >10 times vs. none: greater risk for trunk (OR = 4.2) than head or extremities (OR = 1.1)	detailed exposure information (with respect to dose); subgroup analysis adj. for history of sunburn, hair color, raised nevi, and history of frequent summer sunbathing small cell numbers after stratifying by no. of uses and age Tier 4

Reference Study location Years cases accrued	Study design	Population	Exposure Percent exposed (case/controls)	Effects	Comments Ranking tier
Holly *et al*. 1995 U.S. 1981–1986	population-based case-control	cases: 452 women with melanoma controls: 930 age-matched women in the same counties identified by random-digit dialing	ever use sunlamps (medical or cosmetic); how many times in life (excluding last 3 yr) 37/38	OR for exposure category: lower: 0.9 higher: 1.1 no difference or elevation in risk due different histologic types of melanoma	some subgroup analysis on no. of uses but no definition of lower and higher categories; subgroup analysis calculated for histologic type both medical and cosmetic exposure included Tier 3
Chen *et al*. 1998 U.S. 1/15/87	population-based case-control	cases: 624 newly diagnosed malignant melanoma controls: 512 sex- and age-matched community controls selected by random-digit dialing	sunlamp use assessed by nurse-interviewers with a structured questionnaire and classified by type, year first used, and location, as well as information on potential confounders 23/19	OR for ever use: crude = 1.3 (1.0–1.7) adj. = 1.13 (0.8–1.5) no relationship between risk and total no. of uses age at first use < 25 yr: adj. OR = 1.4 (0.9–2.1) no signif. increased risk for any type of sunlamp used > 2 types of lamp: adj. OR = 3.5 (1.3–9) adj. OR for location: home: 1.4 (1–2) commercial 0.8 (0.5–1.3) used before 1970: adj. OR = 1.3 (0.8–2.1)	sunlamps major focus of study; detailed exposure assessment, including attempt to define type of lamp used; detailed analysis adj. for phenotype index (hair and eye color, skin type or tanning ability) and recreational sun exposure insufficient follow-up time for later exposures Tier 4

Reference Study location Years cases accrued	Study design	Population	Exposure Percent exposed (case/controls)	Effects	Comments Ranking tier
Walter *et al*. 1999 Ontario, Canada 1984–1986 reanalysis of Walter *et al.* 1990	population-based case-control	cases: 583 newly diagnosed (1984–1986), histologically confirmed controls: 608 selected from property tax assessment and chosen to match the case distributions with respect to age, sex, and municipality of residence	exposure to sunlamp use, including year, duration, location, and part of body exposed, assessed by in-person interview with a structured questionnaire 26/18	OR for ever use: crude = 1.6 (1.2–2.2) adj. = 1.5 (1.2–2.1) no difference in risk by body location risk for lentigo maligna highest: OR = 2.8 (1.4–5.3); risk signif. for superficial spreading and *in situ*: OR = 1.5 (1.1–2.0); elevated for all types no difference in risk by skin reaction, but signif. elevated only for burners (larger sample size) no difference by age at diagnosis	good exposure assessment; detailed analysis adj. for sex, age, skin sun response potential confounder is recreational sun exposure Tier 4

Reference Study location Years cases accrued	Study design	Population	Exposure Percent exposed (case/controls)	Effects	Comments Ranking tier
Westerdahl *et al*. 2000 Sweden 1995–1997	population-based case-control	cases: 571 malignant melanoma from the population-based Regional Tumor Registry in South Swedish Health Care Region controls: 913 selected by random sampling and matched by sex, age, and parish	exposure to sunbeds, including ever use, regular use, exposure time, no. of times/wk, no. of wk/yr, location, season, age at first and last use, assessed by comprehensive questionnaire 44/41	OR for regular use: crude = 1.6 (1.1–2.4) adj. = 1.8 (1.2–2.7) use at age < 35: OR = 2.3 use at age >35: OR = 1.6 F: OR = 2.1 M: OR = 1.3 darker hair: OR = 2.3 light hair: OR = 1.5 commercial: OR = 2.2 home: OR = 1.5 risk greater for use in winter; small sample size in summer, OR < 1 greater risk individuals aged < 36 risk greatest for lesions of extremities, then trunk; no risk for face; in M, no risk for upper extremities exposure response up to 250 total uses or 15 uses/yr, after which the ORs decreased test for trend, times/yr, 0.06, total uses, 0.26	detailed exposure information and analysis adj. for hair color, skin type, raised nevi, no. of sun exposures not adj. for recreational sun exposure; however, controlling for nevi may take this into account, since they are related to both sun exposure and skin type Tier 4

Table 3-2. Recent epidemiologic studies of the relationship between cancer and medically related UV exposure

Reference Study location	UVR treatment Type of cancer	Study design	Population	Exposure	Effects	Adjustments Potential confounders
Stern *et al*. 1998 U.S.	PUVA basal-cell and squamous-cell carcinoma	cohort multicenter prospective	1,380 psoriasis patients enrolled in 16-university center study from 1/1/75 to 10/1/76 followed-up until 9/1/97 65% males 1,042 basal-cell 1,422 squamous-cell mean age 44 PUVA Follow-up Study	psoralen 0.4–0.6 mg/kg orally, followed by UVA, usual dose 8–15 J/cm^2 4 PUVA dose categories, based on no. of treatments: < 100, 100–159 160–336, > 337 interview, documentation of PUVA therapy and other treatments for psoriasis	squamous-cell carcinoma: overall RR = 17.6 (15.6–19.8); dose-related; substantial risk at all doses high dose adj. for other therapies: RR = 8.6 (4.9–15.2) basal-cell carcinoma: overall RR = 4.1 (3.7–4.6); dose-related; substantial risk only at highest dose high dose adj. for other therapies: RR = 4.7 (3.1–7.3) reference group: PUVA < 100 treatments (low dose)	overall analysis not adj. for other therapies; multivariate analysis for different dose groups adj. for therapies as well as age, sex, area of residence, and anatomic site no psoriasis controls; surveillance bias
Stern *et al*. 1997 U.S.	PUVA melanoma	cohort PUVA Follow-up Study (above)	follow-up until 2/29/96 controls: U.S. population (SEER)	two exposure groups based on no. of treatments: low < 250 high > 250	11 melanoma RR = 2.3 (1.1–4.1) 1975–1990: 4 melanoma RR = 1.1 (0.3–2.9) 1990–1996: 7 melanoma RR = 5.4 (2.2–11.0)	SEER incidence rates used for expected no psoriasis controls; surveillance bias

Reference Study location	UVR treatment Type of cancer	Study design	Population	Exposure	Effects	Adjustments Potential confounders
Lindelof *et al*. 1999 Sweden	PUVA melanoma	cohort multicenter prospective	4,799 patients treated with PUVA at 11 centers 64% psoriasis patients mean follow-up: M 15.9, F 16.2 subcohort of 1,867 followed 15–21 yr	information obtained from patient's records at each center. 77% received oral PUVA. UVA dose varied by disease; average dose for psoriasis patients 400–600 J/cm^2 45 patients received > 400 treatments 537 patients received > 1,000 J/cm^2	entire cohort, RR: melanoma: M: 1.1 (0.5–2.2, n = 8) F: 1.1 (0.4–2.3, n = 7) squamous-cell carcinoma: M: 5.6 (4.4–7.1, n = 68) F: 3.6 (2.1–5.8, n = 17) subcohort, RR: no excess melanoma squamous-cell carcinoma: M: 8.1 (6.1–10.6) F: 6.4 (3.3–11.2)	other therapies no psoriasis controls surveillance bias
Hannuksela-Svahn *et al*. 2000 Finland	UVB squamous-cell carcinoma non-Hodgkin's lymphoma	cohort nested case-control	5,687 psoriasis patients from 1973–1984 PUVA Finnish Cancer Registry follow-up until 1/31/1995 nested study: 67 cases, 199 age- and sex-matched controls chosen from cohort using density sampling principle	exposure assessed from patients' files percent exposed (cases/controls): squamous-cell carcinoma: 70/46 non-Hodgkin's lymphoma: 16/47 laryngeal cancer: 55/38	RR for UVB treatment: squamous-cell carcinoma: 1.6 (0.4–6.4) non-Hodgkin's lymphoma: 0.1 (0.0–0.8)	other therapies small number of cases in nested case-control study

Table 3-3. Recent epidemiologic studies of the relationship between cancer and occupational UV exposure

Reference	UV exposure Type of cancer	Study design	Population	Exposure Percent exposed (cases/ controls)	Effects	Adjustments Potential confounders or limitations
Walter *et al*. 1992 Sweden	fluorescent lighting melanoma	population-based case-control	same population used for sunbeds (Walter *et al*. 1999)	interview: various exposures to solar and nonsolar UVR, residential and occup. use of fluorescent lamps, potential confounders occup. use validated with employers, residential use validated by mail surveys occup. exposed 10 yr ago: M: 77/70 F: 56/56	occupational exp.: M: OR = 1.47 (0.98–2.14) for exp. 10 yr ago, dose-related for yr of cumulative exposure F: OR = 1.06 (0.76–1.48) for exp. 10 yr ago, no dose-response domestic exp.: consistent risk in M but not F for various indices of exposure	adj. for socioeconomic status, sun exp.; most results not altered by adj. for risk factors (history of sunburn, socioeconomic status, occupational sun exp.) fluorescent lighting is ubiquitous retrospective assessment

Reference	UV exposure Type of cancer	Study design	Population	Exposure Percent exposed (cases/ controls)	Effects	Adjustments Potential confounders or limitations
Bajdik *et al*. 1996 Alberta, Canada	nonsolar UVR basal-cell and squamous-cell carcinoma	population-based case-control	cases (1983–1984), 180 squamous-cell 226 basal-cell from Alberta Cancer Registry 406 aged-match controls from Alberta health insurance plan subscriber list	Interview: job history, outdoor exposure, fluorescent lighting, other measures of UV exposure, confounders welding: squamous-cell carcinoma: 31/26 basal-cell carcinoma: 28/26 other exposures: < 10	no increased risk of from nonsolar UVR exposures (e.g., fluorescent lights, welding torches, UV lamps)	small no. of exposed individuals except for fluorescent lights and welding insufficient follow-up exposure misclassification
Holly *et al*. 1996 Western U.S.	cccupational uveal melanoma (intraocular)	population-based case-control	221 cases 1978–1987 447 controls from population within 5-yr age group white males	interview: potential confounders and occup. history 18/11	welding: adj. OR = 2.2 (1.3–3.5), no dose relationship	adj. for age, no. of nevi, eye color, and skin response not adj. for solar radiation exp.

4 Studies of Cancer in Experimental Animals

The IARC reviewed carcinogenicity studies of UVR in rats, mice, and hamsters. The animals were tested with broad-spectrum UVR or with discrete UVA, UVB, or UVC or a combination of these for carcinogenic effects on the skin and eye (IARC 1992; Appendix A).

4.1 Broad-spectrum UVR

4.1.1 Rats

The carcinogenic potential of UVR was recognized from the observation that daily irradiation of six albino rats with broad-spectrum UVR from a mercury-vapor lamp at a distance of 18 inches (46 cm) for one minute, three times a week, resulted in the formation of skin tumors (papillomas) in one rat (Findlay 1930, cited in IARC 1992). Six hundred rats were exposed to solar radiation for an average of five hours a day (exposure around solar noon in the summer was avoided). About 60% of the rats died from sunstroke. Of the 235 surviving rats, 70% developed tumors on the ears, eyes, nose, tail, neck, or paws. Squamous-cell carcinoma and spindle-cell sarcoma were the predominant tumor types. In complementary experiments, rats exposed to filtered sunlight did not develop tumors, but all 150 rats exposed to quartz mercury lamps developed tumors (types and sites unspecified) (Roffo 1934, cited in IARC 1992). Subsequent studies in which 2,000 white rats were exposed to sunlight yielded similar results (Roffo 1939, cited in IARC 1992). The IARC Working Group concluded that these studies provided adequate evidence of carcinogenicity in rats for UVR from sunlight.

In other studies, tumors (papillomas, squamous-cell carcinomas, and occasionally basal-cell carcinomas) were detected in rats (strain not specified) that were almost continuously exposed to broad-spectrum UVR from a quartz mercury lamp for 11 months (Putschar and Holz 1930, cited in IARC 1992). Squamous-cell carcinomas and, rarely, spindle-cell carcinomas and sarcomas, round-cell carcinomas, and basal-cell carcinomas of the skin were seen in 20 rats (strain unspecified) exposed for up to 10 months to broad-spectrum UVR from a mercury-vapor burner at a distance of 75 cm (Hueper 1942, cited in IARC 1992). Two of seven white rats exposed to UVR from a solar lamp, for two hours a day, six days a week, for a year or more, developed spindle-cell sarcomas of the eye (Huldschinsky 1933, cited in IARC 1992). Freeman and Knox (1964, cited in IARC 1992) exposed 66 pigmented and 12 unpigmented rats to UVR from mercury lamps, five days a week, for one year. The doses per session corresponded to approximately 1 MED. A total of 98 eye tumors developed. About two-thirds of the tumors were fibrosarcomas, and the rest were hemangioendotheliomas.

4.1.2 Mice

Daily irradiation of mice with broad-spectrum UVR from a mercury-vapor lamp at a distance of 18 inches (46 cm) for one minute, three times a week, resulted in the formation of skin papillomas within eight months (Findlay 1930, cited in IARC 1992). An unspecified number of mice exposed to sunlight developed squamous-cell carcinomas and spindle-cell sarcomas of the ear, eyes, paws, tail, and nose (Roffo 1939, cited in

IARC 1992). The IARC Working Group concluded that these studies provided adequate evidence of carcinogenicity in mice for UVR from sunlight.

A strain mice were exposed to broad-spectrum UVR at weekly doses of 3.6 to 43×10^7 ergs/cm^2 (40 to 430 kJ/m^2); 5% developed skin and eye tumors (spindle-cell sarcomas or fibrosarcomas, mostly in the cornea) and hemangioendotheliomas (Blum and Lippincott 1942, Lippincott and Blum 1943, Grady *et al.* 1943, all cited in IARC 1992). Of more than 600 A strain mice exposed to daily doses of broad-spectrum UVR at 0.32 to 8.6×10^7 ergs/cm^2 (3 to 86 kJ/m^2) from unfiltered medium-pressure mercury arc lamps, over 90% developed skin tumors, mainly on the ears, the only site for which quantitative data were provided (Blum 1959, cited in IARC 1992).

More recent studies, mostly in mice, provide additional evidence for the carcinogenicity of broad-spectrum UVR (Emmett 1973, Urbach *et al.* 1974, Epstein 1978, 1985, Kripke and Sass 1978, WHO 1979, van der Leun 1984, Forbes *et al.* 1982, Staberg *et al.* 1983, Young *et al.* 1990, Menzies *et al.* 1991, all cited in IARC 1992).

4.1.3 Hamsters

Hemangioendotheliomas and fibrosarcomas developed in 14 eyes in a group of 19 hamsters (nine pigmented, 10 unpigmented) that were exposed to broad-spectrum UVR from mercury lamps at 50 cm from the skin, five days a week, for one year (Freeman and Knox 1964, cited in IARC 1992).

4.1.4 Guinea pigs

No tumors were found in the eyes of 17 guinea pigs that were exposed to broad-spectrum UVR from mercury lamps at 50 cm from the skin, five days a week, for one year (Freeman and Knox 1964, cited in IARC 1992).

4.1.5 Other species

Several researchers have reported skin and eye tumors in domestic animals (cows, goats, sheep, cats, dogs, horses, and swine) following exposure to sunlight (Emmett 1973, Dorn *et al.* 1971, Madewell *et al.* 1981, Nikula *et al.* 1992, all cited in IARC 1992).

Monodelphis domestica, a South American opossum that is unusually prone to photoreactivation, developed actinic keratoses and skin tumors (mostly fibrosarcomas and squamous-cell carcinomas) following exposure to broad-spectrum UVR from a Westinghouse FS-40 sunlamp (280 to 400 nm) (Ley 1985, Ley *et al.* 1987, both cited in IARC 1992). In a later study, 40 opossums (19 male and 21 female) were exposed to broad-spectrum UVR (FS-40 sunlamps, 280 to 400 nm) at a dose of 250 J/m^2, three times weekly, for 70 weeks, and 29 control opossums (14 male and 15 female) were exposed to fluorescent lamps emitting primarily visible light (Kusewitt *et al.* 1991). Both groups of animals had their backs shaved and were housed under red lights to prevent photoreactivation. The UVR-exposed opossums developed a variety of hyperplastic and neoplastic skin lesions on the backs and on a single ear; 20 developed skin tumors (50%), and 13 (32.5%) had more than one tumor. Tumors included 25 papillomas, four keratoacanthomas, seven carcinomas *in situ*, three microinvasive squamous-cell

carcinomas, two invasive squamous-cell carcinomas, one basal-cell tumor, 10 dermal spindle-cell tumors, two benign melanomas, and one malignant melanoma. No skin tumors were observed in the control animals.

4.1.6 Action spectra

The action spectrum for tumor induction in SKH1 albino hairless mice was studied from a database containing information for approximately 1,100 mice treated with 14 different broadband UVR sources with spectral ranges from mainly 254 nm (from a Philips TUV germicidal lamp) to > 400 nm (from a Philips Xe3.0 fluorescent lamp) (de Gruijl *et al.* 1993). UVB at 293 nm was most effective in inducing tumors. However, because of a lack of data, the action spectrum for longer-wavelength UVA (340 to 400 nm) was much less well defined. A follow-up study showed that radiation from a custom-made Philips 365-nm source was carcinogenic in hairless mice but was a factor of 10^{-4} less effective than UVB at 293 nm. UVA radiation at 365 nm induced the same types of skin tumors as UVB exposure (mainly squamous-cell carcinomas and precursor lesions) (de Laat *et al.* 1997).

4.2 Primarily UVA

Numerous experiments have been performed to assess the carcinogenicity of UVA (reviewed in IARC 1992). A large percentage of these studies, conducted primarily in hairless mice, did not detect tumors. The IARC Working Group noted that the doses of radiation (generally in the daily dose range of 160 kJ/m^2) may have been too small, or exposure periods may have been too short. In other experiments, tumors clearly were induced by radiation purported to have been UVA, but the IARC Working Group noted that efforts to eliminate all UVB were likely insufficient. The studies reviewed below were considered to have controlled for the presence of UVB (IARC 1992).

4.2.1 Mice

Groups of 24 male and female SKH1 albino hairless mice were exposed to UVA from a bank of Philips TL40W/09 fluorescent tubes filtered through a 10-mm glass plate that strongly absorbed UVB. Animals were exposed 12 hours a day, seven days a week, for approximately one year. The daily dose was 220 kJ/m^2. Most animals developed scratching lesions before they developed skin tumors. All animals had skin tumors, with a median time to appearance of 265 days. Larger lesions were examined microscopically (selection criteria not disclosed). Of the lesions examined, 60% were classified as squamous-cell carcinomas, 20% as benign tumors, and 20% as mild cellular and nuclear atypia. These lesions were similar to those observed in a parallel experiment with UVB, but the tumor latency period in the UVA-exposed animals was longer (van Weelden *et al.* 1986, 1988, cited in IARC 1992). However, residual UVB radiation was not believed to be responsible for the effect because more than 100,000 times the actual amount of residual UVB present would have been required to induce the observed tumor rate.
Groups of 48 male and female SKH1 albino hairless mice were exposed to UVA (> 340 nm) at 220 kJ/m^2, for two hours per day, seven days per week, for up to 400 days. Radiation was generated from mercury metal iodide lamps and passed through liquid filters. UVB was effectively eliminated from the radiation. Most of the animals developed skin tumors, and 31 exhibited tumors before any observed scratching. The

largest tumors (15/20) were examined microscopically and were classified as squamous-cell carcinomas (Sterenborg and van der Leun 1990, cited in IARC 1992).

In several studies, mice were exposed to UVR sources from which UVB was excluded so vigorously that shorter-wavelength UVA (315 to 340 nm) also was excluded; most of the animals developed squamous-cell carcinomas. In these experiments, exposure was mainly to wavelengths in the region of 340 to 400 nm (van Weelden *et al*. 1988, 1990, Sterenborg and van der Leun 1990, all cited in IARC 1992).

In one of these studies, when female SKH1 mice were exposed to filtered UVR (340 to 400 nm) at daily doses of 360 and 600 kJ/m^2, 19/44 mice surviving at 18 weeks had skin tumors (mostly papillomas). At week 100, 22 surviving mice had 40 tumors, many of which were considered clinically to be squamous-cell carcinomas (it was not clear whether microscopic examination was used in classifying tumors) (Kligman *et al.* 1990, 1992, both cited in IARC 1992).

The carcinogenicity of short-wavelength UVA (315 to 340 nm) was investigated in a study using fluorescent tubes with peak emission near 330 nm and filtering UVB with glass. Groups of 24 male and female SKH1 mice were exposed to average daily doses of 20 or 56 kJ/m^2, seven days per week, for 650 days. All mice in the high-dose group had multiple tumors, initially classified as mainly papillomas, but later as predominantly squamous-cell carcinomas. In the lower-dose group, three mice had skin tumors, all of which were papillomas (Kelfkens *et al.* 1991, cited in IARC 1992).

Bech-Thomsen (1997) investigated the carcinogenic effects of various UVA and UVR sources and their interactions in a series of studies with female C3H/Tif lightly pigmented hairless mice. In the first study (Bech-Thomsen *et al*. 1988), 200 mice were exposed to UVA (341 to 400 nm) from a filtered source at 150 to 200 kJ/m^2, six days a week, for four weeks. No skin tumors were observed during the 57-week observation period (total dose = 4,050 kJ/m^2). Among mice exposed to broad-spectrum UVR (UVA, UVB, and < 1% UVC) for 13 and 26 weeks, 35% and 88%, respectively, developed tumors by 57 weeks. Exposure to UVA (for four weeks at 4,200 KJ/m^2) before exposure to broad-spectrum UVR (for 13 or 26 weeks) significantly delayed tumor development.

In subsequent studies, exposure of female C3H/Tif mice to UVA, alone or before or after exposure to broad-spectrum UVR, increased the incidence of tumors. In one study (Bech-Thomsen *et al.* 1991), mice were divided into 14 groups of 20 animals each, and three UVA sources, emitting varying amounts of UVB, were used either alone or before irradiation with simulated solar (broad-spectrum) UVR. All UVA exposures were for 20 minutes a day, five days a week, for 13 to 98 weeks. Exposure to broad-spectrum UVR was for 10 minutes a day, four days a week, for the lifetimes of the animals. One control group was not exposed to any UVR source, and one control group was exposed to broad-spectrum UVR only. All three UVA sources induced skin tumors. Of the 260 irradiated mice, 232 developed tumors; 230 developed multiple tumors that later fused by growth. Pre-irradiation with UVA sources with relatively high UVB outputs enhanced the carcinogenic effect of broad-spectrum UVR. The carcinogenic potential of UVA sources was directly related to their emission below 320 nm. In a follow-up study, Bech-Thomsen

et al. (1992) administered UVA radiation alone or after 12 weeks of exposure to broad-spectrum (simulated solar) UVR. This study demonstrated that a UVA source with a low carcinogenic potential could significantly increase the carcinogenic effect of broad-spectrum UVR.

Bech-Thomsen and Wulf (1993) also investigated whether the carcinogenic potential of UVA sources could be estimated from the International Commission on Illumination (CIE) human erythema action spectrum, which is used worldwide to assess the risk from UVR-emitting appliances used in the home. Two groups of 40 C3H/Tif mice were exposed to broad-spectrum UVR (with a UVB output of 16.7%) for 84 days. Subsequently, each group was exposed to one of two commercial UVA sources with different levels of UVB emissions (2.2% and 6.9%). After pre-irradiation with identical broad-spectrum UVR, exposure to the same erythemogenic dose from the differing UVA sources resulted in similar times to tumor development. An inverse relationship between the daily exposure dose and the tumor induction time was noted, whether the UVA was administered alone or after broad-spectrum UVR exposure. These researchers concluded that the CIE erythema action spectrum could be used to compare the carcinogenic potential of different UVR sources. The results of the Bech-Thomsen studies are summarized in Tables 4-1 and 4-2.

Table 4-1. Tumor incidences in female C3H/Tif mice exposed to UVA tanning sources with differing UVB emission levels

Daily dose (kJ/m^2)		Duration (weeks)	Tumor incidence	Reference
UVA[a]	UVB[b]			
121	8.9	41	20/20	Bech-Thomsen and Wulf 1993, Bech-Thomsen *et al.* 1991
81	6	59	21/21	Bech-Thomsen and Wulf 1993
245	5.5	75	19/20	Bech-Thomsen and Wulf 1993, Bech-Thomsen *et al.* 1991
162	3.6	86	13/20	Bech-Thomsen and Wulf 1993
289	0.6	98	6/20	Bech-Thomsen and Wulf 1993, Bech-Thomsen *et al.* 1991
21	0.5	88	1/22	Bech-Thomsen and Wulf 1993
199	0.4	97	1/20	Bech-Thomsen and Wulf 1993
82	6.1	47	20/20	Bech-Thomsen *et al.* 1992
163	3.7	74	13/20	Bech-Thomsen *et al.* 1992
199	0.4	85	1/20	Bech-Thomsen *et al.* 1992

[a]281–320 nm; [b]321–400 nm.

Table 4-2. Tumor incidences in female C3H/Tif mice exposed to broad-spectrum UVR and/or UVA

Total dose (kJ/m^2)		Exposure regimen	Duration (weeks)	Tumor incidence
UVA[a]	UVB[b]			
4,050	0	UVA 4 wk	57	0/24
710	230	UVR 13 wk	54	8/23
4,760	230	UVA 4 wk, UVR 13 wk	57	0/25
1,410	460	UVR 26 wk	29	22/25
5,670	480	UVR 3 d, UVA 3.5 wk, UVR 26 wk	38	23/25
4,260	20	UVR 3 d, UVA 3.5 wk	57	0/25

Source: Bech-Thomsen *et al.* 1988
[a]321–400 nm; [b]281–320 nm.

4.2.2 Other species

4.2.2.1 Opossums

M. domestica developed non-melanoma skin tumors or melanocytic hyperplasia (a melanoma precursor lesion) following exposure to UVA (Ley 1997). Thirty dorsally shaved *M. domestica* were exposed three times a week for 81 weeks to 25,000 J/m^2 of UVA radiation from filtered F40BLB fluorescent lamps (black lights). The incidences of non-melanoma skin tumors and melanocytic hyperplasia were 4% and 22%, respectively, in the exposed animals. These data suggest that the action spectra for the induction of melanoma and non-melanoma skin tumors are different.

4.2.2.2 Fish

Heavily pigmented backcross hybrids of the genus *Xiphophorus* (cross between platyfish and swordtails) are very sensitive to melanoma induction by UVR. Groups of six-day-old fish were irradiated with narrow-wavelength bands at 302, 313, 365, 405, and 436 nm and scored for melanomas four months later. Two groups of controls were used because the researchers realized that the initial control group was exposed to some ambient UVA and visible radiation. This could explain the high incidence of melanoma in the first control group. The second control group was kept under subdued yellow light for two months and had a much lower incidence of melanoma. The action spectrum (sensitivity per incident photon as a function of wavelength) for melanoma induction showed appreciable sensitivity at 365, 405, and probably 436 nm (Setlow *et al.* 1993). The tumor incidence for each wavelength is shown in Table 4-3.

Table 4-3. Incidences of melanoma in hybrid fish (*Xiphophorus*) exposed to various wavelengths of UVR

Wavelength (nm)	No. of exposure levels	No. of fish	No. of fish with melanoma (%)
Control[a]	–	124	30 (24.2)
302	4	123	37 (30.1)
313	4	124	46 (37.1)
365	6	85	38 (44.7)
Control[b]	–	20	1 (5.0)
405	4	61	18 (29.5)
436	2	21	5 (23.8)

Source: Setlow *et al.* 1993

[a]Controls were in ambient light in shaded greenhouse for the following irradiations: 313 nm, 7 of 9 at 302 nm, 7 of 9 at 365 nm, and 2 of 5 at 405 nm.

[b]Controls were in covered tanks for 2 months for the following irradiations: 436 nm and for 3 of 5 at 405 nm.

4.3 Primarily UVB

4.3.1 Rats

Skin-tumor induction was studied in a group of 40 (shaved) female NMR rats, eight to 10 weeks old at the initiation of the experiment. Animals were irradiated for 60 weeks (duration and frequency of exposures were not specified) at a distance of 37.5 cm from a commercial sunlamp emitting mainly UVB. Weekly doses of radiation were described as being 5.4 to 10.8×10^4 J/m^2. A total of 25 skin tumors, most of which were papillomas of the ears, developed in 16/40 animals (Stenbäck 1975, cited in IARC 1992).

4.3.2 Mice

Several studies have clearly indicated in albino mice a dose-response to UVB in the development of skin tumors. Forbes *et al.* (1981, cited in IARC 1992) demonstrated a dose-response relationship in the time to onset of skin tumors in SKH1 albino hairless mice exposed to UVB. Groups of 24 male and female mice, six to eight weeks old, were exposed to sunlamps emitting mainly UVB (< 1% below 280 nm; two-thirds from 280 to 320 nm, and one-third above 320 nm). Animals were irradiated five days per week, for up to 45 weeks. Although the duration of daily exposures was not stated, the daily dose of radiation was computed. Time to onset of skin tumors is summarized in Table 4-4.

Table 4-4. Dose-response to (mainly) UVB in SHH1 albino hairless mice.

Daily dose (J/m^2)	Weeks to 50% tumor incidence	Week terminated
420	38.6	45
587	33.3	45
822	29.2	45
1,152	20.0	36
1,613	17.6	36
2,259	12.9	25

Source: Forbes *et al.* 1981, cited in IARC 1992

All animals eventually developed at least one skin tumor, with an inverse-dose-related latency for the appearance of skin tumors in 50% of the animals in the exposure groups. Tumors > 4 mm in diameter tended to be squamous-cell carcinomas, and tumors 1 to 4 mm formed a continuum from carcinoma *in situ* to squamous-cell carcinoma. Tumors < 1 mm in diameter were epidermal hyperplasia and squamous metaplasia, tending toward carcinoma *in situ.* Fibrosarcomas accounted for less than 1% of the tumors.

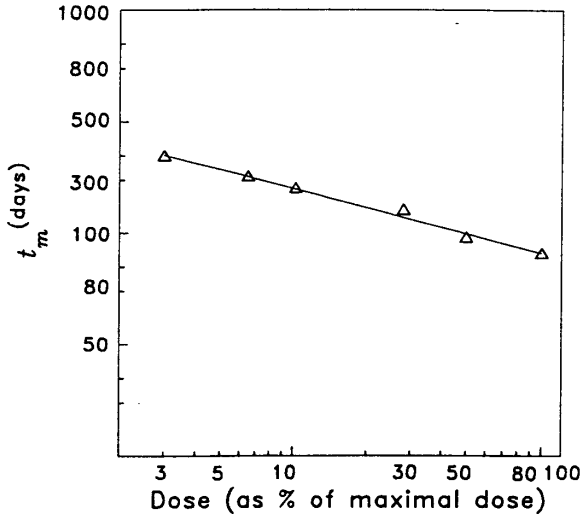
In a similar experiment, six groups of 22 to 44 male and female SKH1 albino hairless mice were exposed to mainly UVB at daily doses ranging from 57 to 1,900 J/m^2 (de Gruijl *et al.* 1983, cited in IARC 1992). Although the highest dose tested was not sufficient to induce erythema, most animals in the study developed skin tumors. There was a clear dose response in the time required for 50% of the animals to develop skin tumors (Figure 4-1). Squamous-cell carcinomas developed in 71% of the mice in the lowest dose group, while only two skin tumors were observed in 24 nonirradiated control mice.

4.3.3 Hamsters

Stenbäck (1975, cited in IARC 1992) irradiated 40 shaved female Syrian golden hamsters, eight to 10 weeks of age at the initiation of the experiment, with mainly UVB. Weekly doses of radiation were 5.4 to 10.8×10^4 J/m^2. A total of 30 skin tumors were observed in 14/40 animals, of which 22 were papillomas (14 animals), four were keratoacanthomas (three animals), one was a squamous-cell carcinoma of the skin, and three were papillomas of the ear (all in one animal).

4.3.4 Guinea pigs

Stenbäck (1975, cited in IARC 1992) irradiated shaved guinea pigs with mainly UVB. Weekly doses of radiation were 5.4 to 10.8×10^4 J/m^2. Only 2/25 animals had skin tumors (a fibroma in one animal and a trichofolliculoma in the other).



Source: de Gruijl *et al.* 1983, cited in IARC 1992

Figure 4-1. Dose-effect relationship for the induction of < 1-mm skin tumors in hairless mice by exposure to UVB over a wide range of daily doses; t_m = median induction time

4.3.5 Other species

4.3.5.1 Opossums

M. domestica developed actinic keratoses, fibrosarcomas, and squamous-cell carcinomas following exposure to a UVR sunlamp (280 to 400 nm). In another study, opossums were shaved and exposed three times per week for 70 weeks to 250 J/m^2 of mainly UVB radiation with relative emissions of 0.04, 0.27, 0.69, 1.0, or 0.09 at wavelengths of 280, 290, 300, 313, or 360 mm, respectively. Melanomas were observed in 5/13 exposed animals and melanocytic hyperplasia in 8/13 exposed animals (Ley *et al.* 1989, cited in IARC 1992). In a subsequent study (Ley 1997), 30 dorsally shaved *M. domestica* were exposed three times a week for 81 weeks to 250 J/m^2 of UV radiation from FS-40 sunlamps (approximately 150 J/m^2 of UVB radiation). The incidences of non-melanoma skin tumors and melanocytic hyperplasia in exposed animals were 71% and 31%, respectively. Although the incidence of non-melanoma skin tumors was significantly higher than observed in opossums exposed to UVA, the incidence of melanocytic hyperplasia was similar to that in UVA-exposed animals (see Section 4.1.5).

4.3.5.2 Fish

Melanocytic neoplasms were induced in a group of 460 hybrid fish (*Xiphophorus*), following exposure to mainly UVB from FS-40 sunlamps. The sunlamps were filtered with acetate sheets transmitting > 290 nm or > 304 nm at various doses (150 or 300 J/m^2 per day for > 290 nm; 850 or 1,700 J/m^2 per day for > 304 nm) for 1 to 20 consecutive days. Melanocytic tumors were found in 19% to 40% of the exposed fish. Of 103 controls

from the two parent strains, 13% and 2% developed these tumors (Setlow *et al.* 1989, cited in IARC 1992).

4.4 Primarily UVC

No studies were found in which animals were exposed solely to UVC. In the studies reviewed below, the source of UVC was a low-pressure mercury discharge germicidal lamp, which emitted 90% to 95% of its radiation at 254 nm, but also emitted significant amounts of UVB, UVA, and visible light.

4.4.1 Rats

Nine groups of six to 12 male CD-1 rats, 28 days of age, were shaved and exposed to varying doses of UVC from a germicidal lamp (Strickland *et al*. 1979, cited in IARC 1992). The dose range was 0.08 to 26.0×10^4 J/m^2. Exposure duration was not specified. Survival ranged from 75% to 92% in the experimental groups. Keratoacanthoma-like skin tumors developed at a yield that was approximately proportional to radiation throughout the dose range of 0.65 to 26.0×10^4 J/m^2. No tumors were observed at or below 0.32×10^4 J/m^2.

4.4.2 Mice

A group of 40 female C3H/HeNCrlBr mice was exposed to radiation from germicidal lamps at a weekly dose rate of 3 x 10^4 J/m^2. The duration of the experiment was not specified. Three animals died without tumors at experimental weeks 9, 43, and 63. All other animals had tumors, with 97% of the mice affected by 52 weeks. The median time to tumor onset was 43 weeks, and the mean number of tumors per tumor-bearing animal was 2.9. Microscopic examination revealed that of the 83 lesions initially considered to be tumors, 66 were squamous-cell carcinomas, 10 were proliferative squamous-cell lesions, and six were invasive fibrosarcomas (Lill 1983, cited in IARC 1992). The IARC Working Group noted that the 4% UVB content of the radiation source provided a weekly dose of 1,170 J/m^2, which could not be excluded as a contributing factor in the induction of skin tumors (IARC 1992).

Groups of 24 male and female SKH1 albino hairless mice, 6 to 10 weeks of age, were exposed to UVC from germicidal lamps seven days per week, for 75 minutes per day, at a dose of 230, 1,460, or 7,000 J/m^2. The highest dose applied was 60% lower during the initial seven days of the experiment. A total of 65 squamous-cell carcinomas of the skin were found. The numbers of animals with tumors were not reported, but the investigators noted that both the numbers of animals with tumors and the numbers of tumors per mouse were strongly dose-related (Sterenborg and van der Leun 1988, cited in IARC 1992). By comparing tumor incidences and onset times in their own UVC experiment to those from experiments with UVB, Sterenborg and van der Leun (1988, cited in IARC 1992) concluded that the UVB emitted from the germicidal lamp was insufficient to cause the tumors observed in their experiment. They estimated that the UVB present would require at least 850 days of exposure to induce skin tumors at the rate at which they had observed tumors after 161 days of exposure to the UVC. Further, they noted a qualitative difference between UVC- and UVB-induced skin tumors in mice, in that UVC-induced tumors were scattered more widely over the skin than were tumors

associated with UVB. Also, the dose-response curve was steeper in UVB-exposed mice than in mice exposed to the germicidal lamp radiation. The IARC Working Group noted that the observations given to exclude UVB as a causative factor in skin tumorigenesis did not rule out a possible interaction between the two types of radiation (IARC 1992).

4.5 Cancer development in human-mouse chimera models

Several researchers investigated UV-induced skin cancers in human skin grafted to mice. Atillasoy *et al.* (1997) grafted white human skin onto 158 recombinase activating gene-1 (RAG-1) knockout mice. Mice were divided into four groups: control, a single administration of dimethyl(*a*)benzanthracene (DMBA), exposure to UVB (290 to 320 nm) at 500 J/m^2 three times per week, or a combination of DMBA and UVB. Mice were examined three times a week, and all surviving mice were euthanized and autopsied after a median observation period of 10 months (range 3 to 16 months). About half of the grafts exposed to UVB (alone or with DMBA) developed milia, compared with 3% of DMBA-exposed grafts and none of the controls. Actinic keratoses were observed in 9% of the grafts exposed to UVB alone and 19% of the grafts exposed to DMBA plus UVB. Invasive squamous-cell carcinomas developed in 10% of the grafts exposed to DMBA plus UVB. None of the controls developed actinic keratoses or squamous-cell carcinomas. Melanocytic hyperplasia was found in 68% of the grafts exposed to UVB only and 77% of the grafts exposed to both UVB and DMBA. One human nodular-type malignant melanoma developed in a graft exposed to both DMBA and UVB (Atillasoy *et al*. 1998).

In a follow-up study (Sauter *et al.* 1998), 25 RAG-1 mice with human skin grafts received a single administration of DMBA followed by three weekly exposures to UVB (500 J/m^2) for at least five months. Cysts, hyperplasia, precancers, or invasive cancers were seen in 24 of 25 exposed grafts, compared with none of the controls. Two squamous-cell carcinomas were observed. Of grafts exposed for seven or more months, 83% (15/18) developed squamous precancer or squamous-cell carcinoma of human origin, and 44% (8/18) developed melanocytic hyperplasia or melanoma. Direct correlations between p53 tumor suppressor gene expression and cell proliferation and the degree of histologic change were observed for both squamous epithelial and melanocytic cells.

Human skin was transplanted to severe combined immunodeficient mice and exposed to UVB (280 to 360 nm) at daily doses of at 7.3×10^5 to 1.8×10^6 J/m^2 for two years (Nomura *et al.* 1997). Actinic keratoses developed in 77.8% (14/18) and squamous-cell carcinoma in 16.7% (3/18) of grafts exposed to UVB. None of the 15 control grafts developed actinic keratoses or squamous-cell carcinomas. The same p53 mutation at codon 242 (C TGC to C CGC) was observed in actinic keratoses and squamous-cell carcinomas, and double or triple mutations were observed in all skin cancers and three of eight actinic keratoses.

4.6 Summary

Broad-spectrum UVR was carcinogenic to albino rats, inducing skin tumors (papilloma, squamous-cell carcinoma, spindle-cell sarcoma and carcinosarcoma, and basal-cell

carcinoma) and eye tumors (spindle-cell sarcoma and squamous-cell carcinoma). Broad-spectrum UVR induced skin or eye tumors (spindle-cell sarcoma or fibrosarcoma, mostly in the cornea) and hemangioendothelioma in mice and hamsters and caused skin tumors (mostly fibrosarcoma and squamous-cell carcinoma) in opossums. Broad-spectrum UVR also has been implicated in tumor development in domestic animals (cows, goats, sheep, cats, dogs, horses, and swine).

UVA induced skin tumors in mice (squamous-cell carcinoma and papilloma), opossums (melanocytic hyperplasia) and fish (melanoma). Prolonged UVB exposure caused skin tumors in rats (papilloma), mice (squamous-cell carcinoma, fibrosarcoma, papilloma, and keratoacanthoma), guinea pigs (fibroma and trichofolliculoma), opossums (melanocytic hyperplasia and melanoma), and fish (melanocytic neoplasms). Exposure of experimental animals to high doses of UVC caused skin tumors in rats (keratoacanthoma-like skin tumors) and mice (squamous-cell carcinoma and fibrosarcoma). Human skin grafts on mice also yielded skin tumors (squamous-cell carcinoma, actinic keratosis, melanocytic hyperplasia, and melanoma) following irradiation with UVB alone or after exposure to DMBA.

5 Genotoxicity

The IARC conducted an extensive review of the literature through 1991 on the genotoxicity of solar and ultraviolet radiation, to develop a better understanding of exposure to UVR, the intermediate biological responses, and their consequences, with emphasis on carcinogenesis (IARC 1992).

This section discusses pertinent genotoxicity information from the IARC review and from recent genotoxicity studies, focusing on UVR, including UVA, UVB, and UVC. It is important to recognize that many exogenously supplied photosensitizers, including some pharmaceuticals, can affect the biological response to UVR. In some cases, interactions with photosensitizers have therapeutic application; for example, UVA may be used in combination with furocoumarins to treat skin diseases or tumors (IARC 1992, Müller *et al.* 1998). However, UVR interactions with exogenous chemical agents are considered outside the scope of this document and are not addressed.

5.1 Methods for identifying and quantifying UVR-induced DNA lesions

Griffiths *et al.* (1998) reviewed the measurement and significance of DNA lesions induced by UVR. UVR-induced DNA lesions and methods for identifying and quantifying them may be categorized as follows:

Single- and double-strand DNA breaks. UVR causes strand breakage interfering with inter- and intra-strand stabilization and inevitably resulting in some degree of α-helical unwinding. Several assays rely on this phenomenon and do not require DNA extraction, but are based on fluorescence labeling of DNA. Examples of such assays are the fluorescence-activated DNA unwinding assay, DNA sedimentation analysis, and the single-cell gel electrophoresis (or comet) assay (Griffiths *et al.* 1998).

Specific DNA sequences containing damage. UVR elicits antigenicity by altering DNA sequences through denaturation. Polyclonal and monoclonal antibodies have been raised against specific lesions that begin with thymine dimers. These antibodies have been used to recognize sequence-specific damage both on fixed section slides and in fluorescence-activated cell-sorter-type flow cytometry systems. For instance, Herbert *et al.* (1994, cited in Griffiths *et al.* 1998) developed a polyclonal antibody specific for a cyclobutane thymidine dimer with an adjacent 3′ or 5′ thymidine.

Specific DNA base lesions. Franklin and Haseltine (1984, cited in Griffiths *et al.* 1998) developed and demonstrated a high-performance liquid chromatographic (HPLC) assay that can separate and quantitate cyclobutane-type pyrimidine dimers and (6-4) photoproducts.

5.2 UVR-induced DNA photoproducts

It is well documented that UVR induces mutations in both prokaryotic and eukaryotic cells, and any cell that is UV-irradiated will likely sustain DNA damage. UVA, UVB, and UVC have induced mutations in bacterial systems and cultured mammalian cells. In addition, UVA has induced mutations in yeast, and UVC has induced mutations in plants

and amphibians (IARC 1992). The type of damage induced depends upon the specific wavelength(s) applied and the competency of an affected cell to repair the damage without error. DNA is a major cellular chromophore absorbing UVR (mainly UVB); it responds to irradiation by yielding single-electron reactive intermediates and, depending on exposing wavelengths and energy produced, various identifiable photoproducts. All photoproducts are expected to have mutagenic potential; however, their specificity and potency vary (IARC 1992).

5.2.1 UVA-induced indirect DNA damage

Over 90% of the UV radiation reaching the surface of the earth is in the form of UVA. Upon absorption of UVA by cells and subsequent generation of activated oxygen, the energy is transferred to DNA. DNA poorly absorbs UVA; therefore, the induced genotoxic damage is due to absorption of photons by other endogenous chromophores (IARC 1992). Examples of endogenous chromophores within mammalian cells are riboflavin, porphyrins, quinones, and reduced nicotinamide cofactors (Griffiths *et al*. 1998).

UVA-excited endogenous photosensitizers produce a much lower level of base loss than does UVB (Cadet *et al*. 1992). The major DNA base lesions induced are 8-hydroxydeoxyguanosine (8-OHdG), produced from guanosine by the action of singlet oxygen; hydroxyhydroperoxides, indirectly generated from the radical cation of thymine under aerobic conditions; and pyrimidine photoproducts (however, their induction requires a six-fold greater energy input than UVC-induced lesions at a similar frequency). UVA does not induce formation of (6-4) photoproducts (Griffiths *et al.* 1998).

5.2.2 UVB-induced direct DNA damage

UVB photons directly cause the following major DNA base modifications: cyclobutane-type pyrimidine dimers, (6-4) photoproducts, the corresponding Dewar isomers, and thymine glycols. The pyrimidine dimers are five to 10 times more abundant than the other DNA base modifications. Depending upon the conditions of exposure, these pyrimidine dimers occur as cytosine-cytosine, thymine-thymine, or mixed dimers. The absorption spectra for cytosine and thymidine match the action spectrum for dimer formation and, in (6-4) photoproduct induction, the cytosines 5′ upstream of adjacent pyrimidines present perfect targets for such DNA damage (Griffiths *et al.* 1998).

UVB also is responsible for induction of DNA strand breaks. The incidence of DNA strand breaks increases as a function of increasing wavelength. Single-base lesions, mainly ring-saturated thymines known as thymine glycols, are also observed. Along with these, 8-OHdG adducts are induced over the dose range of 4 to 750 mJ/cm^2 (Stewart *et al.* 1996, cited in Griffiths *et al.* 1998). UVB exposure also causes DNA-protein crosslinks, mostly affecting cysteine residues. At equivalent doses, UVB induces DNA-protein crosslinks at about one-tenth the frequency that UVA does (Griffiths *et al.* 1998).

5.2.3 Cellular mechanisms for minimizing UVR-induced DNA damage

Healthy eukaryotic cells can minimize UVR-induced DNA damage by several defense mechanisms, which interact to protect cells against toxic effects of UVR. These

mechanisms include production of antioxidant enzymes, production of detoxification enzymes, and repair of UVR-induced DNA lesions by means of direct reversal, base excision repair, nucleotide excision repair, transcription repair coupling, and mitochondrial repair of UV-induced lesions (Griffiths *et al.* 1998).

5.2.4 Cellular responses to UVR-induced DNA damage

Transcriptional activation of mammalian "early response genes" (e.g., *c-fos* and *c-jun*) is induced within minutes of UVR exposure. Early and secondary response genes also include genes mediating protein binding to DNA damage sites, cell proliferation control genes (e.g., growth arrest and DNA damage genes), genes coding for enzymes involved in signal transduction (e.g., protein kinase C) or for antioxidants (e.g., heme oxygenase), and the p53 tumor suppressor gene (Griffiths *et al.* 1998).

UVR-induced photoproducts have genotoxic consequences that vary depending on the particular exposure circumstances. In the survey below, genotoxic effects are classified according to the test system in which they were assessed. Data presented in IARC (1992) are summarized in Table 5-1. Studies that were not reviewed in IARC (1992) are discussed in the following text.

5.3 Prokaryotic systems

5.3.1 Induction of mutation in Salmonella typhimurium

UVC exposure unambiguously increased the frequencies of reverse gene mutations in several *S. typhimurium* tester strains, including repair-defective strains *hisG46* and *hisG428* (Cebula *et al.* 1995) and *recA-uvrB* (Hartmann *et al.* 1996, cited in Griffiths *et al.* 1998).

Table 5-1. Genetic and related effects of UVR exposure reviewed in IARC (1992)

Test system	End point	Results (no. positive/no. studies)			
		UVA	UVB	UVC	UVR[a]
Prokaryotic					
Salmonella typhimurium	mutation	1/1	1/1		
Escherichia coli	mutation	8/8	1/1	6/6	
Escherichia coli	DNA damage			5/5	
Bacillus subtilis	mutation				1/1
Lower eukaryotic					
Saccharomyces cerevisiae	DNA damage or pyrimidine dimers	3/3		2/2	1/1
Saccharomyces cerevisiae	aneuploidy			1/1	
Saccharomyces cerevisiae	mutation			2/2	

Test system	End point	Results (no. positive/no. studies)			
		UVA	UVB	UVC	UVR[a]
Plant					
Wheat	mutation				1/1
Unspecified plant cells	DNA damage			1/1	
Nicotiana tabacum	unscheduled DNA synthesis			1/1	
Chlamydomonas reinhardtii	pyrimidine dimers			1/1	
Chlamydomonas reinhardtii	mutation			1/1	
Tradescantia	chromosomal aberrations		1/1	1/1	
Nonmammalian eukaryotic					
Drosophila melanogaster	DNA damage			1/1	
ICR 2A frog cells	DNA damage			1/1	2/2
ICR 2A frog cells	SCE, chromosomal aberrations		1/1	2/2	1/1
A8W243 *Xenopus* frog cells	chromosomal aberrations			1/1	
Fish (*in vitro*)	DNA damage				1/1
Chick embryo fibroblasts	SCE, chromosomal aberrations			2/2	
Nonhuman mammalian *in vitro*					
Chinese hamster ovary cells	DNA damage	2/2	1/1	1/1	
Chinese hamster ovary cells	SCE, chromosomal aberrations	2/2	1/1	2/2	
Chinese hamster ovary cells	mutation	3/3	2/2	3/3	2/2
Chinese hamster fibroblasts	chromosomal aberrations			2/2	
Chinese hamster V79 lung cells	DNA damage		2/2	1/1	2/2
Chinese hamster V79 lung cells	mutation	2/2	4/4	4/4	3/3

Test system	End point	Results (no. positive/no. studies)			
		UVA	UVB	UVC	UVR[a]
Chinese hamster V79 lung cells	SCE, chromosomal aberrations			3/3	
Chinese hamster CHEF-125 cells	chromosomal aberrations			1/1	
Syrian hamster embryo cells	cell transformation	1/2	1/1	3/3	
C3H 10T1/2 mouse cells	DNA damage				1/1
L5178Y mouse lymphoma cells	mutation	1/1	1/1	1/1	1/1
Mouse splenocytes	micronuclei				1/1
New Zealand black mouse fetal fibroblasts	chromosomal aberrations			1/1	
Mouse epidermal cells, embryo cells, fibroblasts, fibrosarcoma cells	cell transformation			7/7	6/6
Human *in vitro*					
Fibroblasts	DNA damage or pyrimidine dimers	4/4	4/4	8/8	4/4
Fibroblasts	mutation	1/1	1/1	5/5	1/1
Fibroblasts	micronuclei			1/1	1/1
Fibroblasts	SCE, chromosomal aberrations			9/9	2/2
Fibroblasts	cell transformation		1/1	3/3	
Keratinocytes and melanocytes	DNA damage		1/1	1/1	
Epithelial P3 cells	DNA damage	1/1			
Epithelial cells	mutation	1/1	1/1	1/1	
Teratoma or teratocarcinoma cells	DNA damage	3/3	3/3	3/3	
Lymphoblastoid cells	mutation	0/1	0/1	1/1	
HeLa cells	DNA damage				1/1
HeLa cells	mutations			1/1	
Melanoma cells	SCE				1/1
Melanoma cells	mutation			1/1	
Melanoma cells	micronuclei				1/1

Test system	End point	Results (no. positive/no. studies)			
		UVA	UVB	UVC	UVR[a]
Lymphocytes	mutation			2/2	
Lymphocytes	SCE, chromosomal aberrations			4/4	
Nonhuman mammalian *in vivo*					
Mouse skin	DNA damage or pyrimidine dimers		3/3	1/1	1/1
Mouse skin fibroblasts	cell transformation				1/1
Marsupial corneal cells	DNA damage				2/2
Human *in vivo*					
Epidermis or skin cells	DNA damage or pyrimidine dimers	1/1	1/1		2/2
Cornea	unscheduled DNA synthesis		1/1		
Fibroblasts	DNA damage		2/2	2/2	

[a]Includes solar, simulated solar, and sunlamp irradiation.

5.3.2 Induction of mutation in Saccharomyces cerevisiae

UVB and natural sunlight exposure increased the frequencies of pyrimidine dimer formation (Armstrong and Kunz 1992), single-base-pair substitution (Kunz and Armstrong 1998), and gene mutation (Armstrong and Kunz 1990) in *S. cerevisiae.* Natural sunlight and UVB induced similar G-C to A-T transitions; however, natural sunlight induced a higher percentage of G-C to T-A or C-G transversions. Dipyrimidine adducts likely were responsible for the transitions and are now recognized as a signature of sun exposure (Sarasin 1999). These data suggest that one type of DNA damage leads to most of the mutations associated with UVB exposure, whereas two different types of DNA damage may be involved in sunlight mutagenesis (Kunz and Armstrong 1998).

5.4 Plants and lower eukaryotic systems

No additional genotoxicity studies in plant or eukaryotic systems were identified in the current literature.

5.5 Mammalian systems

5.5.1 Nonhuman mammalian in vitro *assays*

Oxidative damage in DNA is caused by UVB irradiation and results in the formation of a DNA adduct, 8-OHdG. Studies demonstrated a decrease in antioxidant enzyme defenses in SKH1 hairless albino mice after UVB radiation, implicating antioxidant status in protection against oxidative damage (Cameron and Pence 1992). A further study by this group examined mechanisms of UVB-induced DNA damage and subsequent modulation

by the antioxidants vitamin C (ascorbic acid), selenite, or Trolox (a water-soluble vitamin E analog). BALB/c MK-2 mouse keratinocytes were exposed to UVB at a dose range of 4 to 750 mJ/cm^2. Adducts were measured via HPLC coupled with electrochemical and UV absorbency detection. Preincubation of the cells for two days with 0.4 or 0.8 μg/ml of ascorbic acid, 10 or 20 μg/ml of Trolox, and 5 or 12.5 μM selenite significantly decreased the number of 8-OHdG adducts per 10^5 deoxyguanines induced by UVB at 500 mJ/cm^2. The results further elucidated mechanisms through which UVB altered DNA exposed *ex vivo* in cultured mouse skin cells and indicated that antioxidant nutrients might protect skin cells against UVB damage (Stewart *et al.* 1996, cited in Griffiths *et al*. 1998).

5.5.2 *Human* in vitro *assays*

Murata-Kamiya *et al*. (1995, cited in Griffiths *et al.* 1998) demonstrated that oxygen free radicals caused DNA base and sugar modifications and DNA strand breaks. They showed that a known mutagen, glyoxal, was produced by exposure of DNA to an oxygen-radical-forming system (5 mM ferrous sulfate–ethylenediaminetetraacetic acid, +37^o C, 60 min). Glyoxal was produced with a 17-times-higher efficiency than 8-OhdG, with adduct formation at guanine sites. The authors predicted that this type of exposure of DNA to an oxygen-radical-forming system, with following glyoxal and guanine adduct formation, constituted one of the major types of UVA-induced DNA damage.

Mizuno *et al.* (1991, cited in Griffiths *et al.* 1998) conducted a study using a thymine dimer-specific monoclonal antibody (TDM-1), which was produced against mouse and human DNA after exposures of cells *ex vivo* to 313-nm UVB in the presence of acetophenone. When UVB-irradiated DNA was incubated with photolyase from *E. coli* and visible light, TDM-1 binding and the presence of thymine dimers were reduced. It was shown that TDM-1 binding to UVB-irradiated DNA was inhibited by photolyase, but not by 64M-1 antibody specific for (6-4) photoproducts. The authors concluded that the TDM-1 antibody had affinity for cyclobutane-type DNA thymine dimers. They measured, by competitive assessments with the two antibodies, the amount of each type of DNA damage in DNA extracted from UVB-irradiated mammalian cells. Repair experiments indicated that (6-4) photoproducts were excised from UVB-irradiated cellular DNA more rapidly than thymine dimers. Excision rates of both photoproducts were lower in mouse (NIH3T3) cells than in human fibroblasts.

Immunocytochemical methods were used to measure cyclobutane pyrimidine dimers, (6-4) photoproducts, and Dewar isomers in normal human mononuclear cells following *ex vivo* irradiation by natural sunlight or a UVB sunlamp (Clingen *et al.* 1995, cited in Griffiths *et al.* 1998). The induced photoproducts were detected following a 30- to 60-minute sunlight exposure, or with sunlamp irradiation as low as 50 to 100 J/m^2. A dose-dependent increase in the binding of monoclonal antibodies specific for pyrimidine dimers, (6-4) photoproducts, and Dewar isomers was observed. The relative ratio of Dewar isomers to (6-4) photoproducts was much greater after exposure to natural sunlight than after exposure to broad-spectrum UVB. Use of the (6-4) monoclonal antibody indicated that binding sites increased slightly after a one-hour exposure to natural sunlight and remained relatively constant with further exposure. The authors

hypothesized that following irradiation with natural sunlight, most (6-4) photoproducts were converted into Dewar isomers, and that this conversion was likely caused by the UVA component. They concluded that the (6-4) photoproducts probably did not contribute directly to sunlight-induced carcinogenesis.

Human skin explants were studied with a [^{32}P]-HPLC method for recognizing and measuring lesions (cyclobutane dimers, [6-4] photoproducts, and Dewar isomers) induced in DNA after exposure to UVA, UVB, or UVC (Bykov and Hemminki 1996). The experimental method was sensitive enough to detect the lesions at a UVB radiation dose of 10 J/m^2. Dewar isomers were detected only at a high doses of UVB. The compounds were identified by their photochemical reactivity and by spiking with prepared standards. Treatment with nuclease P1 was used to identify the 5′-terminal nucleotide. UVA caused no detectable adducts .

5.5.3 Nonhuman mammalian in vivo *assays*

Formation of 8-OHdG adducts was evaluated in the epidermis of hairless mice after repeated exposure to UVB (Hattori *et al.* 1996, cited in Griffiths *et al.* 1998). Exposure of hairless mice to UVB at a dose of either 3.4 kJ/m^2 (2 MED) or 16.8 kJ/m^2 (10 MED), three times a week, for two weeks, induced a 2.5- or 6.1-fold increase, respectively, in the levels of 8-OHdG in DNA. An immunohistochemical method, using a monoclonal antibody specific for 8-OHdG, showed stronger and more extensive staining in the nuclei of UVB-irradiated epidermal cells than in those of nonirradiated cells. Western blots probed with antibodies against 4-hydroxy-2-nonenal-modified proteins confirmed the involvement of reactive oxygen species in the epidermal damage induced by chronic UVB exposure. The authors suggested that three pathways might regulate the formation of 8-OHdG after UVB exposure: photodynamic action, lipid peroxidation, and inflammation. They concluded that 8-OHdG might be active in sunlight-induced skin carcinogenesis.

5.5.4 Human in vivo *assays*

5.5.4.1 DNA damage and repair

DNA synthesis, measured by [^{3}H] thymidine incorporation after lymphocyte activation, was studied in circulating leukocytes from patients with widespread psoriasis who were being treated with PUVA (oral 8-methoxypsoralen and high-intensity UVA) (Kraemer and Weinstein, 1977, cited in IARC 1992). Of 13 psoriasis patients treated with PUVA, seven demonstrated a significant ($P < 0.05$) reduction in lymphocyte incorporation of [^{3}H]thymidine immediately after UVA treatment, compared with incorporation before UVA treatment. In addition to its therapeutic effects on epidermal cells, PUVA treatment affected circulating blood cells in some psoriasis patients. However, in 10 control subjects who received UVA alone, lymphocytes were capable of normal activation and DNA synthetic activity. This study raised the possibility of genotoxic effects in circulating lymphocytes. Strauss *et al*. (1979, 1980) observed induction of presumed mutations at the *HPRT* locus in lymphocytes in UVA-exposed patients, but not in the absence of psoralens. In another study, patients treated with PUVA, but not UVA alone, showed evidence of local and systemic impairment of the delayed cellular hypersensitivity component of the immune response, providing evidence for a possible

mechanism of tumor promotion in the skin (Bridges and Strauss 1980, Strauss 1982). Human studies evaluating PUVA treatment and cancer risk are reviewed in Section 3.

Irradiation of human buttock skin with 300-nm UVR *in situ* induced thymine dimers and (6-4) photoproducts (Chadwick *et al.* 1995, cited in Griffiths *et al.* 1998). Irradiation of human buttock skin with UVC (260 nm) immediately followed by UVA (320 nm) induced the Dewar isomers of the (6-4) lesions. All three lesions were detected in methanol-fixed paraffin sections through the use of specific monoclonal antibodies. The lesions were analyzed in an automated image analysis system, and the level of immuno-diaminobenzidine-peroxidase was measured in individual epidermal-cell nuclei. Staining patterns indicated a decrease with depth of about 2.5% per cell layer. Following irradiation with a shorter wavelength (260 nm), staining decreased rapidly with depth (39% per cell layer). The results showed effective penetration and damage induction by UVB in human skin after *in vivo* exposure.

Hori *et al.* (1992, cited in Griffiths *et al.* 1998) studied DNA extracted from a variety of human skin tumors and control tissues, including femoral skin and white blood cells, with an immunoblotting method using antibodies against UV-irradiated calf thymus DNA. The antibodies used were reactive to cyclobutane-type pyrimidine dimers. Immunoprecipitates were observed for facial actinic keratosis and keratosis-derived squamous-cell carcinoma specimens. Through the use of photoreactivation enzyme plus visible light, both immunoprecipitates were found to be specific for cyclobutane-type pyrimidine dimers. Immunofluorescence studies of actinic keratosis tissue showed that unremoved photodamage in DNA remained in the nucleus of actinic keratosis cells. The authors suggested that the tumor cells might be deficient in an enzyme required for repairing cyclobutane-type pyrimidine dimer damage.

Clingen *et al*. (1995, cited in Griffiths *et al.* 1998) used specific monoclonal antibodies *in situ* and a computer-assisted image analysis system to determine the relative induction of cyclobutane dimers, (6-4) photoproducts, and Dewar isomers in human mononuclear cells and fibroblasts following irradiation with UVC, broad-spectrum UVB, and narrow-spectrum UVB. DNA lesions were produced in different proportions, with broad-spectrum UVB inducing a greater combined yield of (6-4) photoproducts and Dewar isomers per cyclobutane dimer than UVC or narrow-spectrum UVB. Relative induction ratios of (6-4) photoproducts versus cyclobutane dimers were 0.15, 0.21, and 0.10 following irradiation with UVC or broad- or narrow-spectrum UVB, respectively.

5.5.4.2 Tumor suppressor and ras gene mutations

Brash *et al.* (1991, cited in IARC 1992) reported five C to T, four C to A, and three CC to TT mutations at various codons of the p53 tumor suppressor gene in 24 invasive squamous-cell carcinomas taken from sun-exposed skin; about 90% of squamous-cell carcinomas examined in this study contained p53 mutations. CC to TT transitions have not been found in any internal tumors, suggesting that sun exposure plays a role in p53 mutations. Pierceall *et al.* (1991, cited in IARC 1992) reported one C to T transition and one C to A transversion in 10 squamous-cell carcinomas examined. Ouhtit *et al.* (1997) investigated the frequency of p53 mutations in normal skin from Japanese patients. More mutations were found in skin samples taken from sites chronically exposed to the sun

than from covered sites. A recent study showed that 50% of mutations of the PTCH tumor suppressor gene found in basal-cell carcinomas were UVR-specific (Quinn 1997).

Melanomas from 37 patients with varying sun exposure were examined for N-*ras* mutations (van 't Veer *et al*. 1989, cited in IARC 1992). N-*ras* mutations were found in tumors from seven patients who were continuously exposed to the sun. All mutations were base substitutions at TT or CC sites that are potential targets for UV photoproducts. In other studies, N-*ras*, Ki-*ras*, and Ha-*ras* base substitution mutations were found in melanomas, basal-cell carcinomas, and squamous-cell carcinomas (Sekiya *et al.* 1984, Corominas *et al.* 1989, Keijzer *et al.* 1989, Shukla *et al.* 1989, van der Schroeff *et al.* 1990, all cited in IARC 1992).

5.5.5 *Other* in vitro *and* in vivo *end points*

DNA 8-hydroxy-2′-deoxyguanosine is a mutation-prone (G-C to T-A transversion) DNA base-modified product generated by reactive oxygen species or photodynamic action. G-C to T-A transversions were observed in the p53 and *ras* genes of UVB-induced skin tumors from mice and in squamous- and basal-cell carcinomas from human skin exposed to sunlight (Hattori *et al.* 1996, cited in Griffiths *et al.* 1998).

5.5.6 *Molecular epidemiological studies of DNA repair capacity*

Wei *et al*. (1994) evaluated the relationship between DNA repair capacity and basal-cell carcinoma in 88 cases and 135 controls. Cases were Caucasian patients with histopathologically confirmed primary basal-cell carcinoma recruited from physician practices in the Baltimore area between 1987 and 1990. Controls were patients from the same physician practices who were cancer-free and were frequency-matched to cases by age. Cancer patients and controls provided a blood sample and completed a self-administered questionnaire that collected information with respect to demographics, family history, and potential confounders for basal-cell carcinoma. Lymphocytes were isolated from the blood. DNA repair was assessed with the host-cell reactivation assay, which measures the ability of lymphocytes from the participants to repair damaged DNA. Plasmids containing UVR-irradiated (0, 350, or 700 J/m^2) chloramphenicol acetyl transferase (CAT) reporter genes were transfected into lymphocytes, and the ratio of CAT gene expression of irradiated plasmids to that of non-irradiated plasmids was calculated as the percentage of residual repair activity at a given UVR dose. The mean DNA repair capacity of all basal-cell carcinoma patients was 5% lower than that of controls, a difference of borderline significance. However, among subjects with red hair and skin type I, DNA repair capacity was significantly lower in cancer patients than in controls. Moreover, among subjects who reported frequent sunbathing, poor tanning ability, a history of multiple sunburns, exposure to chemicals, or multiple medical irradiations, the basal-cell carcinoma patients had significantly lower DNA repair capacity than the controls ($P < 0.05$), which suggested that DNA repair might be a susceptibility factor and the underlying molecular mechanism of sunlight-induced skin carcinogenesis in the general population.

Hall *et al.* (1994) used the host-cell reactivation assay to evaluate the relationship between DNA repair capacity and basal- or squamous-cell carcinoma in a population-

based case-control study. The study participants were residents of Australia between the ages of 40 and 64 who were listed on the electoral roll. They were invited to attend a skin cancer screening clinic, where they were examined by a dermatologist and interviewed. Cases were 87 individuals who had one or more skin cancers diagnosed at the survey or in the preceding year. Controls (86) were chosen by random sampling of the remaining survey attendees and matched by age and sex. DNA repair capacity was greater in subjects with skin cancer than in controls, but the difference was not statistically significant; for each 350-J/m^2 increment in UV dose to the plasmids, repair capacity was greater by a factor of 1.07 (95% CI = 0.94 to 1.26) in subjects with basal-cell carcinoma and by a factor of 1.04 (95% CI = 0.85 to 1.26) in subjects with squamous-cell carcinoma.

5.6 Summary

The IARC (1992) summarized genetic and related effects of UVR according to type (predominant wavelengths), test system, result (positive, negative, or conditional), and study reference (see Appendix A, Tables 32–35). Table 5-2 (updated from IARC 1992) summarizes genetic and related effects according to test system, UV irradiation type, and result.

5.6.1 UVA

UVA (315 to 400 nm) was genotoxic in prokaryotic and lower eukaryotic systems. Its biological effects are indirect and largely the result of energy transferred through active oxygen intermediates. In mammalian cell *ex vivo* exposure systems, UVA induced gene mutation, cytogenetic damage, and other forms of DNA damage. Few data are available on DNA damage in human skin and circulating blood from UVA *in vivo* exposures. The IARC (1992) cited twelve studies in prokaryotic systems; results were positive in nine for gene mutation and three for DNA damage. Of ten cited nonhuman mammalian *in vitro* studies, results were positive in two for DNA damage, six for gene mutation, and two for cytogenetic damage. Of 11 cited human *in vitro* studies, results were positive in eight for DNA damage and three for gene mutation. The one human *in vivo* study gave positive results. UVA radiation can induce cellular and viral gene expression. Based on the published literature, UVA (without exogenous photosensitizers) is a less potent genotoxic agent than UVB or UVC.

5.6.2 UVB

UVB (280 to 315 nm) was genotoxic in prokaryotic, lower eukaryotic, and plant systems. UVB photons are absorbed by DNA, and direct damage occurs through DNA base modifications. In mammalian cell *ex vivo* exposure systems, UVB induced gene mutation, cytogenetic damage, and other forms of DNA damage. In a number of studies, UVB caused DNA damage and gene mutation in human skin and circulating blood after *in vivo* exposure. IARC (1992) cited three studies in prokaryotic systems; two showed gene mutation, and one showed cytogenetic damage. Of 12 cited nonhuman mammalian *in vitro* studies, results were positive in three for DNA damage, seven for gene mutation, and two for cytogenetic damage. Of 11 cited human *in vitro* studies, results for gene mutation were positive in two studies and negative in one study; results were positive in two studies for cytogenetic damage and eight studies for DNA damage. Five animal *in*

vivo studies were cited, all with positive results. The two cited human *in vivo* studies both demonstrated DNA damage. UVB radiation can induce cellular and viral gene expression. Based on the published literature, UVB is a more potent genotoxic agent than UVA, but less potent than UVC.

5.6.3 UVC

UVC (100 to 280 nm) was genotoxic in prokaryotic, fungal, plant, and insect test systems. UVC photons are absorbed by DNA, and direct damage occurs through high-energy reactions. In mammalian cell *ex vivo* exposure systems, UVC induced gene mutation, cytogenetic damage, and other forms of DNA damage. In the few *in vivo* studies reviewed, UVC caused DNA damage and gene mutation in animal and human blood and skin. The IARC (1992) cited twenty-three studies in prokaryotic and lower eukaryotic systems; positive results were found in nine for gene mutation, two for cytogenetic damage, and 12 for DNA damage. Of 24 cited mammalian *in vitro* studies, two showed DNA damage, eight showed gene mutation, and 14 showed cytogenetic damage. Of 39 cited human *in vitro* studies, positive results were found in 14 for DNA damage, 11 for gene damage, and 14 for cytogenetic damage. The one cited animal *in vivo* study showed positive results for DNA damage, as did the two cited human *in vivo* studies. UVC radiation can induce cellular and viral gene expression. Based on the published literature, UVC is a more potent genotoxic agent than UVA or UVB.

Table 5-2. Genetic and related effects of UVA, UVB, and UVC exposure reviewed in IARC (1992)

Nonmammalian systems								Mammalian systems																						
Prokary-otic		Lower eukaryotic			Plant			*In vitro*											*In vivo*										
								Animal cell					Human cell						Animal						Human				
D	G	D	G	A	D	G	C	D	G	S	C	T	D	G	S	M	C	T	D	G	S	M	C	A	D	S	M	C	A
UVA																														
	+	+					0	+1	+	+1	+1		+	+											+1				
UVB																														
	+	+	+				+1	+	+	+1		+	+	+				+1	+						+				
UVC																														
+	+	+	+	+1	+	+1	+1	+1	+	+	+	+	+	+	+	+1	+	+	+1						+1				

Source: Adapted from IARC 1992

A – aneuploidy; **C** – chromosomal aberrations; **D** - DNA damage; **G** – gene mutation; **M** – micronuclei; **S** – sister chromatid exchange; **T** – cell transformation

Consensus of IARC Working Group: **+** = positive for the specific end point and level of biological complexity.

+ 1 = positive, but only one valid study was available to the Working Group.

6 Other Relevant Data

6.1 Absorption and transmission of UVR in biological tissues

UVR may be transmitted, reflected, scattered, or absorbed by chromophores (biological molecules that absorb radiant energy) in tissue, such as the skin. Absorption of UVR depends on the wavelength of the UVR and the properties of the target chromophores. Absorption of UVR by a tissue chromophore is a prerequisite for any photochemical or photobiological effect; however, absorption does not necessarily have a biological consequence (IARC 1992, Gould *et al*. 1995). A molecule's absorption spectrum (the range of wavelengths in which it absorbs UVR) differs from its action spectrum (the range of wavelengths in which biological responses are produced), but this range is the same in most instances (Gould *et al*. 1995). Measured transmission of UVR was maximal in the cornea at 380 nm, 80% in the aqueous humor at 400 nm, 90% in the lens at 320 nm, and 80% in the vitreous humor at 350 nm (Boettner and Wolter 1962, cited in IARC 1992). UV transmission at 300 to 400 nm in normal human lenses decreases with age (Lerman 1988, cited in IARC 1992).

Skin epidermis (the outer layer of the skin) can be divided into two regions based on function: an outermost, nonliving part called stratum corneum and an inner region of living cells (IARC 1992). In the skin, UVR is absorbed by the chromophores. The main chromophores present in the skin are melanin, DNA (λ_{max} 260 nm at pH 4.5), urocanic acid (λ_{max} 277 nm at pH 4.5), and the aromatic amino acids tryptophan (λ_{max} 280 nm at pH 7) and tyrosine (λ_{max} 275 nm at pH 7) (Morrison 1985, cited in IARC 1992). Urocanic acid, the deamination product of histidine, exists in two isomeric forms; the *trans* isomer is converted to *cis* upon UVR exposure. The amino acids tryptophan and tyrosine absorb UVR through the epidermis. Melanins are produced by melanocytes and are transferred to keratinocytes; they absorb broadly over the UVR spectrum (IARC 1992).

The depth to which UVR penetrates the human skin also is wavelength dependent. The atmosphere filters out UVC, the shortest wavelength produced by sunlight and the most potentially harmful to the genome, before it reaches the earth's surface. Therefore, UVC plays only a minimal role in biological photochemical reactions. UVC produced by artificial sources and reaching the skin can penetrate only the epidermis. UVB has the potential to penetrate the epidermis and upper layer of the dermis, or papillary dermis. Although UVB makes up only 5% of the UV photons reaching the earth's surface, it is the most biologically important component of sunlight. UVA, with the longest wavelength, reaches the deeper layer of the dermis, or reticular dermis (Table 6-1) (Gould *et al*. 1995, Farmer and Naylor 1996).

Table 6-1 Characteristics of UVR

Type of UV[a]	Percent of solar radiation reaching earth's surface	Wavelength (nm)	Depth of skin penetrance
UVA	6.3	320–400	papillary, reticular dermis
UVB	1.7	290–320	epidermis, papillary dermis
UVC	0	200–290	epidermis

Source: Gould *et al*. 1995

[a]Wavelength classifications of UVA, UVB, and UVC are slightly different from the CIE designations.

6.2 Mechanisms of UV-induced skin cancer

The frequency of skin cancer, including melanoma, has increased dramatically over the past 40 years and currently accounts for about 40% of all cancer in the United States (Whittaker 1996, Quinn 1997, Gilchrest *et al.* 1999). Although the reasons for this rapid increase in skin cancer are not completely understood, increased exposure to solar radiation and altered patterns of sun exposure are strongly implicated (Stary *et al.* 1997, Gilchrest *et al.* 1999). Aging is an important risk factor for skin cancer; however, even when age is excluded, UVR emerges as a primary factor in the three major types of skin cancer (squamous-cell carcinoma, basal-cell carcinoma, and melanoma) (Gilchrest *et al.* 1999).

Risk factors for non-melanoma skin cancer and melanoma are different (Ablett *et al.* 1998, Gilchrest *et al.* 1999). Squamous-cell and basal-cell carcinomas are most often found on areas of the body receiving maximum sun exposure (i.e., face, forearms, and backs of hands). In these cases, total cumulative UVR exposure is an important risk factor. Melanoma appears to be related to intense, intermittent UVR exposure. Several recent reviews and studies support UVR exposure as an important risk factor for melanoma (see Section 3 for a discussion of human studies on intermittent sun exposure and melanoma). Rünger (1999) suggested that UVA may play an important role in the pathogenesis of malignant melanoma. UVA induces melanoma in the platyfish-swordtail hybrid fish model and melanoma hyperplasia in the opossum *Monodelphis domestica* (see Section 4). Atillasoy *et al.* (1998) reported that chronic UVB irradiation, with or without an initiating carcinogen, could induce melanoma (see Section 4).

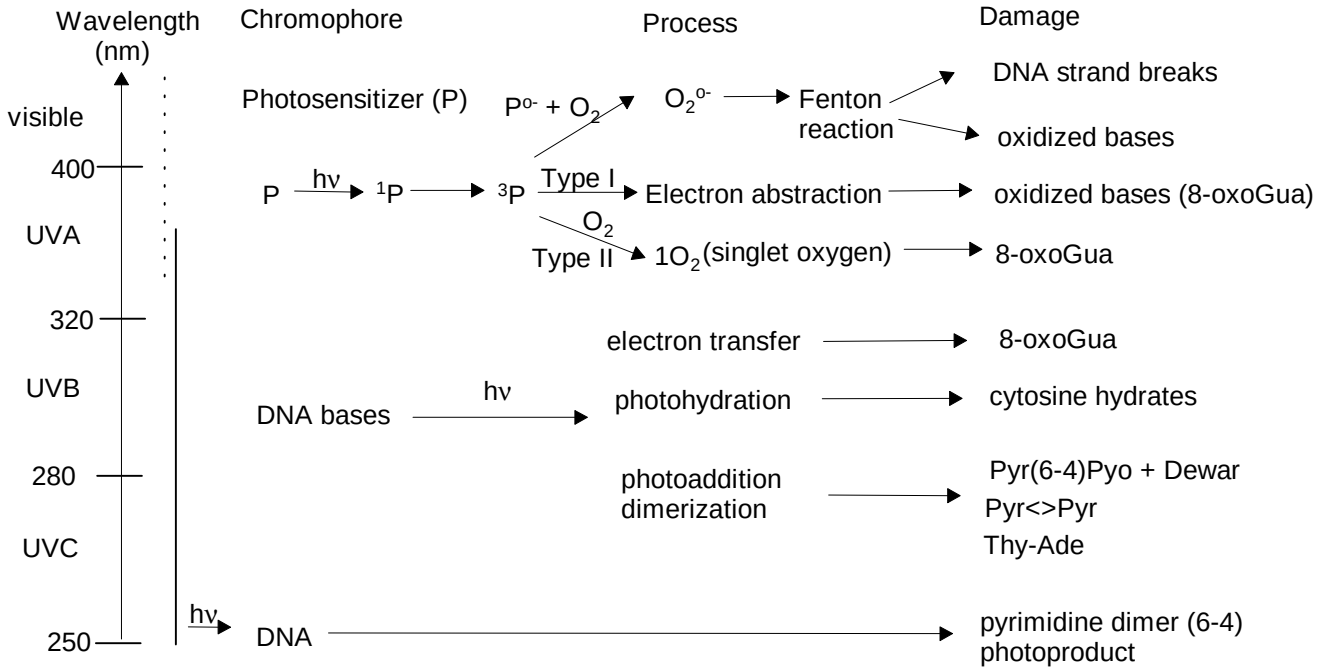
Human-mouse chimera models, in which human skin is grafted onto SCID/RAG mice, have been used to study etiological factors important in the genesis of human tumors (Satyamoorthy *et al.* 1999). UVB in combination with DMBA induced precancerous lesions and invasive squamous-cell carcinoma and melanoma (see Section 4.5).

UVR produces both direct and indirect damage to DNA that may alter gene expression and lead to mutations in protooncogenes and tumor suppressor genes. If unrepaired, these lesions can result in cancer. Other factors (e.g., immunological responses, antioxidant defenses, and genetic predisposition) also are important considerations (Streilein *et al.* 1994, Sarasin 1999). The evidence for DNA damage, DNA repair, and

immunosuppression as important mechanisms in UVR carcinogenesis is reviewed in the following sections.

6.2.1 DNA damage

UVR damage to biological systems occurs via phototoxic reactions that are either direct or mediated by photosensitizers in the target tissues (Cadet *et al.* 1997). In the skin, the effects of UVR are mediated by photosensitization reactions characterized by structural and functional changes in keratinocytes, melanocytes, Langerhans cells, and fibroblasts (Pathak 1996). The mechanism of UVR-induced DNA damage differs distinctly with wavelength (Cadet *et al.* 1997, Ito and Kawanishi 1997) (Figure 6-1). Damage to DNA by UVA proceeds indirectly via photosensitizers (non-DNA molecules) in photosensitization reactions, because DNA does not readily absorb UVA. In contrast, wavelengths shorter than 320 nm (UVB, UVC) directly photoactivate the DNA molecule to generate mainly pyrimidine photoproducts. Direct and indirect mechanisms of DNA damage are discussed below.



P= photosensitizer, hυ = radiation, Pyr = pyridine, Pyo = pyrimidone, Thy = thymidine, Ade = adenine, Gua = guanine.

Source: Cadet *et al*. 1997, Ito and Kawanishi 1997

Figure 6-1. Mechanisms of UV-induced DNA damage

6.2.1.1 Direct mechanisms

DNA is the primary cellular chromophore for UVB (Griffiths *et al.* 1998). The direct excitation of DNA bases by the UVB component of UVR gives rise, predominantly through oxygen-independent reactions, to three base modifications: cyclobutane-type pyrimidine dimers, pyrimidine (6-4) pyrimidone photoproducts, and related Dewar isomers (Cadet *et al.* 1997, Griffiths *et al.* 1998, Sarasin 1999). These mutagenic photoproducts result in C to T or CC to TT transitions that are always at pyrimidine–pyrimidine sequences and are now considered a signature of sun exposure (Sarasin 1999). In addition, UVB may cause some DNA strand breaks and single-base lesions. The yield of strand breaks increases with increasing wavelength, and single-base lesions are primarily thymine glycols (Griffiths *et al.* 1998).

Although UVB is more effective than UVA in generating direct DNA damage, UVA does induce some direct damage. Young *et al.* (1998) demonstrated that both UVA (320 to 360 nm) and UVB (300 nm) readily induced thymine dimers in both melanocytes and keratinocytes from human skin that was not exposed to sunlight. Furthermore, these data showed that thymine dimer levels in melanocytes were comparable to those observed in keratinocytes.

Like UVB, UVC causes direct excitation of DNA bases, through oxygen-independent reactions, leading mainly to formation of dimeric pyrimidine photolesions and relatively minor yields of DNA photoproducts that include the thymine-adenine photo-adducts, the "cytosine photohydrates" (Herrlich *et al.* 1994, Cadet and Vigny 1990, cited in Cadet *et al*. 1997), and a few purine decomposition products (Cadet *et al*. 1997).

Formation of 5,6-dihydroxydihydrothymine-type lesions (thymine glycols) in DNA following UVC irradiation also have been observed. It has been suggested that this photoproduct arises from the action of UVR-produced hydroxyl radicals (Hariharan and Cerruti 1976, 1977, cited in IARC 1992). Thymine compounds irradiated with UVC in the frozen state rapidly lose their absorption (Beukers *et al.* 1958, cited in IARC 1992); a dimer of thymine (two molecules linked by a cyclobutane ring involving the 5 and 6 carbon atoms) was shown to be responsible for the loss of absorption (Beukers and Berends 1960, Wulff and Fraenkel 1961, cited in IARC 1992). Continued irradiation leads to a wavelength-dependent equilibrium between dimer formation and dimer splitting to reform the monomer. Dimer formation is favored where the ratio of the dimer to monomer absorbency is relatively small (at wavelengths > 260 nm), whereas monomerization is favored at shorter wavelengths (around 240 nm), where the ratio is larger (Johns *et al*. 1962, cited in IARC 1992).

Pigmented mouse melanocytes, melan-b (brown) and melan-a (black), were more resistant than melan-c (albino) melanocytes to being killed by UVC or UVA, but were less resistant to being killed by UVB or UVA + UVB. In both the melanocytes and mouse melanoma cells, more pyrimidine dimer DNA damage was observed in pigmented cells than in nonpigmented cells. These results indicate that pigment does not protect against direct DNA damage in the form of pyrimidine dimers, nor does it necessarily protect against cell death (Hill *et al.* 1997).

6.2.1.2 Indirect mechanisms

In vitro experiments have firmly established that UVA is genotoxic by indirect mechanisms. Endogenous chromophores (photosensitizers) for UVA include riboflavin, porphyrins, quinones, tryptophan, and reduced nicotinamide cofactors (NADH and NADPH) (Ito and Kawanishi 1997, Cadet *et al.* 1997, Griffiths *et al.* 1998). The effects of exogenous photosensitizers, such as psoralens, porphyrins, coal tar, some antibiotics, and some nonsteroidal anti-inflammatory agents (Gould *et al.* 1995), are outside the scope of this document and are not discussed.

Following absorption of UVA, chromophores generate reactive oxygen species and radicals that can damage DNA (Griffiths *et al.* 1998). There are two competitive photosensitized reactions: type I reactions do not require oxygen and produce a radical intermediate via an electron transfer, whereas type II reactions require oxygen and produce singlet oxygen ($^1O_2$) (Ito and Kawanishi 1997).

Griffiths *et al.* (1998) reviewed indirect mechanisms of UVA-induced DNA damage. UVA interactions with photosensitizers in the target tissues promote the formation of three base lesions, as well as base loss (at a much lower level). One base lesion is 8-OHdG, the formation of which from guanosine appears to be mediated by singlet oxygen and is reported to be induced by UVA in mammalian cells at 10 times the rate of DNA strand breaks. Another base lesion is isomeric hydroxyhydroperoxides, produced through indirect generation of the radical cation of thymine in the presence of oxygen. The third base lesion is pyrimidine photoproducts; however, UVA generates this type of lesion much less efficiently than does UVB.

For both type I and type II mechanisms, 8-OHdG appears to be the major oxidation product of guanine in DNA (Ito and Kawanishi 1997). Peak *et al.* (1990, cited in Ito and Kawanishi 1997) reported the formation of H_2O_2 in human cells exposed to UVA. Neither O_2^- nor H_2O_2 can cause DNA damage in aqueous solution. However, in the presence of metal ions, highly reactive species, such as the hydroxyl radical (OH) and metal-oxygen complexes, can be generated via metal-catalyzed reactions. Hydroxyl radicals generated from the Fenton reaction of iron with H_2O_2 may react with any of the bases and sugar moieties of DNA (Cadet *et al.* 1997, Ito and Kawanishi 1997).

6.2.2 DNA repair

Yarosh and Kripke (1996, cited in NTP 1997) found that UV-induced DNA photoproducts produced a variety of cellular responses contributing to skin cancer. Unrepaired DNA photoproducts cause the release of cytokines that contribute to tumor promotion, tumor progression, immunosuppression, and the induction of latent viruses. DNA repair enzymes are an important gene protection mechanism, because they can repair DNA photoproducts and block the carcinogenic responses triggered by cytokines. See Sections 3 and 5 for discussion of xeroderma pigmentosum patients and the role of DNA repair capacity in skin cancer.

6.2.3 Mutations

The photoproducts formed from UVR exposure as a result of DNA damage have varying mutagenic potentials. Cyclobutane-type thymine dimers, the major UVR photoproducts, are only weakly mutagenic (Banerjee *et al*. 1988, 1990, both cited in IARC 1992), whereas the less common (6-4) thymine-thymine photoproduct is highly mutagenic (LeClerc *et al*. 1991, cited in IARC 1992). UVR-induced cyclobutane dimer formation is directly involved in UVR carcinogenesis. Such dimers prevent gene transcription. Malignant transformation of the cell may result when the affected gene is a growth-regulating gene, such as an oncogene or tumor suppressor gene. DNA repair mechanisms include excision repair and photoreactivation. In the latter, the photoreactivating enzyme repairs UVR-induced cyclobutane dimers and (6-4) photoproducts; the enzyme is activated by UVA and visible light. Thus, photoreactivation repair of cyclobutane dimers effectively reduced the incidence of UVR-induced tumors in the opossum *M. domestica* (Ley *et al.* 1991, cited in Grabbe and Granstein 1994).

The mutagenicity also varies with the type of UVR. Peak *et al.* (1987, cited in Robert *et al.* 1996) found that the frequency of single-strand breaks per genome per lethal event was higher upon exposure of a human teratoma cell line to UVA than to UVB and/or UVC. This is consistent with the finding that UVA induces a greater proportion of rearrangements than UVB, 39% vs. 24%, possibly as a result of repair of single-strand breaks (Robert *et al*. 1996).

6.2.4 Tumor suppressor gene expression and mutation

Loss of p53 function is an important factor in multistep carcinogenesis. Burren *et al.* (1998) exposed human skin to sunlight and analyzed the skin for p53 expression and pyrimidine dimers. The exposed human skin showed increased levels of pyrimidine dimers and p53 protein expression. These effects varied according to the dose and wavelength of UVR. At equivalent biological doses, p53 expression was twice as high after exposure to simulated solar radiation than after exposure to UVA. At lower doses of UVA, expression of p53 was limited to the basal-cell keratinocytes; however, at higher doses, all layers of the epidermis were affected. The researchers found that even sub-erythemal doses of simulated solar radiation induced both pyrimidine dimers and p53 expression in human skin *in situ* (Burren *et al.* 1998).

Berg *et al*. (1996, cited in Griffiths *et al*. 1998) unequivocally demonstrated that constitutive p53 tumor suppression gene product alterations are an early event in the induction of skin cancer and are causally linked to UVB exposure. Sequencing data from a large number of skin tumors showed that p53 was mutated in over 90% of squamous-cell carcinomas (Brash *et al.* 1991, Ziegler *et al*, 1993, Wikonkal *et al*. 1997, cited in Wikonkal and Brash 1999). These p53 mutations were found in 74% of sun-exposed normal skin, compared with 5% in unexposed skin, indicating a strong association with sun exposure. The majority of the mutations were C to T transitions occurring at dipyrimidine sites, with single C to T transitions occurring in 70% of the cases and tandem CC to TT in 10% of the cases, suggesting a causal relationship between pyrimidine photoproducts and UVB carcinogenesis. The p53 tumor suppression gene product is involved in cell-cycle regulation and is responsible for initiating cell apoptosis.

Lack of p53 tumor suppressor gene product results in failure to arrest the cell cycle in G_1 phase or to initiate the apoptotic pathway of cell death. Attempts by cells to replicate the damaged genome will result in accumulated mutations that will, in turn, contribute to genomic instability and reduced efficiency of DNA repair, leading to carcinogenesis (Hanawalt 1996). Although detection of p53 mutations in skin tumor cells suggests that p53 mutations are involved in some malignant melanomas, the role of p53 mutations in melanoma may not be as large as their roles in skin basal-cell carcinoma or squamous-cell carcinoma (Griffiths *et al*. 1998).

Sarasin (1999) reported that the PTCH tumor suppressor gene might have a role in skin cancer development. This gene is involved in signal transduction related to cell development and differentiation. Point mutations in *PTCH* were found in patients with Gorlin's syndrome (nevoid basal-cell carcinoma syndrome), who have a high incidence of basal-cell carcinomas; in 30% to 60% of basal-cell carcinomas from DNA-repair-proficient individuals; and in 50% to 80% of basal-cell carcinomas from xeroderma pigmentosum patients.

6.2.5 Immunosuppression

Exposure to solar radiation and UVR has altered immune function in experimental animals and humans (IARC 1992). Studies of patients with DNA repair disorders such as xeroderma pigmentosum, cockayne syndrome, and sun-sensitive trichothiodystrophy have shown that DNA repair defects and elevated levels of sunlight-induced mutations in the skin are insufficient to explain the high incidence of skin cancer in xeroderma pigmentosum patients. Therefore, UVR-induced mutations in critical genes may be necessary but not sufficient for skin cancer (Bridges 1998). Immunosuppression has been suggested as a possibly important tumor-controlling mechanism (Quinn 1997, Bridges 1998, Sarasin 1999).

A study of mice with a defective XPA gene showed the full XP phenotype. These mice were hypersensitive to UVB and showed several immunological defects similar to those seen in human xeroderma pigmentosum patients (Bridges 1998). Quinn (1997) noted several other findings indicating that immunosuppression is related to skin cancer incidence: (1) immunosuppressed organ transplant recipients showed a marked increase in skin cancer, particularly squamous-cell carcinoma, (2) UVR decreased the ability to mount a delayed-type hypersensitivity response, and (3) mice exposed to low levels of UVR failed to reject highly immunogenic tumor cell lines.

UVB increases tumor necrosis factor, which may suppress the function of a neoplastic population of clonal T-cells in the skin, in a process mediated by urocanic acid and serving as an immune upregulator. Urocanic acid, one of the main chromophores present in the skin, exists in two isomeric forms, *trans* and *cis.* UVB converts *trans*-urocanic acid into *cis*-uracanic acid, which is reported to be immunosuppressive (Streilein 1993, Streilein *et al*. 1994, Herrmann *et al*. 1995). c*is*-Urocanic acid is thought to exert its immunosuppressive action by causing a local accumulation of tumor necrosis factor-α (Streilein *et al*. 1994), in turn preventing normal induction of contact hypersensitivity in the skin (Streilein 1993, Cadet *et al*. 1997). Pre-irradiation of mice with low doses of UVB (100 to 700 J/m^2 of fluorescent sunlamp radiation daily for four hours) suppressed

the development of contact hypersensitivity to sensitizing chemicals (such as 2,4-dinitrofluorobenzene) subsequently applied to the irradiated skin (Toews *et al.* 1980, Elmets *et al.* 1983, cited in IARC 1992). Local suppression of contact hypersensitivity by UVB radiation also was observed in hamsters (Streilein and Bergstresser 1981, cited in IARC 1992).

UVB radiation decreases the alloactivating and antigen-presenting capacity of Langerhans cells and increases interleukin-2 and interleukin-6 production by human keratinocytes (Herrmann *et al.* 1995). In UV-irradiated skin cells, cell markers for Langerhans cells are diminished. In concert with and because of the resultant abrogation of the antigen-presenting function of Langerhans cells in these skin cells, suppressor T-cell activation and tolerance to antigen results in immunosuppression. Such immunosuppression has resulted in the growth of immunogenic neoplasms in mice and may facilitate the growth of human neoplasms (Baadsgaard 1991).

6.3 Initiation and promotion

The evidence indicates that UVR is a complete carcinogen; that is, it both initiates and promotes carcinogenesis (Matsui and DeLeo 1991, IARC 1992, Soballe *et al.* 1996, Wikonkal and Brash 1999). The carcinogenic effects of UVR have been attributed largely to UVB, which has been reported to be at least 5,000 times more effective as a complete carcinogen than UVA (Forbes 1985, cited in Matsui and DeLeo 1991). However, in some animal studies, UVA administered alone hasinduced skin cancer (see Section 4.2).

Matsui and DeLeo (1991) reviewed the evidence that UVA acts as a classic promoter and discussed possible mechanisms. UVA was shown to promote squamous-cell carcinoma in albino hairless mice. A constant dose of UVA was least effective in inducing cancer, and a regimen of UVA plus UVB was most effective. Other studies indicated that UVA (320 to 400 nm) induced responses *in vivo* and in cultured mammalian cells similar to treatment with the phorbol ester tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate. Current evidence indicates that UVA's promotional effects are through modulation of protein kinase C, whereas UVB and UVC do not affect protein kinase C activity. UVA may also promote carcinogenesis through mechanisms involving reactive oxygen species (de Laat and de Gruijl 1996).

6.4 Summary

UVA is the most abundant component of UVR that reaches the surface of the earth. Although UVB is partially filtered out by the atmosphere, it is the most biologically significant component of solar UVR reaching the earth's surface, because it is absorbed by biologically critical targets in the skin, such as DNA. UVR may be transmitted, reflected, scattered, or absorbed by tissue chromophores in a wavelength- and chromophore-dependent manner. UVB and UVC induce damage to biological systems directly, whereas UVA-induced damage is indirect, mediated via endogenous photosensitizers in the target tissues in photodynamic or nonphotodynamic phototoxic reactions. These reactions result in damage to DNA (base mutations and dimerizations, strand breaks, and DNA-protein crosslinks for UVA; base dimerizations and strand breaks for UVB; and base dimerizations and glycol formation, strand breaks, and elevation of gene transcription for UVC). UVB causes skin cancer via mechanisms that

include DNA damage, immunosuppression, tumor promotion, and mutations in the p53 gene. There is some evidence that UVA, under certain conditions, may act as a complete carcinogen; however, there is more evidence that UVA acts as a tumor promoter. UVC radiation is filtered by the earth's atmosphere and does not occur in sunlight. UVC is known to cause direct damage to DNA, as does UVB; therefore, its potential role in human carcinogenicity would result from exposure to artificial sources of UVR, such as germicidal lamps, rather than sunlight.

7 References

1. Ablett,E., J.Pedley, P.A.Dannoy, R.A.Sturm P.G.Parsons. (1998). UVB-specific regulation of gene expression in human melanocytic cells: cell cycle effects and implication in the generation of melanoma. *Mutat Res* 422:31-41.

2. ACGIH. 1996. Threshold limit values for chemical substances and physical agents and biological exposure indicies. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

3. Adam,S.A., J.K.Sheaves, N.H.Wright, G.Mosser, R.W.Harris, and M.P.Vessey. (1981). A case-control study of the possible association between oral contraceptives and malignant melanoma. *Br J Cancer* 44:45-50.

4. Adami,J., G.Gridley, O.Nyren, M.Dosemeci, M.Linet, B,Glimelius, A.Ekbom, S.H.Zahm. (1999). Sunlight and non-Hodgkin's lymphoma: a population-based cohort study in Sweden. *Int J Cancer* 80:641-645.

5. Armstrong,B.K. and A.Kricker. (1996). Epidemiology of sun exposure and skin cancer. *Cancer Surv* 26:133-153.

6. Armstrong,J.D. and B.A.Kunz. (1992). Photoreactivation implicates cyclobutane dimers as the major promutagenic UVB lesions in yeast. *Mutat Res* 268:83-94.

7. Armstrong,J.D. and B.A.Kunz. (1990). Site and strand specificity of UVB mutagenesis in the SUP4-o gene of yeast. *Proc Natl Acad Sci USA* 87:9005-9009.

8. Atillasoy,E.S., R.Elenitsas, E.R.Sauter, P.W.Soballe, M.Herlyn. (1997). UVB induction of epithelial tumors in human skin using a RAG-1 mouse xenograft model. *J Invest Dermatol* 109:704-9.

9. Atillasoy,E.S., J.T.Seykora, P.W.Soballe, R.Elenitsas, M.Nesbit, D.E.Elder, K.T.Montone, E.Sauter, and M.Herlyn. (1998). UVB induces atypical melanocytic lesions and melanoma in human skin. *Am J Pathol* 152:1179-86.

10. Autier,P., M.Joarlette, F.Lejeune, D.Lienard, J.Andre and G.Achten. (1991). Cutaneous malignant melanoma and exposure to sunlamps and sunbeds: a descriptive study in Belguim. *Melanoma Res* 1:69-74.

11. Autier,P., J.F.Dore, F.Lejeune, K.F.Koelmel, O.Geffeler, P.Hille, J.P.Cesarini, D.Lienard, A.Liabeuf, M.Joarlette, P.Chemal, K.Hakim, A.Koeln, and U.R.Kleeberg. (1994). Cutaneous malignant melanoma and exposure to sunlamps or sunbeds: an EORTC multicenter case-control study in Belgium, France and Germany. EORTC Melanoma Cooperative Group. *Int J Cancer* 58:809-813.

12. Baadsgaard,O. (1991). In vivo ultraviolet irradiation of human skin results in profound perturbation of the immune system. Relevance to ultraviolet-induced skin cancer [published erratum appears in Arch Dermatol 1991 Sep;127(9):1368]. *Arch Dermatol* 127:99-109.

13. Bajdik,C.D., R.P.Gallagher, G.Astrakianakis, G.B.Hill, S.Fincham, and D.I.McLean. (1996). Non-solar ultraviolet radiation and the risk of basal and squamous cell skin cancer. *Br J Cancer* 73:1612-1614.

14. Banerjee,S.K., R.B.Christensen, C.W.Lawrence, and J.E.LeClerc. (1988). Frequency and spectrum of mutations produced by a single *cis-syn* thymine cyclobutane dimer in a single-stranded vector. *Pro. Nat. Aca. Sci USA* 85:8141-8145.

15. Banerjee,S.K., A.Borden, R.B.Christensen, J.E.LeClerc, and C.W.Lawrence. (1990). SOS-dependent replication past a single *trans-syn* T-T cyclobutane dimer gives a different mutation spectrum and increased error rate compared to replication past this lesion in uninduced cells. *J Bacteriol*. 172:2105-2112.

16. Bech T.N., H.C.Wulf, T.Poulsen, and K.Lundgren. (1988). Pretreatment with long-wave ultraviolet light inhibits ultraviolet-induced skin tumor development in hairless mice. *Arch Dermatol* 124:1215-1218.

17. Bech-Thomsen,N. (1997). Aspects of exposure to UVA tanning sources. Carcinogenic effect in mice and melanogenic effect in man and mice. *Dan Med Bull* 44:242-256.

18. Bech-Thomsen,N. and H.C.Wulf. (1993). Carcinogenic potential of fluorescent UV tanning sources can be estimated using the CIE erythema action spectrum. *Int J Radiat Biol* 64:445-450.

19. Bech-Thomsen,N., H.C.Wulf, T.Poulsen, F.G.Christensen, and K.Lundgren. (1991). Photocarcinogenesis in hairless mice induced by ultraviolet A tanning devices with or without subsequent solar-simulated ultraviolet irradiation. *Photodermatol Photoimmunol Photomed* 8:139-145.

20. Bech-Thomsen,N., T.Poulsen, F.G.Christensen, K.Lundgren, and H.C.Wulf. (1992). UVA tanning devices interact with solar-simulated UV radiation in skin tumor development in hairless mice. *Arch Dermatol Res* 284:353-357.

21. Beitner,H., S.E.Norell, U.Ringborg, G.Wennersten, and B.Mattson. (1990). Malignant melanoma: aetiological importance of individual pigmentation and sun exposure. *Br J Dermatol* 122:48-51.

22. Bentham,G. and A.Aase. (1996). Incidence of malignant melanoma of the skin in Norway, 1955-1989: associations with solar ultraviolet radiation, income and holidays abroad. *Int J Epidemiol* 25:1132-1138.

23. Beral,V, S.Evans, H.Shaw, and G.Milton. (1982). Malignant melanoma and exposure to fluorescent lighting at work. *Lancet* 2(8293):290-3.

24. Berg,R.J., H.J.van Kranen, H.G.Rebel, A.de Vries, W.A.van Vloten, C.F.Van Kreijl, J.C.van der Leun, and F.R.de Gruijl. (1996). Early p53 alterations in mouse skin carcinogenesis by UVB radiation: immunohistochemical detection of mutant p53 protein in clusters of preneoplastic epidermal cells. *Proc Natl Acad Sci U.S.A.* 93:274-278.

25. Beukers,R., J.Ylstra, and W.Berends. (1958). The effect of ultraviolet light on some components of nucleic acids. II. In rapidly frozen solutions. *Recl Trav chlim Pays-Bas* 77:729-732.

26. Beukers,R. and W.Berends. (1960). Isolation and identification of the irradiation product of thymidine. *Biochim Biophys Acta* 41:550-551.

27. Bhate,S.M., G.R.Sharpe, J.M.Marks, S.Shuster, and W.M.Ross. (1993). Prevalence of skin and other cancers in patients with psoriasis. *Clin Exp Dermatol* 18**:**401-4.

28. Blum,H.F. (1959) *Carcinogenesis by Ultraviolet Light*, Princeton, NJ:Princeton University Press.

29. Blum,H.F. and S.W.Lippincott. (1942). Carcinogenic effectiveness of ultraviolet radiation of wavelength 2537 Δ. *J Natl Cancer Inst* 3:211-216.

30. Boettner,E.A. and J.R.Wolter. (1962). Transmission of the ocular media. *Invest Ophthalmol* 1:776-783.

31. Brash,D.E., J.A.Rudolph, J.A.Simon, A.Lin, G.J.McKenna, H.P.Baden, A.J.Halperin, and J.Ponten. (1991). A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc Natl Acad Sci USA* 88:10124-10128.

32. Bridges,B.A. (1998). UV-induced mutations and skin cancer: how important is the link? *Mutat Res* 422:23-30.

33. Bridges,B. and G.Strauss. (1980). Possible hazards of photochemotherapy for psoriasis. *Nature* 283:523-524.

34. Bruynzeel,I., W.Bergman, H.M.Hartevelt, C.C.Kenter, V.van d, A.A.Schothorst, and D.Suurmond. (1991). "High single-dose" European PUVA regimen also causes an excess of non-melanoma skin cancer. *Br J Dermatol* 124:49-55.

35. Burren,R., C.Scaletta, E.Frenk, R.G.Panizzon, L.A.Applegate. (1998). Sunlight and carcinogenesis: expression of p53 and pyrimidine dimers in human skin following UVA I, UVA I + II and solar simulating radiations. *Int J Cancer* 76:201-6.

36. Bykov,V.J. and K.Hemminki. (1996). Assay of different photoproducts after UVA, B and C irradiation of DNA and human skin explants. *Carcinogenesis* 17:1949-1955.

37. Cadet,J. and P.Vigny. (1990). The photochemistry of nucleic acids. In: *Bioorganic Photochemistry*, H. Morrison, ed. (New York: Wiley and Sons), pp 1-272.

38. Cadet,J., C.Anselmino, T.Douki, and L.Voituriez. (1992). Photochemistry of nucleic acids in cells. *J Photochem Photobiol B* 15:277-298.

39. Cadet,J., M.Berger, T.Douki, B.Morin, S. Raoul, J.L.Ravanat, and S.Spinelli. (1997). Effects of UV and visible radiation on DNA-final base damage. *Biol Chem* 378:1275-1286.

40. Cameron,G.S. and B.C.Pence. (1992). Effects of multiple applications of tumor promoters and ultraviolet radiation on epidermal proliferation and antioxidant status. *J Invest Dermatol* 99:189-192.

41. Cebula,T.A., E.N.Henrikson, P.E.Hartman, and W.H.Biggley. (1995). Reversion profiles of coolwhite fluorescent light compared with far ultraviolet light: homologies and differences. *Photochem Photobiol* 61:353-359.

42. Chadwick,C.A., C.S.Potten, O.Nikaido, T.Matsunaga, C.Proby, and A.R.Young. (1995). The detection of cyclobutane thymine dimers, (6-4) photolesions and the Dewar photoisomers in sections of UV-irradiated human skin using specific antibodies, and the demonstration of depth penetration effects. *J Photochem Photobiol B* 28:163-170.

43. Chen,Y.T., R.Dubrow, T.Zheng, R.L.Barnhill, J.Fine, and M.Berwick. (1998). Sunlamp use and the risk of cutaneous malignant melanoma: a population- based case-control study in Connecticut, USA. *Int J Epidemiol* 27:758-765.

44. Cleaver,J.E. and K.Kraemer. (1989). Xeroderma pigmentosum. In *The Metabolic Basis of Inherited Diseases II*, C.R.Scriver, A.L.Beaudet, W.S.Sly, and D.Valle, eds. McGraw-Hill, New York. pp 2949-2971.

45. Clingen,P.H., C.F.Arlett, J.Cole, A.P.Waugh, J.E.Lowe, S.A.Harcourt, N.Hermanova, L.Roza, T.Mori, and O.Nikaido. (1995). Correlation of UVC and UVB cytotoxicity with the induction of specific photoproducts in T-lymphocytes and fibroblasts from normal human donors. *Photochem Photobiol* 61:163-170.

46. Corominas M, H.Kamino, J.Leon, and A.Pellicer. (1989). Oncogene activation in human benign tumors of the skin (keratoacanthomas): is H-*ras* involved in differentiation as well as proliferation? *Proc Natl Acad Sci USA* 86:6372-6376.

47. Currie C.L. and B.E. Monk. (2000). Welding and non-melanoma skin cancer. *Clin Exp Dermatol* 25(1):28-9.

48. Daya-Grosjean,L., N.Dumaz, and A.Sarasin. (1995). The specificity of p53 mutation spectra in sunlight induced human cancers. *J Photochem Photobiol B* 28:115-124.

49. de Gruijl,F.R., H.J.C.M.Sterenborg, P.D.Forbes, R.E.Davies, C.Cole, G.Kelfkens, H.van Weelden, H.Slaper, and J.C.van der Leun. (1993). Wavelength Dependence of Skin Cancer Induction by Ultraviolet Irradiation of Albino Hairless Mice. *Cancer Research* 53:53-60.

50. de Gruijl,F.R., J.B.Van Der Meer, and J.C.van der Leun. (1983). Dose-time dependency of tumor formation by chronic UV exposure. *Photochem Photobiol* 37:53-62.

51. de Laat,J.M., and F.R.de Gruijl. (1996). The role of UVA in the aetiology of non-melanoma skin cancer. *Cancer Surv* 26:173-91.

52. de Laat,A., J.C.van der Leun, and F.R.de Gruijl. (1997). Carcinogenesis induced by UVA (365-nm) radiation: the dose-time dependence of tumor formation in hairless mice. *Carcinogenesis* 18(5):1013-1020.

53. Dorn,C.R., D.O.Taylor, and R.Schneider. (1971). Sunlight exposure and risk of developing cutaneous and oral squamous cell carcinomas in white cats. *J Natl Cancer Inst* 46:1073-8.

54. Dubin,N., M.Moseson, and B.S.Pasternack. (1989). Sun exposure and malignant melanoma among susceptible individuals. *Environ Health Perspect* 81:139-151.

55. Dunn-Lane,J., B.Herity, M.J.Moriarty, and R.Conroy. (1993). A case control study of malignant melanoma. *Irish Med J* 86:57-59.

56. Elmets,C.A., P.R.Bergstresser, R.E.Tigelaar, P.J.Wood, and J.W.Streilein. (1983). Analysis of the mechanism of unresponsiveness produced by haptens painted on skin exposed to low dose ultraviolet radiation. *J Exp Med* 158:781-794.

57. Elwood,J.M. (1996). Melanoma and sun exposure. *Semin Oncol* 23:650-666.

58. Elwood,J.M. and J.Jopson. (1997). Melanoma and sun exposure: an overview of published studies. *Int J Cancer* 73:198-203.

59. Elwood J.M., C.Williamson, and P.J.Stapleton. (1986). Malignant melanoma in relation to moles, pigmentation, and exposure to fluorescent and other lighting sources. *Br J Cancer* 53:65-74.

60. Emmett,E.A. (1973). Ultraviolet radiation as a cause of skin tumors. *CRC Crit Rev Toxicol* 2:211-255.

61. English,D.R., B.K.Armstrong, A.Kricker, C.Fleming. (1997). Sunlight and cancer. *Cancer Causes Control* 8:271-283.

62. Epstein,J.H. (1978). Photocarcinogenesis: a review. *Natl Cancer Inst Monogr* 13-25.

63. Epstein,J.H. (1985). Animal models for studying photocarcinogenesis. In: *Models in Dermatology*, H.Maibach and N.Lowe, eds., Vol.2, (Basel, Karger), pp 303-312.

64. Farmer,K.C. and M.F.Naylor. (1996). Sun exposure, sunscreens, and skin cancer prevention: a year-round concern. *Ann Pharmacother* 30:662-673.

65. FDA. (1996). http://www.fda.gov/fdac/features/496_sun.html.

66. Findlay,G.M. (1930). Cutaneous papillomata in the rat following exposure to ultra-violet light. *Lancet* i:1229-1231.

67. Forbes,P.D., H.F.Blum, and R.E.Davies. (1981). Photocarcinogenesis in hairless mice: Dose-response and the influence of dose-delivery. *Photochem Photobiol* 34:361-365.

68. Forbes,P.D., R.E.Davies, F.Urbach, D.Berger, and C.Cole. (1982). Simulated stratospheric ozone depletion and increased ultraviolet radiation: effects on photocarcinogenesis in hairless mice. *Cancer Res* 42(7):2796-803.

69. Forbes P.D. (1985). UV-A and photocarcinogenesis. *Photochem Photobiol* 42:7S.

70. Forman,A.B., H.H.Roenigk Jr, W.A.Caro, and M.L.Magid. (1989). Long-term follow-up of skin cancer in the PUVA-48 cooperative study. *Arch Dermatol* 125:515-9.

71. Franklin,W.A. and W.A.Haseltine. (1984). Removal of UV light-induced pyrimidine-pyrimidone(6-4) products from Escherichia coli DNA requires the uvrA, uvrB, and urvC gene products. *Proc Natl Acad Sci U.S.A.* 81:3821-3824.

72. Freedman,D.M., S.H.Zahm, and M.Dosemeci. (1997). Residential and occupational exposure to sunlight and mortality from non-Hodgkin's lymphoma:composite (threefold) case-control study. *BMJ* 314:1451-1455.

73. Freeman,R.G. and J.M.Knox. (1964). Ultraviolet-induced corneal tumors in different species and strains of animals. *J Invest Dermatol* 90: 814-817.

74. Gallagher,R.P., J.M.Elwood, and G.B.Hill. (1986). Risk factors for cutaneous malignant melanoma: the western Canada melanoma study. *Recent Results Cancer Res* 102:38-55.

75. Garbe,C., J.Weiss, S.Krüger, E.Garbe, P.Büttner, J.Bertz, H.Hoffmeister, I.Guggenmoos-Holzmann, E.G.Jung, and C.E.Orfanos. (1993). The German melanoma registry and environmental risk factors implied. *Recent Results Cancer Res* 128:69-89.

76. Gasparro,F.P. (2000). Sunscreens, skin photobiology, and skin cancer: the need for UVA protection and evaluation of efficacy. *Environ Health Perspect* 108 (Suppl 1):71-8.

77. Gilchrest,B.A., M.S.Eller, A.C.Geller, and M.Yaar. (1999) The pathogenesis of melanoma induced by ultraviolet radiation. *N Engl J Med* 340:1341-8.

78. Gould,J.W., M.G.Mercurio, and C.A.Elmets. (1995). Cutaneous photosensitivity diseases induced by exogenous agents. *J Am Acad Dermatol* 33:551-573.

79. Grabbe,S., and R. D.Granstein. (1994). Mechanisms of ultraviolet radiation carcinogenesis. *Chem. Immunol*. 58:291-313.

80. Grady,H.G., H.F.Blum, and J.S.Kirby-Smith. (1943). Types of tumor induced by ultraviolet radiation and factors influencing their relative incidence. *J Natl Cancer Inst* 3:371-378.

81. Griffiths,H.R., P.Mistry, K.E.Herbert, and J.Lunec. (1998). Molecular and cellular effects of ultraviolet light-induced genotoxicity. *Crit Rev Clin Lab Sci* 35:189-237.

82. Hall,J., D.R.English, M.Artuso, B.K.Armstrong and M.Winter. (1994). DNA repair capacity as a risk factor for non-melanocytic skin cancer—a molecular epidemiological study. *Int J Cancer* 58:179-184.

83. Hanawalt,P.C. (1996). Role of transcription-coupled DNA repair in susceptibility to environmental carcinogenesis. *Environ Health Perspect* 104(Suppl 3):547-551.

84. Hannuksela-Svahn,A., E.Pukkala, E.Läärä, K.Poikolainen, and J.Karvonen. (2000). Psoriasis, its treatment, and cancer in a cohort of Finnish patients. *J Invest Dermatol* 114:587-590.

85. Hariharan,P.V. and P.A.Cerutti. (1976). Excision of ultraviolet and gamma ray products of the 5,6-dihydroxy- dihydrothymine type by nuclear preperations of xeroderma pigmentosum cells. *Biochim Biophys Acta* 447:375-378.

86. Hariharan,P.V. and P.A.Cerutti. (1977). Formation of products of the 5,6-dihydroxydihydrothymine type by ultraviolet light in HeLa cells. *Biochemistry* 16:2391-2395.

87. Hartge,P., S.S.Devesa, D.Grauman, T.R.Fears, and J.F.J.Fraumeni. (1996). Non-Hodgkin's lymphoma and sunlight. *J Natl Cancer Inst* 88:298-300.

88. Hartmann,A., H.Blaszyk, and J.S.Cunninghamn. (1996). Overexpression and mutations of p53 in metastatic malignant melanoma. *Int J Cancer* 67:313-317.

89. Hattori,Y., C.Nishigori, T.Tanaka, K.Uchida, O.Nikaido, T.Osawa, H.Hiai, S.Imamura, and S.Toyokuni. (1996). 8-hydroxy-2'-deoxyguanosine is increased in epidermal cells of hairless mice after chronic ultraviolet B exposure [published erratum appears in J Invest Dermatol 1997 Feb;108(2):237]. *J Invest Dermatol* 107:733-737.

90. Herbert,K.E., N.Mistry, H.R.Griffiths, and J.Lunec. (1994). Immunochemical detection of sequence-specific modifications to DNA induced by UV light. *Carcinogenesis* 15:2517-2521.

91. Herrlich,P., C.Sachsenmaier, A.Radler-Pohl, S.Gebel, C.Blattner, and H.J.Rahmsdorf. (1994). The mammalian UV response: mechanism of DNA damage induced gene expression. *Adv Enzyme Regul* 34:381-395.

92. Herrmann,J.J., H.H.J.Roenigk, and H.Honigsmann. (1995). Ultraviolet radiation for treatment of cutaneous T-cell lymphoma. *Hematol Oncol Clin North Am* 9:1077-1088.

93. Hill,H.Z., W.Li, P.Xin, and D.L.Mitchell (1997). Melanin: A two edged sword? *Pigment Cell Res* 10:158-161.

94. Holly,E.A., J.W.Kelly, S.N.Shpall and S.Chiu. (1987). Number of melanocytic nevi as a major risk factor for malignant melanoma. *J Am Acad Dermatol* 17:459-468.

95. Holly,E.A., D.A.Aston, R.D.Cress, D.K.Ahn, and J.Kristiansen. (1995). Cutaneous melanoma in women. *Am J Epidemiol* 141:923-933.

96. Holly,E.A., D.A.Aston, D.K.Ahn, and A.H.Smith. (1996). Intraocular melanoma linked to occupations and chemical exposures. *Epidemiology* 7:55-61.

97. Holman,C.D.J., B.K.Armstrong, P.J.Heenan, J.B.Blackwell, F.J.Cumming, D.R.English, S.Holland, G.R.H.Kelsall, L.R.Matz, I.L.Rouse, A.Singh, R.E.J.Ten Seldam, J.D.Watt, and Z.Xu. (1986). The causes of malignant melanoma: results from the west Australian lions melanoma research project. *Recent Results Cancer Res* 102:18-37.

98. Hori,M., M.U.Udono, H.Yoshida, Y.Urata, K.Koike, and M.Ihara. (1992). Immunochemical detection of unrepaired cyclobutane-type pyrimidine dimers of DNAs extracted from human skin tumours. *Arch Dermatol Res* 284:283-289.

99. Hueper,W.C. (1942). Morphological aspects of experimental actinic and arsenic carcinomas in the skin of rats. *Cancer Res* 2:551-559.

100. Huldschinsky,K. (1933). Eye sarcoma in rats caused by abnormally long UV (Ger). *Dtsch med Wochenschr* 59:530-531.

101. IARC. (1982). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Chemicals, Industrial Processes and Industries Associated with Cancer in Humans (Volumes 1 to 29).* International Agency for Research on Cancer, World Health Organization, Lyon, France. Suppl 4.

102. IARC. (1987). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42.* International Agency for Research on Cancer, World Health Organization, Lyon, France. Suppl 7.

103. IARC. (1992). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Solar and Ultraviolet Radiation*. International Agency for Research on Cancer, World Health Organization, Lyon, France 55:1-316.

104. Ito,K. and S.Kawanishi. (1997). Site-specific DNA damage induced by UVA radiation in the presence of endogenous photosensitizer. *Biol Chem* 378:1307-1312.

105. Jagger,J. (1985). *Solar-UV Actions on Living Cells*. Praeger, New York.

106. Johns,H.E., S.A.Rapaport, and M.Delbruck. (1962). Photochemistry of thymine dimers. *J Mol Biol* 4:104-114.

107. Keijzer,W., M.P.Mulder, J.C.Langeveld, E.M.Smit, J.L.Bos, D.Bootsma, J.H.Hoeijmakers. (1989). Establishment and characterization of a melanoma cell line from a xeroderma pigmentosum patient: activation of N-*ras* at a potential pyrimidine dimer site. *Cancer Res* 49:1229-35.

108. Kelfkens,G., F.R.de Gruijl, and J.C.van der Leun. (1991). Tumorigenesis by short-wave ultraviolet A: papillomas versus squamous cell carcinomas. *Carcinogenesis* 12:1377-1382.

109. Kim,Y.O., H.J.Chung, S.T.Chung, J.H.Kim, J.H.Park, K.S.Kil, and D.H.Cho. (1999). Phototoxicity of melatonin. *Arch Pharm Res* 22:143-50.

110. Klepp,O. and K.Magnus. (1979). Some environmental and bodily characteristics of melanoma patients. A case control study. *Int J Cancer* 23:482-486.

111. Kligman,L.H., M.J.Crosby, S.A.Miller, V.M.Hitchins, and J.Z.Beer. (1990). Skin cancer induction in hairless mice by long-wavelength UVA radiation: a process report (Abstract). *Photochem Photobiol* 51:18S-19S.

112. Klingman,L.H., M.J.Crosby, S.A.Miller, V.M.Hitchins, and J.Z.Beer. 1992. Carcinogenesis by long wavelength UVA and failure of reciprocity. In *Biological Responses to Ultraviolet A Radiation* F.Urbach ed. Valdenmar, Overland Park, KS, pp301-308.

113. Kraemer,K.H. and G.D.Weinstein. (1977). Decreased thymidine incorporation in circulating leukocytes after treatment of psoriasis with psoralen and long-wave ultraviolet light. *J Invest Dermatol* 69:211-214.

114. Kripke,M.L. and E.R.Sass, eds. (1978). International conference on ultraviolet carcinogenesis. (50). *National Cancer Institute Monograph*.

115. Kunz,B.A. and J.D.Armstrong. (1998). Differences in the mutational specificities of sunlight and UVB radiation suggest a role for transversion-inducing DNA damage in solar photocarcinogenesis. *Mutat Res* 422:77-83.

116. Kusewitt,L.A., L.A.Applegate, and R.D.Ley. (1991). Ultraviolet Radiation-induced Skin Tumors in a South American Opossum (Monodelphis domestica). *Vet Pathol* 28:55-65.

117. Larko,O. and G.Swanbeck. (1982). Is UVB treatment of psoriasis safe? A study of extensively UVB-treated psoriasis patients compared with a matched control group. *Acta Derm Venereol* 62:507-12.

118. LeClerc,J.E., A.Borden, and C.W.Lawrence. (1991). The thymine-thymine pyrimidine-pyrimidone (6-4) ultraviolet light photoproduct is highly mutagenic and specifically induces 3′-thymine-to-cytosine transitions in *Escherichia coli*. *Proc. Natl. Acad. Sci.* USA 88:9685-9689.

119. Lerman,S. (1988). Ocular phototoxicity [editorial]. *N Engl J Med* 319:1475-1477.

120. Ley,R.D. (1985). Photoreactivation of UV-Induced pyrimidine dimers and erythema in the marsupial *Monodelphis domestica*. *Proc Natl Acad Sci USA* 82:2409-2411.

121. Ley,R.D. (1997). Ultraviolet radiation A-induced precursors of cutaneous melanoma in *Monodelphis domestica*. *Cancer Res* 57:3682-4.

122. Ley,R.D., L.A.Applegate,T.D.Stuart, and R.J.M.Fry. (1987). UV radiation-induced skin tumors in *Monodelphis domestica*. *Photodermatology* 4:144-147.

123. Ley,R.D., L.A.Applegate, R.S.Padilla, and T.D.Stuart. (1989). Ultraviolet radiation-induced melanoma in *Monodelphis domestica*. *Photochem Photobiol* 50:1-5.

124. Ley,R.D., L.A.Applegate, R.J.M.Fry, and A.B.Sanchez. (1991). Photoreactivation of ultraviolet radiation-induced skin and eye tumors of *Monodelphis domestica*. *Cancer Res*. 51:6539-6542.

125. Lill,P.H. (1983). Latent period and antigenicity of murine tumors induced in C3H mice by short-wavelength ultraviolet radiation. *J Invest Dermatol* 81:342-346.

126. Lindelof B., B.Sigurgeirsson, E.Tegner, O.Larko, A.Johannesson, B.Berne, O.B.Christensen, T.Andersson, M.Torngren, L.Molin, *et al.* (1991). PUVA and cancer: a large-scale epidemiological study. *Lancet* 338(8759):91-3.

127. Lindelof,B., B.Sigurgeirsson, E.Tegner, O.Larko, A.Johannesson, B.Berne, B.Ljunggren, T.Andersson, L.Molin, E.Nylander-Lundqvist, and L.Emtestam. (1999). PUVA and cancer risk: the Swedish follow-up study. *Br J Dermatol* 141**:**108-12.

128. Lippincott,S.W. and H.F.Blum. (1943). Neoplasms and other lesions of the eye induced by ultraviolet radiation in strain A mice. *J Natl Cancer Inst*. 3:545-554.

129. MacKie,R.M., T.Freudenberger, and T.C.Aitchison. (1989). Personal risk-factor chart for cutaneous melanoma. *Lancet* 2:487-490.

130. Madewell,B.R., J.D.Conroy, E.M.Hodgkins. (1981). Sunlight-skin cancer association in the dog: a report of three cases. *J Cutaneous Pathol* 8:434-443.

131. Matsui,M.S. and V.A.DeLeo. (1991). Longwave ultraviolet radiation and promotion of skin cancer. *Cancer Cells* 3:8-12.

132. McMichael,A.J. and G.G.Giles. (1996). Have increases in solar ultraviolet exposure contributed to the rise in incidence of non-Hodgkin's lymphoma? *Br J Cancer* 73:945-950.

133. Maier,H., M.Schemper,, B.Ortel,, M.Binder, A.Tanew, and H.Honigsmann. (1996). Skin tumors in photochemotherapy for psoriasis: a single-center follow-up of 496 patients. *Dermatology* 193:185-91.

134. Menzies,S.W., G.E.Greenoak, V.E.Reeve, and C.H.Gallagher. (1991). Ultraviolet radiation-induced murine tumors produced in the absence of ultraviolet radiation-induced systemic tumor immunosuppression. *Cancer Res*. 51:2773-2779.

135. Mizuno,T., T.Matsunaga, M.Ihara, and O.Nikaido. (1991). Establishment of a monoclonal antibody recognizing cyclobutane-type thymine dimers in DNA: a comparative study with 64M-1 antibody specific for (6-4)photoproducts. *Mutat Res* 254:175-184.

136. Moan,J., A.Dahlback, and R.B.Setlow. (1999). Epidemiological support for an hypothesis for melanoma induction indicating a role for UVA radiation. *Photochem Photobiol* 70:243-7.

137. Morrison,H. (1985). Photochemistry and photobiology of urocanic acid. *Photodermatology* 2:158-165.

138. Morrison,W.L. (1992). Phototherapy and photochemotherapy. *Adv Dermatol* 7:255-270.

139. Muller,L., P.Kasper, B.Kersten, J.Zhang. (1998). Photochemical genotoxicity and photochemical carcinogenesis--two sides of a coin? *Toxicol Lett*;102-103:383-7.

140. Murata-Kamiya,N., H.Kamiya, N.Iwamoto, and H.Kasai. (1995). Formation of a mutagen, glyoxal, from DNA treated with oxygen free radicals. *Carcinogenesis* 16:2251-2253.

141. NASA. (2000). http://imagine.gsfc.nasa.gov/docs/science/know_11/emspectrum.html

142. Newton,R., J.Ferlay, G.Reeves, V.Beral, D.M.Parkin. (1996). Effect of ambient solar ultraviolet radiation on incidence of squamous-cell carcinoma of the eye. *Lancet* 347(9013):1450-1.

143. Nikula,K.J., S.A.Benjamin, G.M.Angleton, W.J.Saunders, A.C.Lee. (1992). Ultraviolet radiation, solar dermatosis, and cutaneous neoplasia in beagle dogs. *Radiat Res* 129:11-8.

144. Nomura,T., H.Nakajima, T.Hongyo, E.Taniguchi, K.Fukuda, L.Y.Li, M.Kurooka, K.Sutoh, P.M.Hande, T.Kawaguchi, M.Ueda, H.Takatera. (1997). Induction of cancer, actinic keratosis, and specific p53 mutations by UVB light in human skin maintained in severe combined immunodeficient mice. *Cancer Res* 57:2081-4.

145. NTP. (1997). Report on Carcinogens. *Solar Radiation and Exposure to Sunlamps or Sunbeds*. U.S. DHHS, National Toxicology Program.

146. Østerland,A., M.A.Tucker, B.J.Stone, and O.M.Jensen. (1988). The Danish case-control study of cutaneous malignant melanoma. II. Importance of UV-light exposure. *Int J Cancer* 42:319-324.

147. Ouhtit,A., M.Ueda, H.Nakazawa, M.Ichihashi, N.Dumaz, A.Sarasin, and H.Yamasaki. (1997). Quantitative Detection of Ultraviolet-specific p53 Mutations in Normal Skin from Japanese Patients. *Cancer Epidemiology, Biomarkers & Prevention* 6:433-438.

148. Pasker-de Jong,P. C., G.Wielink,., P.G.van der Valk, and G.J.van der Wilt. (1999). Treatment with UV-B for psoriasis and nonmelanoma skin cancer: a systematic review of the literature. *Arch Dermatol* 135:834-40.

149. Pathak,M.A. (1996). Sunscreens: Progress and Perspectives on Photoprotection of Human Skin against UVB and UVA Radiation. *The Journal of Dermatology* 23:783-800.

150. Peak,M.J., C.A.Jones, B.A.Sedita, E.J.Dudek, D.R.Spitz, and J.G.Peak. (1990). Evidence that hydrogen peroxide generated by 365-nm UVA radiation is not important in mammalian cell killing. *Radiat Res* 123:220-223.

151. Peak,M.J., J.G.Peak, and B.A.Carnes. (1987). Induction of direct and indirect single-strand breaks in human cell DNA by far- and near-ultraviolet radiations: Action spectrum and mechanisms. *Photochem. Photobiol*. 45:381-387.

152. Phillips,R. (1983). *Sources and Applications of Ultraviolet Radiation*. Academic Press, London.

153. Pierceall,W.E., L.H.Goldberg, M.A.Tainsky, T.Mukhopadhyay, H.N.Ananthaswamy. (1991). Ras gene mutation and amplification in human nonmelanoma skin cancers. *Mol Carcinog* 4:196-202.

154. Pittelkow,M.R., H.O.Perry, S.A.Muller, W.Z.Maughan, P.C.O'Brien. (1981). Skin cancer in patients with psoriasis treated with coal tar. A 25-year follow-up study. *Arch Dermatol* 117:465-8.

155. Putschar,W. and F.Holtz (1930). Production of skin tumors in rats by long duration UV irradiation (Ger.). *Z Krebsforsch*. 33:219-260.

156. Quinn,A.G. (1997). Ultraviolet radiation and skin carcinogenesis. *Br J Hosp Med* 58:261-264.

157. Robert,C., B.Muel, A.Benoit, L.Dubertret, A.Sarasin, and A.Stary. (1996). Cell survival and shuttle vector mutagenesis induced by ultraviolet A and ultraviolet B radiation in a human cell line. *J Invest Dermatol*. 106:721-728.

158. RoC. (2000). 9th Report on Carcinogens. U.S. DHHS, National Toxicology Program.

159. Roffo,A.H. (1934). Cancer and the sun: carcinomas and sarcomas caused by the action of the sun in toto (Fr.). *Bull Assoc fr Etude Cancer* 23:590-616.

160. Roffo,A.H. (1939). Physico-chemical etiology of cancer (with special emphasis on the associaation with solar radiation) (Ger.). *Strahlentherapie* 66:238-350.

161. Rosenthal,F.S., S.K.West, B.Munoz, E.A.Emmett, P.T.Strickland, and H.R.Taylor. (1991). Ocular and facial skin exposure to ultraviolet radiation in sunlight: a personal exposure model with application to a worker population. *Health Phys* 61:77-86.

162. Runger,T.M. (1999). Role of UVA in the pathogenesis of melanoma and non-melanoma skin cancer. A short review. *Photodermatol Photoimmunol Photomed* 15:212-6.

163. Sarasin,A. (1999). The molecular pathways of ultraviolet-induced carcinogenesis. *Mutat Res* 428:5-10.

164. Satyamoorthy,K, F.Meier, M.Y.Hsu, C.Berking, and M.Herlyn. (1999). Human xenografts, human skin and skin reconstructs for studies in melanoma development and progression. *Cancer Metastasis Rev* 18:401-5.

165. Sauter,E.R., S.A.Klein, E.Atillasoy, K.T.Montone, T.Goodrow, R.L.Binder, J.T.Seykora, and M.Herlyn. (1998). Ultraviolet B-induced squamous epithelial and melanocytic cell changes in a xenograft model of cancer development in human skin. *Mol Carcinog* 23:168-174.

166. Seddon,J.M., E.S.Gragoudas, R.J.Glynn, K.M.Egan, D.M.Albert, and P.H.Blitzer. (1990). Host factors. UV radiation and risk of uveal melanoma. A case-control study. *Arch Ophthalmol*. 108:1274-1280.

167. Sekiya,T., M.Fushimi, H.Hori, S.Hrohashi, S.Nishimura, and T.Sugimura. (1984). Molecular cloning and the total nucleotide sequence of the human c-Ha-*ras*-1 gene activated in a melanoma from a Japanese patient. *Proc Natl Acad Sci USA*. 81:4771-4775.

168. Setlow,R.B., A.D.Woodhead, and E.Grist. (1989). Animal model for ultraviolet radiation-induced melanoma: platyfish-swordtail hybrid. *Proc Natl Acad Sci USA*. 86:8922-8926.

169. Setlow,R.B., E.Grist, K.Thompson, and A.D.Woodhead. (1993). Wavelengths effective in induction of malignant melanoma. *Proc Natl Acad Sci USA* 90:6666-6670.

170. Shukla,V.K., D.C.Hughes, L.E.Hughes, F.McCormick, and R.A.Padua. (1989). *ras* Mutations in human melanotic lesions: K-*ras* activation is a frequent and early event in melanoma development. *Oncogene Res* 5:121-127.

171. Siemiatycki,J. (1991). *Risk Factors for Cancer in the Workplace*. CRC Press, Boco Raton, FL.

172. Smith,K.C. (1989). *The Science of Photobiology*, K.C.Smith ed. Plenum, New York.

173. Soballe,P.W., K.T.Montone, K.Satyamoorthy, M.Nesbit, M.Herlyn. (1996) Carcinogenesis in human skin grafted to SCID mice. *Cancer Res* 56:757-764.

174. Staberg,B., H.C.Wulf, P.Klemp, T.Poulsen, and H.Brodthagen. (1983). The carcinogenic effect of UVA irradiation. *J Invest Dermatol* 81:517-519.

175. Stary,A., C.Robert, A.Sarasin. (1997). Deleterious effects of ultraviolet A radiation in human cells. *Mutat Res* 383:1-8.

176. Stenback,F. (1975). Studies on the modifying effect of ultraviolet radiation on chemical skin carcinogenesis. *J Invest Dermatol* 64:253-257.

177. Sterenborg,H.J. and J.C.van der Leun. (1988). Change in epidermal transmission due to UV-induced hyperplasia in hairless mice: a first approximation of the action spectrum. *Photodermatol* 5:71-82.

178. Sterenborg,H.J. and J.C.van der Leun. (1990). Tumorigenesis by a long wavelength UV-A source. *Photochem Photobiol* 51:325-330.

179. Stern,R.S. (1990). Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. The Photochemotherapy Follow-up Study. *N Engl J Med* 322**:**1093-1097.

180. Stern,R.S. and N.Laird. (1994). The carcinogenic risk of treatments for severe psoriasis. *Cancer* 73:2759-2764.

181. Stern,R.S., N.Laird, J.Melski, J.A.Parrish, T.B.Fitzpatrick, and H.L.Bleich. (1984). Cutaneous squamous-cell carcinoma in patients treated with PUVA. *N Engl J Med* 310**:**1156-61.

182. Stern,R.S., and R.Lange. (1988). Non-melanoma skin cancer occurring in patients treated with PUVA five to ten years after first treatment *J Invest Dermatol* 91:120-4.

183. Stern,R.S., E.J.Liebman, and L.Vakeva. (1998). Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-up Study. *J Natl Cancer Inst* 90:1278-1284.

184. Stern,R.S., K.T.Nichols, and L.H.Vakeva. (1997). Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA Follow-Up Study [see comments]. *N Engl J Med* 336:1041-1045.

185. Stern,R.S., L.A.Thibodeau, J.A.Parrish, and T.B.Fitzpatrick. (1979). Skin cancer after PUVA treatment for psoriasis [letter]. *N Engl J Med* 301:555.

186. Stern, R.S., S.Zierler, and J.A.Parrish. (1980). Skin carcinoma in patients with psoriasis treated with topical tar and artificial ultraviolet radiation. *Lancet* 1(8171):732-5.

187. Stewart,M.S., G.S.Cameron, and B.C.Pence. (1996). Antioxidant nutrients protect against UVB-induced oxidative damage to DNA of mouse keratinocytes in culture. *J Invest Dermatol* 106:1086-1089.

188. Strauss,G.H. (1982). PUVA: gambling with a system. *Int J Dermatol* 21:136-137.

189. Strauss,G.H., B.A.Bridges, M.Greaves, P.Hall-Smith, M.Price, and D.Vella-Briffa. (1980). Inhibition of delayed hypersensitivity reaction in skin (DNCB test) by 8-methoxypsoralen photochemotherapy. Possible basis for pseudo- promoting action in skin carcinogenesis? *Lancet* 2:556-559.

190. Strauss,G.H., R.J.Albertini, P.A.Krusinski, and R.D.Baughman. (1979). 6-Thioguanine resistant peripheral blood lymphocytes in humans following psoralen, long-wave ultraviolet light (PUVA) therapy. *J Invest Dermatol* 73:211-216.

191. Streilein,J.W. (1993). Sunlight and skin-associated lymphoid tissues (SALT): if UVB is the trigger and TNF alpha is its mediator, what is the message? *J Invest Dermatol* 100:47S-52S.

192. Streilein,J.W. and P.R.Bergstresser. (1981). Langerhans cell function dictates induction of contact hypersensitivity or unresponsiveness to DNFB in Syrian hamsters. *J Invest Dermatol* 77:272-277.

193. Streilein,J.W., J.R.Taylor, V.Vincek, I.Kurimoto, J.Richardson, C.Tie, J.P.Medema, and C.Golomb. (1994). Relationship between ultraviolet radiation-induced immunosuppression and carcinogenesis. *J Invest Dermatol* 103(Suppl 5):107S-111S.

194. Strickland,P.T., F.J.Burns, and R.E.Albert. (1979). Induction of skin tumors in the rat by single exposure to ultraviolet radiation. *Photochem Photobiol* 30:683-688.

195. Studniberg,H.M. and P.Weller. (1993). PUVA, UVB, psoriasis, and nonmelanoma skin cancer. *J Am Acad Dermatol* 29:1013-1022.

196. Swerdlow,A.J., J.S.English, R.M.MacKie, C.J.O'Doherty, J.A.Hunter, J.Clark, and D.J.Hole. (1988). Fluorescent lights, ultraviolet lamps, and risk of cutaneous melanoma [published erratum appears in BMJ 1988 Nov 5;297(6657):1172]. *BMJ* 297:647-650.

197. Swerdlow,A.J. and M.A.Weinstock. (1998). Do tanning lamps cause melanoma? An epidemiologic assessment. *J Am Acad Dermatol* 38:89-98.

198. Toews,G.B., P.R.Bergstresser, and J.W.Streilein. (1980). Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. *J Immunol* 124:445-453.

199. Urbach,F., J.H.Epstein, and P.D.Forbes. (1974). Ultraviolet carcinogenesis: experimental, global,and genetic aspects. In *Sunlight and Man. Normal and Abnormal Photobiological Responses*. M.A.Pathak, L.C.Harber, M.Seiji, and A.Kukita, eds. University of Tokyo Press, Tokyo. pp. 259-283.

200. van der Leun,J.C. (1984), Yearly review: UV-carcinogenesis. *Photochem Photobiol* 39:861-868.

201. van der Schroeff,J.G., L.M.Evers, A.J.M.Boot, and J.L.Bos. (1990). *Ras* Oncogene mutations in basal cell carcinomas and squamous cell carcinomas of human skin. *J Invest Dermatol*. 94:423-425.

202. van't Veer,L.J., B.M.T.Burgering, R.Versteeg, A.J.M.Boot, D.J.Ruiter, S.Osanto, P.I.Schrier, and J.L.Bos. (1989). Effects of ultraviolet B light on cutaneous immune responses of humans with deeply pigmented skin. *J Invest Dermatol* 97: 729-734.

203. van Weelden,H., F.R.de Gruijl, and J.C.van der Leun. (1986). Carcinogenesis by UVA, with an attempt to assess the carcinogenic risks of tanning with UVA and UVB. In *The Biolgical Effects of UVA Radiation*, F.Urbach and R.W.Gange, eds. Praeger , New York pp. 137-146.

204. van Weelden,H., F.R.de Gruijl, S.C.van der Putte, J.Toonstra, and J.C.van der Leun. (1988). The carcinogenic risks of modern tanning equipment: is UV-A safer than UV-B? *Arch Dermatol Res* 280:300-307.

205. van Weelden,H., S.C.van der Putte, J.Toonstra, and J.C.van der Leun. (1990). UVA-induced tumours in pigmented hairless mice and the carcinogenic risks of tanning with UVA. *Arch Dermatol Res* 282:289-294.

206. Vitasa,B.C., H.R.Tylor, P.T.Strickland, F.S.Rosenthal, S.West, H.Abbey, S.K.Ng, B.Munoz, and E.A.Emmett. (1990). Association of nonmelanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Mryland watermen. *Cancer* 65:2811-2817.

207. Walter,S.D., W.D.King, and L.D.Marrett. (1999). Association of cutaneous malignant melanoma with intermittent exposure to ultraviolet radiation: results of a case-control study in Ontario, Canada. *Int J Epidemiol* 28:418-27.

208. Walter,S.D., L.D.Marrett, L.From, C.Hertzman, H.S.Shannon, and P.Roy. (1990). The association of cutaneous malignant melanoma with the use of sunbeds and sunlamps. *Am J Epidemiol* 131:232-43.

209. Walter,S.D., L.D.Marrett, H.S.Shannon, L.From, and C.Hertzman. (1992). The association of cutaneous malignant melanoma and fluorescent light exposure. *Am J Epidemiol* 135:749-62.

210. Wei,Q., G.M.Matanoski, E.R.Farmer, M.A.Hedayati, and L.Grossman. (1994). DNA repair and susceptivility to basal cell carcinoma: a case-control study. *Am J Epidemiol* 140:598-607.

211. Wei,Q., G.M.Matanoski, E.R.Farmer, M.A.Hedayati, and L.Grossman. (1995). DNA repair capacity for ultraviolet light-induced damage is reduced in peripheral lymphocytes from patients with basal cell carcinoma. *J Invest Dermatol* 104:933-936.

212. Westerdahl,J., C.Ingvar, A.Masback, N.Jonsson,., and H.Olsson, H. (2000). Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UV-A carcinogenicity. *Br J Cancer* 82:1593-9.

213. Westerdahl,J., H.Olsson, A,Masback, C.Ingvar, N.Jonsson, L.Brandt, P.E.Jonsson, and T.Moller. (1994). Use of sunbeds or sunlamps and malignant melanoma in southern Sweden. *Am J Epidemiol* 140:691-699.

214. Whitmore,S.E. and W.L.Morison. (1997) Melanoma after PUVA therapy for psoriasis [letter; comment]. *N Engl J Med* 337:502-3.

215. WHO. (1979). Ultraviolet Radiation. In: *Environmental Health Criteria 14* World Health Organization, Geneva.

216. Wikonkal,N.M., R.J.Berg, C.W.van Haselen, I.Horkay, E.Remenyik, A.Begany, J.Hunyadi, W.A.van Vloten, and F.R.de Gruijl. (1997). bcl-2 vs p53 protein expression and apoptotic rate in human nonmelanoma skin cancers. *Arch Dermatol* 133:599-602.

217. Wikonkal,N.M. and D.E.Brash. (1999). Ultraviolet radiation induced signature mutations in photocarcinogenesis. *J Investig.Dermatol.Symp.Proc.* 4:6-10.

218. Whittaker,S. (1996). Sun and skin cancer. *British Journal of Hospital Medicine* 56:515-518.

219. Wulff,D.L. and G.Fraenkel. (1961). On the nature of the thymine photoproduct. *Biochim Biophys Acta* 51:332-339.

220. Yarosh,D.B. and M.L.Kripke. (1996). DNA repair and cytokines in antimutagenesis and anticarcinogenesis. *Mutat. Res*. 350:255-260.

221. Young,A.R., S.L.Walker, J.S.Kinley, S.R.Plastow, D.Averbeckm, P.Morliere, and L.Dubertret. (1990). Phototumorigenesis studies of 5-methosypsoralen in bergamot oil: evaluation and modification of risk of human use in an albino mouse skin model. *J Photochem Photobiol B Biol* 7:231-250.

222. Young,A.R., C.S.Potten, O.Nikaido, P.G.Parsons, J.Boenders, J.M.Ramsden, C.A.Chadwick. (1998). Human melanocytes and keratinocytes exposed to UVB or UVA in vivo show comparable levels of thymine dimers. *J Invest.Dermatol.* 111:936-40.

223. Zanetti,R., S.Rosso, F.Faggiano, R.Roffino, S.Colonna, and G.Martina. (1988). A case-control study on cutaneous malignant melanoma in the province of Torino, Italy. *Rev Epidem et Santé Publ* 36:309-317.

224. Ziegler,A., D.J.Leffell, S.Kunala, H.W.Sharma, M.Gailani, J.A.Simon, A.J.Halperin, H.P.Baden, P.E.Shapiro, A.E.Bale, and D.Brash. (1993). Mutation hotspots due to sunlight in the p53 gene of nonmelanoma skin cancers. *Proc Natl Acad Sci USA* 90:4216-20.

Appendix A: IARC Monograph of Evaluation of Carcinogenic Risks to Humans. Solar and Ultraviolet Radiation. Vol. 55. Lyon, France. World Health Organization. 1992. pp. 43-279.

SOLAR AND ULTRAVIOLET RADIATION

1. Exposure Data

1.1 Nomenclature

1.1.1 *Optical radiation*

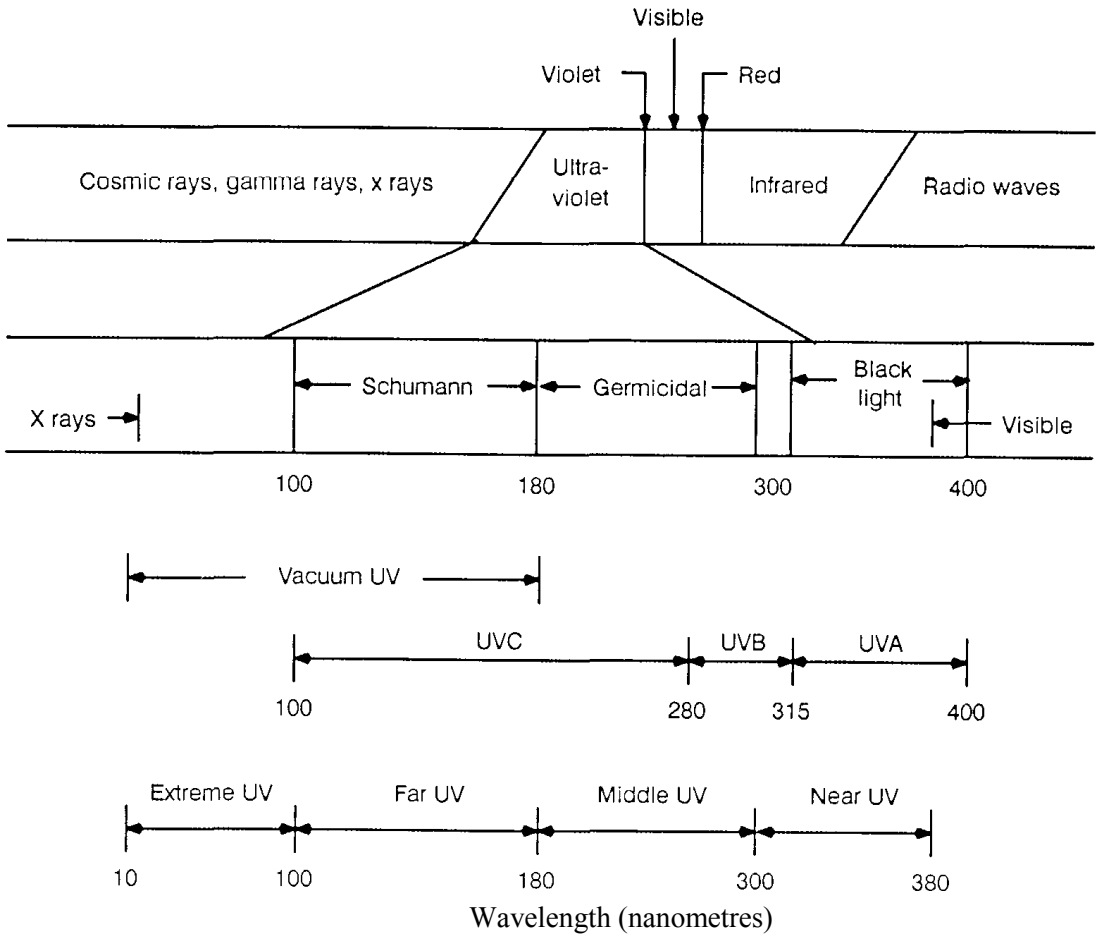
Optical radiation is radiant energy within a broad region of the electromagnetic spectrum that includes ultraviolet (UV), visible (light) and infrared radiation. Ultraviolet radiation (UVR) is characterized by wavelengths between 10 and 400 nm—bordered on the one side by x rays and on the other by visible light (Fig. 1). Solar radiation is largely optical radiation, although ionizing radiation (i.e., cosmic rays, gamma rays and x rays, which have wavelengths less than approximately 10 nm) and radio-frequency radiation (i.e., wavelengths greater than 1 mm: microwaves and longer radio waves) are also present in the spectrum.

The optical radiation spectrum is generally considered to fall between 10 nm and 1 mm, and several different conventions have been developed to describe different bands within this spectrum. It is important to recognize that no single convention is uniquely 'correct' but that each may be useful for a particular branch of science and technology. For example, in optics, it is convenient to separate the spectrum into different bands on the basis of the transmission and absorption properties of optical materials (e.g.. glass and quartz). In one optical convention, shown in Figure 1, UVR is divided into vacuum UV, extending from 10 to 180 nm; middle UV, from 180 nm to 300 nm: and near UV, from 300 nm to 380 or 400 nm. Meteorological scientists typically define optical spectral regions on the basis of atmospheric windows. Some spectral designations are based on uses, e.g.. 'germicidal' and 'black-light' regions.

For the purposes of this monograph, the photobiological designations of the Commission Internationale de l'Eclairage (CIE, International Commission on Illumination) are the most relevant and are used throughout to define the approximate spectral regions in which certain biological absorption properties and biological interaction mechanisms may dominate (Commission Internationale de l'Eclairage, 1987). The CIE bands are: UVC (100-280 nm), UVB (280-315 nm) and UVA (315-400 nm). Visible light is the region between 400 nm and 780 nm.

It is important to recognize that these spectral band designations are merely short-hand notations and cannot be considered to designate fine dividing lines below which an effect is present and above which it does not occur. The reader should also be alerted to the fact that the CIE nomenclature is not always followed rigorously and that some authors introduce slight variations; for example, distinguishing between UVB and UVA at 320 rather than 315 nm (frequently used in the USA) and defining UVC as 200-280 nm (Moseley, 1988). The German Industrial Standard (DIN 5031) defines UVA as radiation between 315 and 380 nm (Mutzhas, 1986).

Figure 1. Electromagnetic spectrum with enlargement of ultraviolet (UV) region



Adapted from WHO (1979), Morison (1983a) Sylvania (undated)

From the viewpoint of photochemistry and photobiology, interactions of optical radiation with matter are considered to occur when one photon interacts with one molecule to produce a photochemically altered molecule or two dissociated molecules (Phillips, 1983; Smith, 1989). In any photochemical interaction, the energy of the individual photon is important, since this must be sufficient to alter a molecular bond. 'fee photon energy is generally expressed in terms of electron volts (eV). A wavelength of 10 nm corresponds to a photon energy of 194 eV, and 400 nm to an energy of 3.1 eV (WHO, 1979). The number of altered molecules produced relative to the number of absorbed photons is referred to as the ‘quantum yield’ (Phillips. 1983). The efficacy of photochemical interaction per incident quantum and the photobiological effects per unit radiant exposure typically vary widely with wavelength. A quantitative plot of such spectral variation, usually normalized to unity at the most effective wavelength, is referred to as an 'action spectrum' (Jagger, 1985).

1.1.2 *Quantities and units*

Two systems of quantities and units are used to describe the characteristics of light and light sources: the radiometric and the photometric systems. Radiometry can be applied to all optical sources and to all exposures to optical radiation (including solar radiation and UVR). Photometry can be used only to describe visible light sources. and photometric quantities are used in illumination engineering. The basic photometric unit is the lumen, which is defined in terms of the spectral response of the human eye (specifically, the spectral response of the CIE 'standard observer'), i.e., the action spectrum of vision, which is initially a photochemical process. It is important to recognize that radiometric quantities and units are absolute, while photometric quantities and units are related to standardized human perception; the relationship between the two sets of units varies significantly with the spectrum of radiation. The effects of optical radiation (including light), other than vision, must therefore be measured and quantified in terms of radiometric units and spectral characteristics rather than photometric units. This is particularly important in relation to the photobiological effects of UVR. Most lamps used for illumination are rated by manufacturers only in photometric terms (e.g., lumen output) and not in terms of UVR emission (Phillips, 1983).

The most important radiometric quantities and units commonly used to describe optical radiation are given in Table 1. Certain terms are used primarily to describe source characteristics, e.g., radiance, radiant intensity; whereas other terms are generally used to describe exposure (irradiance, radiant exposure). The term ‘spectral’ placed before any of the quantities implies restriction to a unit wavelength band, e.g., spectral irradiance (watts per square metro per nanometre) (Moseley, 1988). For a more detailed discussion of these parameters, see various standard textbooks on radiometry, such as Boyd (1983).

The quantities of radiometry are expressed in terms of absolute energy (Jagger, 1985). Radiant intensity is the power emitted per unit solid angle of a source. Radiance is the radiant intensity per unit area of source. Thus, a fluorescent lamp dries not have very high radiance in comparison to the filament of a flashlight bulb, even though it has a high radiant power output. The radiometric term expressed in units of watts per square metre (dose rate) is irradiance, which is also the power striking a unit area of surface.

The energy of UVR falling on a unit surface area of an object was defined in 1954 by the First International Congress of Photobiology as the 'dose'; it has also been referred to as 'exposure dose'. The equivalent radiometric quantity is radiant exposure, expressed in joules per square centimetre or per square metro. Radiant exposure has been referred to as 'energy fluence' in some texts; however, fluence is a radiometric quantity, with the same units as radiant exposure, but referring to energy arriving at a plane of unit area from all directions, including backscatter. Thus, fluence is quite correctly of value in describing an exposure dose at a depth inside tissue: it has, however, seldom been calculated in photobiological studies of the effects of UVR, in which the radiant exposure incident upon the skin is normally measured. Radiant exposure is the amount of energy crossing a unit area of space normal to the direction of propagation of a beam of UVR. If the radiant energy arrives from many directions, as from the sky, then the fluence at one point is the sum of all the component fluences entering a unit sphere of space. The energy fluence rate is the power

that crosses a unit area normal to the direction of propagation, or the energy per unit area per unit time

Table 1. Some basic terminology used to quantify optical radiation

Term	International symbol	Definition	SI unit	Synonyms and comments
Wavelength	λ		nm	Nanometre = 10^{-9} m (also called millimicron, mμ)
Radiant energy	Q_e	$\Sigma(P_e \times dt)$	J	Joule; 1 joule = 1 watt x second; total energy contained in a radiation field or total energy delivered to a given receiver by such a radiation field
Radiant flux	P_e	dQ_e/dt	W	Watt; rate of delivery of radiant energy ('radiant power'); also expressed as ø
Irradiance	E_e	dP_e/dA	W/m^2	Radiant flux arriving over a given area ('fluence rate', 'dose rate', 'intensity', 'radiant incidence'). In photobiology, has also been expressed in W/cm^2, mW/cm^2 and $\mu W/cm^2$
Radiant intensity	I_e	$dP_e/d\Omega$	W/sr	Watt/steradian; radiant flux emitted by source into a given solid angle (solid angle expressed in steradians)
Radiance	L_e	$dP_e/dA \times d\Omega$	$W/m^2 \times sr$	Watt/m2 x steradian; radiant flux per unit solid angle per unit area emitted by an extended source
Radiant exposure	H_e	$E_e \times t$	J/m^2	Radiant energy delivered to a given area ('fluence', 'exposure dose', 'dose'); t = time in seconds. Has also been expressed as J/cm^2, mJ/cm^2 and $\mu J/cm^2$

Adapted from WHO (1979), Boyd (1983), Jagger (1985), Hoffman (1987) and Weast (1989)

($J/m^2/s$ or W/m^2). The terms dose (J/m^2) and dose rate (W/m^2) pertain to the energy and power, respectively, striking a unit surface area of an irradiated object (Jagger, 1985).

In terms of visible light perceived by humans, the photometric analogue of the radiance of a source is luminance (brightness), and irradiance is illuminance (measured in 'lux' or lumen per square metre). In photometry, the lumen is the unit of luminous power (Jagger, 1985).

1.1.3 *Units of biologically effective ultraviolet radiation*

In addition to general radiometric quantities, specialized quantities of effective irradiance relative to a specified photochemical action spectrum are used in photochemistry and photobiology. Effective radiant exposures to produce erythema (Jagger, 1985) or photokeratitis are examples. Effective irradiance or radiant exposure is not limited to photobiology, and a similar approach has been used to quantify the photocuring of inks, in photopolymerization (Phillips, 1983) and in assessing the hazards of UVR. In order to weight a

source spectrally, the general formula involves an action spectrum and a spectral radiometric quantity. The effective irradiance of a given photobiological process is defined as:

$$\sum_{\lambda_1}^{\lambda_2} E_\lambda \times S_\lambda \times \Delta_\lambda$$

expressed in W/m^2, where E_λ is the spectral irradiance (W/m^2 x nm) at wavelength A (nm) and Δ_λ is the wavelength interval ($\lambda_1 \rightarrow \lambda_2$) used in the summation (in nm). So, is a measure of the effectiveness of radiation of wavelength λ (nm), relative to some reference wavelength, in producing a particular biological end-point. As it is a ratio, S_λ has no units (American Conference of Governmental Industrial Hygienists, 1991).

Effective irradiance is equivalent to a hypothetical irradiance of monochromatic radiation with a wavelength at which S_λ is equal to unity. The time integral of effective irradiance is the effective radiant exposure (also called the 'effective dose').

A unit of effective dose commonly used in cutaneous photobiology is the 'minimal erythema dose' (MED). One MED has been defined as the lowest radiant exposure to UVR that is sufficient to produce erythema with sharp margins 24 h after exposure (Morison, 1983a). Another end-point often used in cutaneous photobiology is a just-perceptible reddening of exposed skin; the dose of UVR necessary to produce this 'minimal perceptible erythema' is sometimes also referred to as an MED. In unacclimatized, white-skinned populations, there is an approximately four-fold range in the MED of exposure to UVB radiation (Diffey & Farr, 1989). When the term MED is used as a unit of exposure dose, however, a representative value is chosen for sun-sensitive individuals. If, in the above expression for effective irradiance. So is chosen as the reference action spectrum for erythema (McKinley & Diffey, 1987) and a value of 200 J/m^2 at wavelengths for which S_λ is equal to unity is assumed for the MED, the dose (expressed in MED) received after an exposure period of *t* seconds is $t \times \Sigma E_\lambda \times S_\lambda \times \Delta_\lambda/200$.

Notwithstanding the difficulties of interpreting accurately the magnitude of such an imprecise unit as the MED, it has the advantage over radiometric units of being related to the biological consequences of the exposure.

1.2 Methods for measuring ultraviolet radiation

UVR can be measured by chemical or physical detectors, often in conjunction with a monochromator or band-pass filter for wavelength selection. Physical detectors include radiometric devices, which depend for their response on the heating effect of the radiation, and photoelectric devices, in which incident photons are detected by a quantum effect such as the production of electrons. Chemical detectors include photographic emulsions, actinometric solutions and UV-sensitive plastic films.

1.2.1 Spectroradiometry

The fundamental way of characterizing a source of UVR is on the basis of its spectral power distribution in a graph (or table) which indicates the radiated power as a function of wavelength. The data are obtained by a technique known as spectroradiometry. Spectral

measurements are often not required as ends in themselves but are used to calculate biologically weighted radiometric quantities. A spectroradiometer comprises three essential components (Gibson & Diffey, 1989):

(i) input optics, such as an integrating sphere or Teflon diffuser, which collects the incident radiation and conducts it to
(ii) the entrance slit of a monochromator, which disperses the radiation by means of one or two wavelength dispersive devices (either diffraction grating or prism). The monochromator also incorporates mirrors to guide the radiation from the entrance slit to the dispersion device and on to the exit slit, where it is incident on
(iii) a radiation detector, normally a photodiode or, for higher sensitivity, a photomultiplier tube.

Spectroradiometry is generally considered to be the best way of specifying UV sources, although the accuracy of spectroradiometry, particularly with respect to the UVB waveband of terrestrial radiation, is affected by a number of parameters including wavelength calibration, band width, stray radiation, polarization, angular dependence, linearity and calibration sources. It is therefore essential to employ a double monochromator for accurate characterization of terrestrial UVR and particularly UVB (Garrison *et al.,* 1978; Kostkowski *et al.,* 1982; Gardiner & Kirsch, 1991).

1.2.2 *Wavelength-independent (thermal) detectors*

General-purpose radiometers incorporate detectors that have a flat response over a wide range of wavelengths. Such thermal detectors operate on the principle that incident radiation is absorbed by a receiving element, and the temperature rise of the element is measured, usually by a thermopile or a pyroelectric detector. A thermopile, which comprises several thermocouples connected in series for improved sensitivity, must have a window made of fused silica for measuring UVR at wavelengths down to at least 250 nm. Pyroelectric detectors rely on a voltage generated by temperature changes in a lithium tantalate crystal. Thermal detectors are normally used to measure the total radiant power of a source rather than just the UV coinponent (Moseley, 1988).

Instruments for measuring broad-band solar radiation fall into three categories: pyroheliometers, pyranometers and pyranometers with a shading device (Iqbal. 1983). These types of instrument find their applications in meteorology rather than in UV photobiology.

1.2.3 *Wavelength-dependent detectors*

Detectors of this type have a spectral response that varies widely depending on the types of detector and filters that may be incorporated. Detectors can be designed to have a spectral response that matches a particular action spectrum for a photobiological end-point. The success with which this is achieved is variable. The most widely used device, particularly for measuring solar UVR, has been the Robertson-Berger meter (Robertson, 1972; Berger, 1976), which incorporates optical filters, a phosphor and a vacuum phototube or photovoltaic cell. This device measures wavelengths of less than 330 nm in the global spectrum with a spectral response that rises sharply with decreasing wavelength. It has been used to monitor natural UVR continuously at several sites throughout the world (Berger & Urbach, 1982; Diffey, 1987a).

Detectors incorporating a photodiode or vacuum photocell in conjunction with optical filter(s) and suitable input optics (e.g., a quartz hemispherical detector) have been produced to match a number of different action spectra. One such detector is the International Light Model 730 UV Radiometer, which has a spectral response close to the action spectrum designated by the American Conference of Governmental Industrial Hygienists for evaluating the hazard to health of exposure to UVR, and has been used to measure irradiance over different terrains (Sliney, 1986).

Wavelength-dependent detectors with spectral responses largely in the UVA waveband are used, for example, in measuring the output of irradiation units for the treatment of psoriasis by psoralen photochemotherapy (Morison, 1983a).

A different yet complementary approach is the use of various photosensitive films as UV dosimeters. The principle is to relate the degree of deterioration of the films, usually in terms of changes in their optical properties, to the dose of incident UVR. The principal advantages of the film dosimeter are that it provides a simple means of integrating exposure continuously and allows simultaneous comparison of numerous sites that are inaccessible to bulky, expensive instruments (Diffey, 1987a). The most widely used photosensitive film is polymer polysulfone (Diffey, 1989a). Personal dosimeters of polysulfone film have been developed and used in a number of dosimetric studies (Challoner *et al.,* 1976, 1978; Leach *et al.,* 1978: Holman *et al.,* 1983a: Larkö & Diffey, 1983; Diffey, 1987a; Schothorst *et al.,* 1987a; Slaper, 1987; Rosenthal *et al.,* 1990).

It is difficult to achieve a prescribed UVR spectral response with wavelength-dependent detectors. Accurate results can be achieved only if the detectors are calibrated against the appropriate source spectrum using a spectroradiometer (Gibson & Diffey,1989). Unless this is done, severe dosimetric errors can arise, particularly with measurements of solar UVR (Diffey, 1987a; Sayre & Kligman, 1992).

Accurate measurement of UVB radiation is far more difficult than would appear initially. The primary problem is that the UVB produced by most optical sources—the sun as well as incandescent and fluorescent lamps used for illumination—is only a very small fraction (i.e., less than 0.3%) of the total radiant energy emitted. Additionally, biological action spectra (e.g., for erythema and photokeratitis) typically decrease dramatically within the same waveband in which the source spectrum increases (Diffey & Farr, 1991a). This means that either a spectroradiometer or a direct-reading filtered 'erythemal' or 'hazard' meter must reject out-of-band radiant energy to better than one part in 10^4 or even 10^5. The spectral band-width of a monochromator can also greatly affect measurement error: too large a band-width can reduce the steepness of reported action spectra.

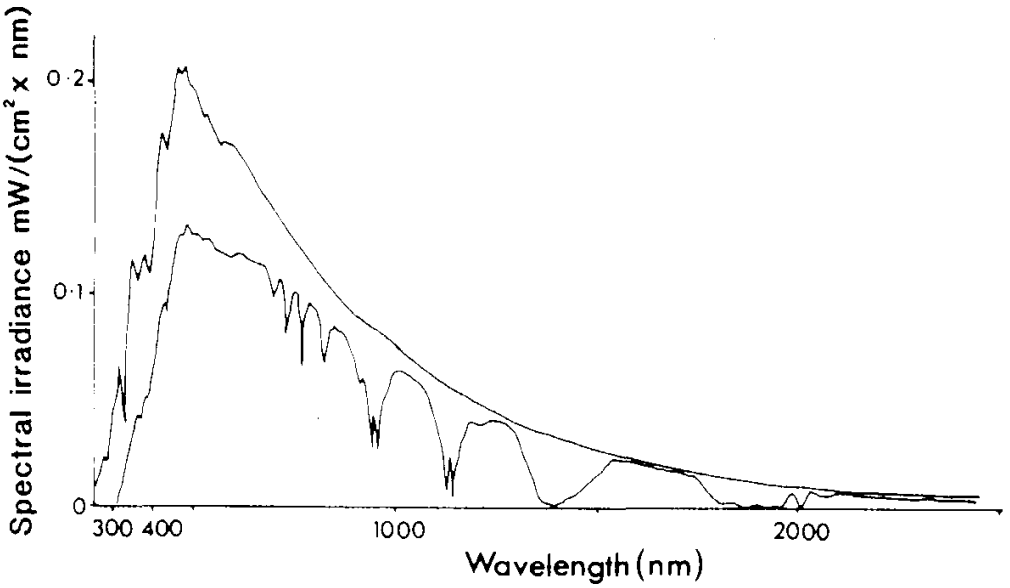
1.3 Sources and exposures

In the broadest sense, UVR may be produced when a body is heated (incandescence) or when electrons that have been raised to an excited state return to a lower energy level, as occurs in fluorescence, in an electric discharge in a gas and in electric arcs (optical plasma) (Sliney & Wolbarsht, 1980; Phillips, 1983; Moseley, 1988). The characteristics of exposures to both terrestrial solar radiation (an incandescent source) and artificial light sources are discussed in the following sections.

1.3.1 *Solar ultraviolet radiation*

Optical radiation from the sun is modified significantly as it passes through the Earth's atmosphere (Fig. 2), although about two-thirds of the energy from the sun that impinges on the atmosphere penetrates to ground level. The annual variation in extra-terrestrial radiation is less than 10%, but the variation in the modifying effect of the atmosphere is far greater (Moseley, 1988). Measurements corrected for atmospheric absorption show that the visible portion comprises approximately 40% of the total radiation received at the surface of the Earth. While UVR comprises only a small proportion of the total radiation (approximately 5%), this component is extremely important in various biological processes. The principal effect of infrared radiation is to warm the earth; approximately 55% of the solar radiation received at the surface of the earth is infrared (Foukal, 1990).

Fig. 2. Spectral irradiance from the sun outside the Earth's atmosphere (upper curve) and at sea level (lower curve)



From Moseley (1988)

On its path through the atmosphere, solar radiation is absorbed and scattered by various constituents of the atmosphere. It is scattered by air molecules, particularly oxygen and nitrogen (Rayleigh scattering), which produce the blue colour of the sky. It is also scattered by aerosol and dust particles (Mie scattering) and is scattered and absorbed by atmospheric pollution. Total solar irradiance and the relative contributions of different wavelengths vary with altitude. Clouds attenuate solar radiation, although their effect on infrared radiation is greater than on UVR. Reflection of sunlight from certain ground surfaces may contribute significantly to the total amount of scattered UVR. An effective absorber of solar UVR is ozone in the stratosphere (Moseley, 1988). An equally important absorber in the longer wavelengths (infrared) is water vapour (Diffey, 1991); a secondary absorber in this range is carbon dioxide. These two filter out much of the solar energy with wavelengths longer than 1000 nm (Sliney & Wolbarsht, 1980).

The quality (spectral distribution) and quantity (total UV irradiance) of UVR reaching the Earth's surface depend on the radiated power from the sun and the transmitting properties of the atmosphere. Although UVC exists in the extra-terrestrial solar spectrum, it is filtered out completely by the ozone layer in the atmosphere. UVB radiation, which represents about 5% of the total solar UVR that reaches the Earth (Sliney & Wolbarsht, 1980), has been considered to be the most biologically significant part of the terrestrial UV spectrum. The levels of UVB radiation reaching the surface of the Earth, although heavily attenuated, are also largely controlled by the ozone layer.

Ozone (O_3) is a gas which comprises approximately one molecule out of every two million in the atmosphere. It is created by the reaction of molecular oxygen (O_2) with atomic oxygen (O), formed by the dissociation of O2 by short-wavelength UVR (< 242 nm) in the stratosphere at altitudes between about 25 and 100 km. Absorption of UVR at wavelengths up to about 320 nm converts the ozone back to O_2 and O, and it is this dissociation of ozone that is responsible for preventing radiation at wavelengths less than about 290 nm from reaching the Earth's surface (Moseley, 1988; Diffey, 1991). Molina and Rowland (1974) first proposed that chlorofluorocarbons and other gases released by human activity could alter the natural balance of creative and destructive processes and lead to depletion of the stratospheric ozone layer. Substantial reductions, of up to 50%, in the ozone column observed in the austral spring over Antarctica were first reported in 1985 and may continue. There are, however, serious limitations in our current understanding of and ability to quantify ozone depletion at the present levels of contaminant release and in our ability to predict the effects on stratospheric ozone of any further increases (United Nations Environment Programme, 1989; United Kingdom Stratospheric Ozone Review Group, 1991).

A number of factors influence terrestrial UVR levels:

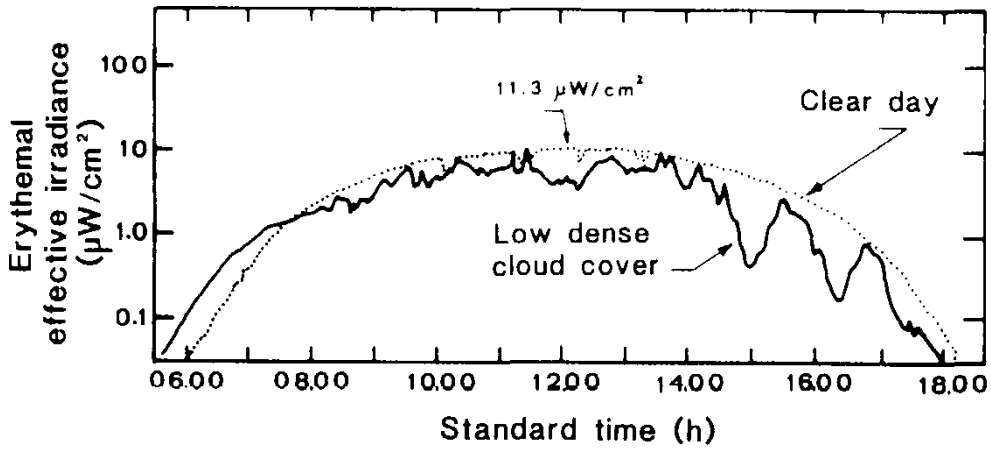
- *Variations in stratospheric ozone with latitude and se*ason (United Nations Environment Programme. 1989)
- *Time of day*: In summer, about 20-30% of the total daily amount of UVR is received between 11:00 and 13:00 h and 75% between 9:00 and 15:00 h (Diffey, 1991: Table 2 and Fig. 3). Although the amount of visible light falling on the ground in the summer may vary by only 30% between 12:00 and 15:00 h (local solar time), the short-wavelength component of the UVB spectrum undergoes a dramatic change during

Table 2. Percentage of daily UVB and WA radiation received during different periods of a clear summer's day. Solar noon is assumed to be at 12:00 h, i.e., no allowance is made for daylight saving time

Latitude (˚N)	UVB		UVA	
	11:00-13:00 h	9:00-15:00 h	11:00-13:00 h	9:00-15:00 h
20	30	78	27	73
40	28	75	25	68
60	26	69	21	60

From Diffey (1991)

Fig. 3. Daily variation in ultraviolet radiation: erythemal effective irradiance falling on a horizontal earth surface at Denver, CO, USA, on one summer's day



From Machta et al. (1975)

this period. At a wavelength of 300 nm, the spectral irradiance decreases by 10 fold, from approximately 1.0 to 0.1 μW/(cm^2 x nm) (Sliney, 1986).

- *Season:* Seasonal variation in terrestrial UV irradiance, especially UVB, at the Earth's surface is significant in temperate regions but much less nearer the equator (Table 3).

Table 3. Typical values for ambient daily and annual UVB radiation expressed in minimal erythema dose (MED)

Latitude (°N)	Diurnal UVB (MED)			
	Winter	Spring/Autumn	Summer	Annual
20 (Hawaii, USA)	14	20	25	6000
30 (Florida, USA)	5	12	15	4000
40 (Spain)	2	7	12	2500
50 (Belgium)	0.4	3	10	1500

From Diffey (1991)

- *Geographical latitude:* Annual UVR exposure dose decreases with increasing distance from the equator (Table 3).
- *Clouds:* Clouds reduce UV ground irradiance; changes in UVR are smaller than those of total irradiance because water in clouds attenuates solar infrared radiation much more than UVR. Even with heavy cloud cover, the scattered UVB component of sunlight (often called skylight) is seldom less than 10% of that under clear sky; however, very heavy cloud cover can virtually eliminate UVB even in summer. Light clouds scattered over a blue sky make little difference in sunburning effectiveness unless they directly cover the sun. Complete light cloud cover prevents about 50% of UVB energy, relative to that from a clear sky, from reaching the surface of the Earth (Diffey, 1991).

- *Surface reflection:* The contribution of reflected UVR to a person's total UVR exposure varies in importance with a number of factors (Table 4). A grass lawn scatters about 37 of incident UVB radiation. Sand reflects about 10-15%, so that sitting under an umbrella on the beach can lead to sunburn both from scattered UVB from the sky and reflected UVB from the sand. Fresh snow has been reported to reflect up to 85-90% of incident UVB radiation, although reflectance of about 30-50% is probably more typical. Ground reflectance is important, because parts of the body that are normally shaded are exposed to reflected radiation (Diffey, 1990a).

Table 4. Representative terrain reflectance factors for horizontal surfaces measured with a UVB radiometer at 12:00 h (290-315 nm) in the USA

Material	Reflectance (%)
Lawn grass, summer, Maryland, California and Utah	2.0-3.7
Lawn grass, winter, Maryland	3.0-5.0
Wild grasslands, Vail Mountain, Colorado	0.8-1.6
Lawn grass, Vail, Colorado	1.0-1.6
Flower garden, pansies	1.6
Soil, clay/humus	4.0-6.0
Sidewalk, light concrete	10-12
Sidewalk, aged concrete	7.0-8.2
Asphalt roadway, freshly laid (black)	4.1-5.0
Asphalt roadway, two years old (grey)	5.0-8.9
House paint, white, metal oxide	22
Boat dock, weathered wood	6.4
Aluminium, dull, weathered	13
Boat deck, wood, urethane coating	6.6
Boat deck, white fiberglass	9.1
Boat canvas, weathered, plasticized	6.1
Chesapeake Bay, Maryland, open water	3.3
Chesapeake Bay, Maryland, specular component of reflection at Z = 45 ˚N	13
Atlantic Ocean, New Jersey coastline	8.0
Sea surf, white foam	25-30
Atlantic beach sand, wet, barely submerged	7.1
Atlantic beach sand, dry, light	15-18
Snow, fresh	88
Snow, two days old	50

From Sliney (1986)

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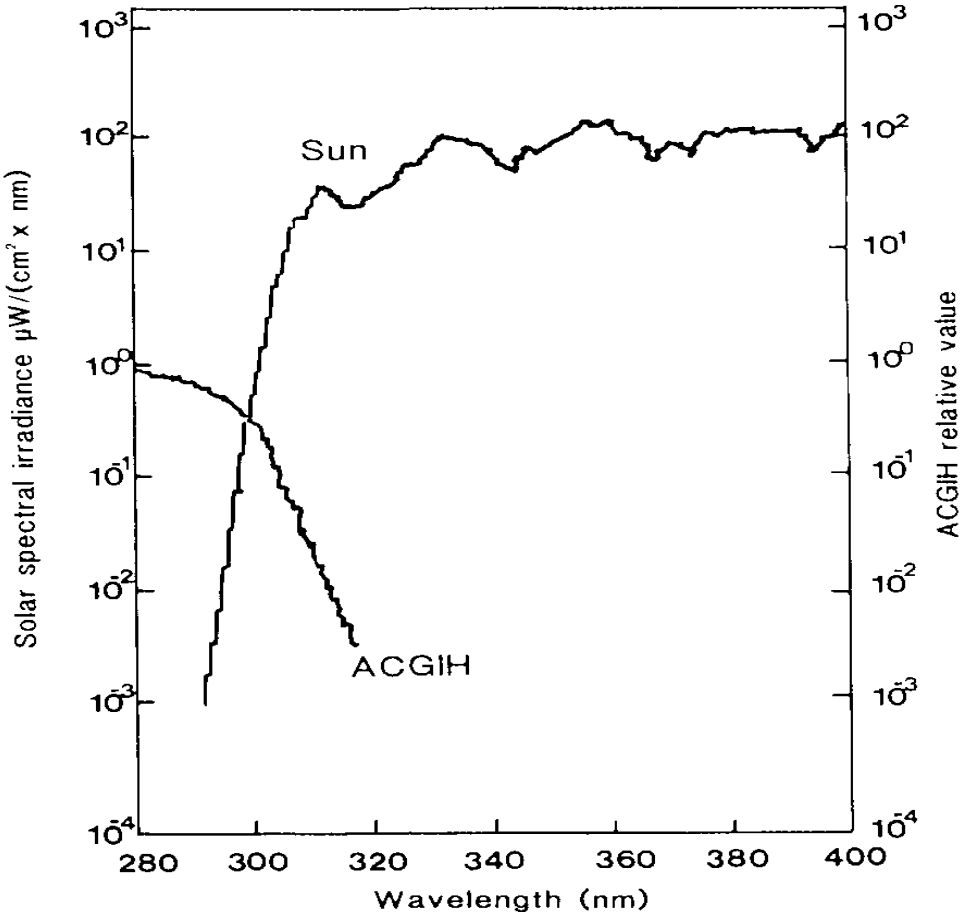
- *Altitude:* In general, each 300-m increase in altitude increases the sunburning effectiveness of sunlight by about 4%. Conversely, places on the Earth's surface below sea level have lower UVB exposures than nearby sites at sea level (Diffey, 1990a).

- *Air pollution:* Tropospheric ozone and other pollutants can decrease UVR, particularly in urban areas (Frederick, 1990).

(a) Measurements of terrestrial solar radiation

Since UVR wavelengths between about 295 and 320 nm (UVB radiation) in the terrestrial solar spectrum are thought to be those mainly responsible for adverse health effects, a number of studies have concentrated on measuring this spectral region (Sliney, 1986). Accurate measurements of UVR in this spectral band are difficult to obtain, however, because the spectral curve of terrestrial solar irradiance increases by a factor of more than five between 290 and 320 nm (Fig 4). Nevertheless, extensive measurements of ambient

Fig. 4. Action spectrum designated by the American Conference of Governmental Industrial Hygienists (ACGIH) for assessing the hazard of ultraviolet radiation (very similar to erythemal action spectrum from 300-230 nm) and the solar spectrum. The ACGIH action spectrum, which is unitless, is closely fit by some radiometers; however, because of the small overlap of the terrestrial solar spectrum with the action spectrum, problems of stray light must be dealt with by constant checks with a filter that blocks wavelengths of less than 320 nm

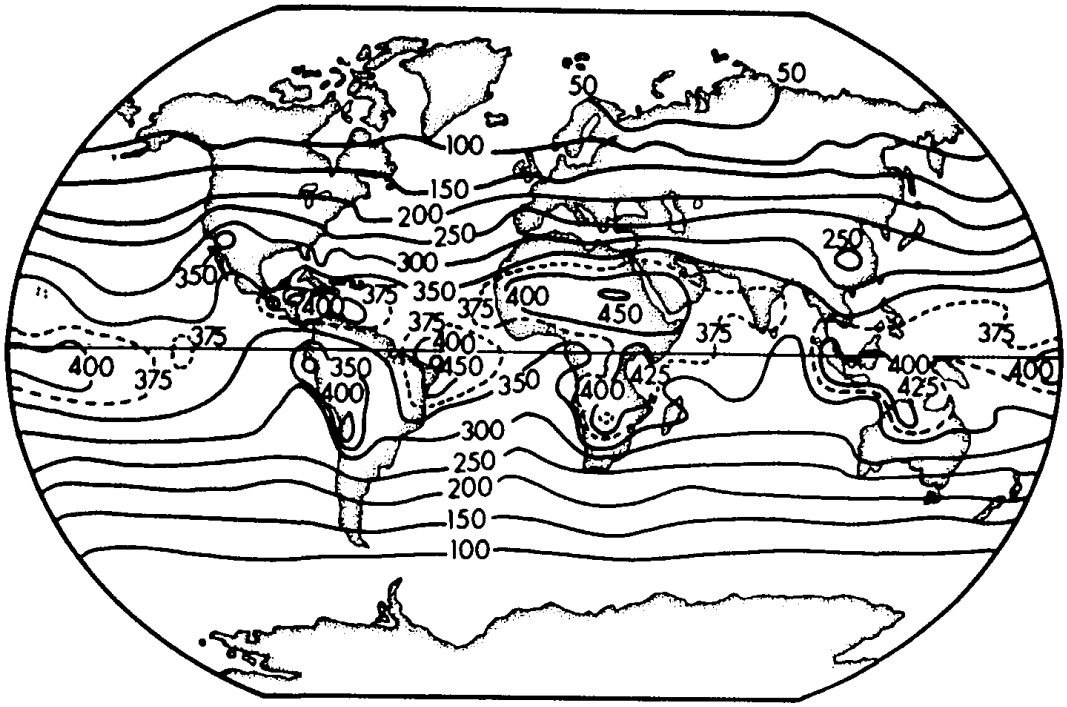


Adapted from Sidney *et al.* (1990)

UVR in this spectral band have been performed worldwide (Schulze, 1962; Schulze & Gräfe, 1969; Henderson, 1970; Sundararaman *et a*/., 1975; Garrison *et al.,* 1978; Doda & Green, 1980; Mecherikunnel & Richmond, 1980; Kostkowski *et al*., 1982; Ambach & Rehwald, 1983; Blumthaler *et al*., 1983; Livingston, 1983; Blumthaler *et al.*, 1985a,b; Kolari *et al*., 1986; Hietanen, 1990; Sliney *et al*., 1990). Longer-wavelength UVR (UVA) was measured at the same time in many of these studies. Measurements of terrestrial solar UVA radiation are less subject to error than measurements of UVB, since the spectrum does not vary widely with zenith angle and the spectral irradiance curve is relatively flat.

Maps of annual UVR exposure, such as that shown in Figure 5, have been compiled for epidemiological studies of skin cancer and other diseases (Schulze, 1962, 1970; Scotto *et al.,* 1976). Despite the large numbers of measurements, their interpretation in relation to human exposure has been complicated by three factors: (i) the considerable variation in UVB spectral irradiance with solar position throughout the day and with season; (ii) the effect of the geometry of exposure of individuals; and (iii) variation between humans in outdoor exposure and the parts of their bodies that are exposed.

Fig. 5. Global distribution of ultraviolet radiation

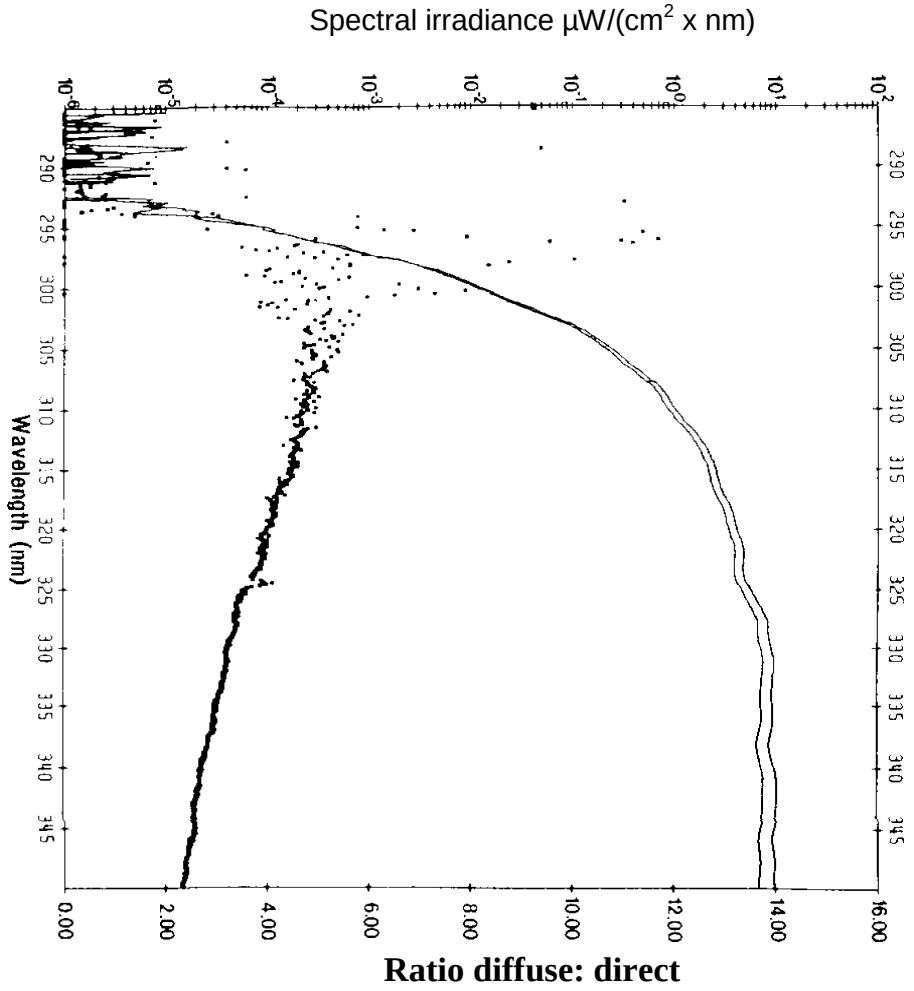


From Schulz (1970); WHO (1979)

The total solar radiation that arrives at the Earth's surface is termed ‘global radiation’, and measurements of terrestrial UVR most frequently pertain to this quantity, i.e., the radiant energy falling upon a horizontal surface from all directions (both direct and scattered radiation). Global radiation comprises two components, referred to as ‘direct’ and ‘diffuse’.

Approximately 70% of the UVR at 300 nm is in the diffuse component rather than in the direct rays of the sun (Fig. 6). The ratio of diffuse to direct radiation increases steadily from less than 1.0 at 340 nm to at least 2.0 at 300 nm (Garrison *et a.,* 1978).

Fig. 6. Diffuse and direct solar spectral irradiance (solar zenith angle, 45°)

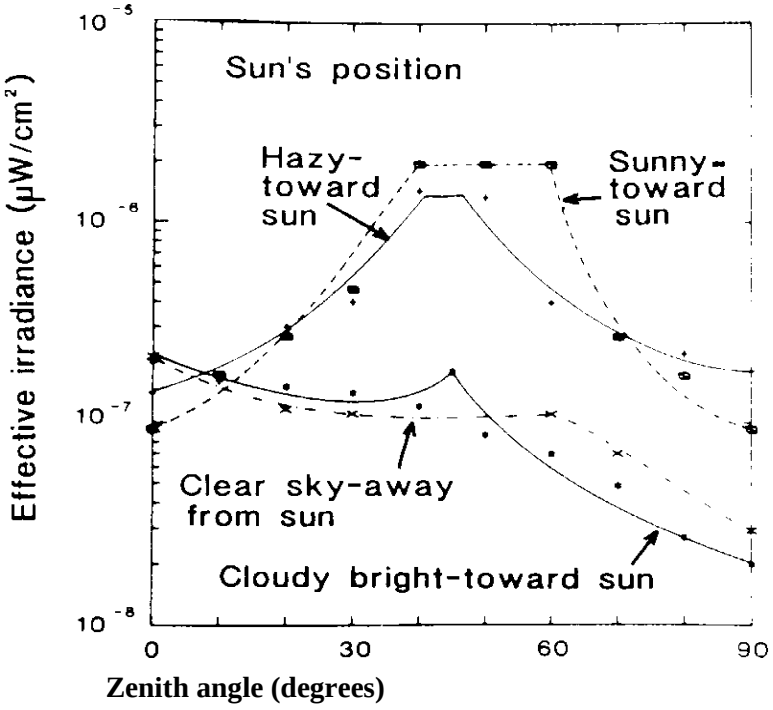


From Garrison *et al*. (1978)

UVR reflected from the terrain (the albedo) may also be important; however, essentially all measurement programmer have been limited to the direct and total diffuse components of sunlight. While such measurements are of interest in calculating the exposure dose of UVR of a prone individual, they are of very limited value in estimating exposure of the eye and shaded skin surfaces (e.g., under the chin), where the UVB radiation incident upon the body from terrain reflectance and horizon sky is of far greater importance. Sliney (1986) and Rosenthal *et al.* (1988) reported measurements of outdoor ambient UVR that included the reflected component to the eye. Exposure data for different anatomical sites is of value in developing biological dose-response relationships (Diffey *et al*., 1979). The fact that ocular exposure differs significantly from cutaneous exposure is emphasized by the finding that photokeratitis is seldom experienced during sunbathing yet the threshold for UV photo-keratitis is less than that for erythema of the skin (Sliney, 1986).

Measurements of the angular distribution of UVR relative to solar position and cloud distribution have been reported (Sliney, 1986; Fig. 7). A cloud obscuring the sun had no effect upon the UV radiance of open blue sky or the horizon sky; however, when the sun was 'out' (i.e., in an open sky), clouds near the horizon opposite the sun apparently reflected more UVR than would otherwise be present from the blue sky. This confirms the findings of studies of photographs of the sky taken through a narrow-band filter at 320 nm (Livingston, 1983), which revealed that the sky looks almost uniformly bright even when clouds are present and the clouds disappear into a uniformly hazy sky. Only the sun stands out, as would be expected from the plots on Figure 7. When the sun is near the horizon and can be looked at without great discomfort (i.e., at Z = 75-90 ˚), the effective UV irradiance is again of the order of 0.3 μW/cm^2, e.g., about 0.08-1.1 μW/cm^2 at an elevation angle of 12-15 ˚ (Sliney, 1986).

Fig. 7. Semilogarithmic plots of the angular dependence of skylight for 290-315 nm ultraviolet radiation (UVR) with the sun at zenith angle of about 45 °. A narrow field-of-view detector was scanned from zenith to the horizon. Uppermost curves show that direct UVR from the sun is more than 10 times greater than scattered UVR normally incident upon the eye at near-horizon angles where the zenith angle Z = 70-90 ˚. Most surprising is the similarity of blue sky and cloudy sky UV irradiances at zenith or near the horizon



Adapted from Sliney (1986)

(b) *Personal exposures*

The exposure of different anatomical sites to solar UVR depends not only on ambient UVR and orientation of sites with respect to the sun but also on cultural and social behaviour, type of clothing and whether spectacles are worn.

Measurements of ambient UVR are useful in that they provide upper limits on human exposure (Scotto *et al.,* 1976). They are of lesser value for assessing exposure doses received by groups of individuals. Polysulfone film has been used to monitor personal exposure to solar UVR (see p. 49). The wide variations in recorded exposure doses reflect diversity of behaviour and, in most cases, the small numbers (< 30) of subjects monitored. Nevertheless, it can be estimated that recreational (excluding vacations) exposure to the sun of people in northern Europe (where most of these studies were carried out) results in an annual solar exposure dose to the face of 20-100 MED, depending on the propensity for outdoor pursuits. The annual weekday UV exposure dose of indoor workers is around 30 MED; as a two-week outdoor vacation can result in a further 30-60 MED, the total annual exposure dose to the face of most indoor workers is probably in the range 40-160 MED. Outdoor workers at the same latitudes receive about two to three times these exposure doses, typically around 250 MED (Diffey, 1987b; Slaper, 1987).

An alternative approach to estimating personal exposure is to combine measured data on ambient UVR with a behavioural model of exposure. This approach was applied to a group of more than 800 outdoor workers in the USA (40 ˚N) by Rosenthal *et al.* (1991). These investigators estimated annual facial exposure doses of 30-200 MED, which are considerably lower than those estimated for outdoor workers in northern Europe, perhaps because Rosenthal *et al.* assumed facial exposure to be about 5-10% of ambient. A number of researchers have used polysulfone film badges on both human subjects (Holman *et al.,* 1983a; Rosenthal *et al.,* 1990) and mannequins (Diffey *et al*., 1977. 1979; Gies *et al.,* 1988) to measure solar UVR exposure on the face relative to ambient exposure. The results vary considerably, reflecting factors such as positioning of film badges, behaviour of individuals, solar altitude and the influence of shade. Examination of the data suggests, however, that the exposure of an unprotected face is probably close to 20% of the ambient. Using this estimate, the annual facial exposure doses in the outdoor worker group studied by Rosenthal *et al.* (1991) would be about 80-500 MED. These data demonstrate clearly the current uncertainties associated with estimates of population exposure doses.

1.3.2 *Exposure to artificial sources of ultraviolet radiation*

(a) Sources

Six artificial sources that often produce UVR incidental to the production of visible light (Sliney & Wolbarsht, 1980; Phillips, 1983; Moseley, 1988) are described below.

(i) *Incandescent sources*

Optical radiation from an incandescent source appears as a continuous spectrum. Incandescent sources are usually ascribed a certain 'colour temperature', defined as the temperature of a black body that emits the same relative spectral distribution as the source. UVR is emitted in significant quantity when the colour temperature exceeds 2500 °K (2227 °C). Tungsten-halogen lamps in a quartz envelope (colour temperature, 3000 ° K [2727 ˚C]) may emit significant UVR, whereas the US emission of an ordinary tungsten light bulb is negligible.

(ii) *Gas discharge lamps*

Another method of producing optical radiation is to pass an electric current through a gas. The emission wavelengths are determined by the type of gas present in the lamp and appear as spectral lines. The width of the lines and the amount of radiation in the interval between them (the continuum) depend on the pressure in the lamp. At low pressures, fine lines with little or no continuum are produced; as pressure is increased, the lines broaden and their relative amounts alter. Low-pressure discharge lamps, commonly containing mercury, argon, xenon, krypton or neon, are useful for spectral calibration. Medium-pressure mercury lamps operate at an envelope temperature in the region of 600-800 °C.

(iii) *Arc lamps*

Arc lamps operate at high pressures (20-100 atm [2020-10133 kPa]) and are very intense sources of UVR. Commonly available lamps contain xenon, mercury or a mixture of the two elements, which are effective sources of UVR. Xenon arc lamps operate at a colour temperature of 6000 ° K (5727 ˚C); they are often used as the light source in solar simulation or are combined with a monochromator in spectral illumination systems. Deuterium arc lamps provide a useful source of UVC radiation and find their main use in spectrophotometers and as a calibration source for spectroradiometers.

(iv) *Fluorescent lamps*

The primary source of radiation in a fluorescent lamp arises from a low-pressure mercury discharge, which produces a strong emission at 254 nm, which in turn excites a phosphor-coated lamp to produce fluorescence. By altering the composition and thickness of the phosphor and the glass envelope, a wide variety of emission spectral characteristics can be obtained. The output is thus chiefly the fluorescent emission spectrum from the coating, with a certain amount of breakthrough of UVB mercury lines at 297,303 and 313 nm, as well as those in the UVA and visible regions (WHO, 1979).

(v) *Metal halide lamps*

The addition of other metals (as halide salts) to a mercury discharge lamp allows for the addition of extra lines to the mercury emission spectrum. Most such tubes are basically medium-pressure discharge lamps with one or more metal halide additives, usually iodide. Advantage has been taken of the strong lead emission lines at 364, 368 and 406 nm in the lead iodide lamp, in which there is a 50% increase in output in the region between 355 and 380 nm compared to a conventional mercury lamp. Antimony and magnesium halide lamps provide spectral lines in the UVB and UVC regions.

(vi) *Electrodeless lamps*

A type of lamp recently introduced on a large scale is the electrodeless lamp. In this design, the discharge tube absorbs microwave energy fed, via waveguides, into a microwave chamber containing the tube. Two 1500-W magnetrons generate microwave energy at 2450 MHz. The life of such lamps is longer than that of electrode lamps, and a greater range of metal halides is available. Electrodeless lamps are used extensively for UV curing of inks and coatings, particularly when a short lamp length is adequate for the area to be irradiated. They have often been the first choice for curing prints on containers such as two-piece cans, plastic pots and bottles, and tubes.

(b) *Human exposure*

Although the sun remains the main source of UVR exposure for humans, the advent of artificial UVR sources has increased the opportunity for both intentional and unintentional exposure.

Intentional exposure is most often to acquire a tanned skin, frequently using sunbeds and solaria emitting principally UVA (315-400 nm) radiation (Diffey, 1987c). Another reason for intentional exposure to artificial UVR is the treatment of skin diseases, notably psoriasis.

Unintentional exposure is most often the result of occupation, and workers in many industries (see p. 66) may be exposed to UVR from artificial sources. The general public is exposed to low levels of UVR from sources such as fluorescent lamps used for indoor lighting and may be exposed in shops and restaurants where UVA lamps are employed in traps to attract flying insects.

(i) *Cosmetic use*

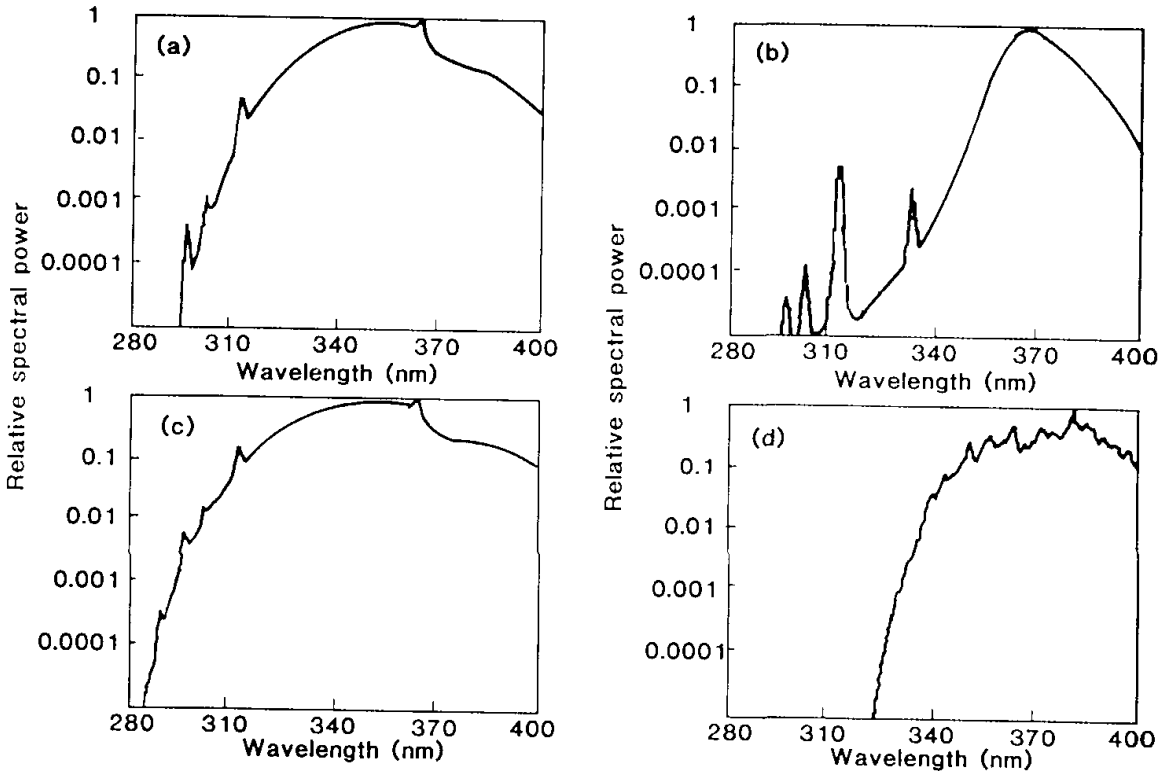
To some individuals, a tanned skin is socially desirable. A ‘suntanning industry’ has grown up, particularly in northern Europe and North America, in which artificial sources of UVR supplement exposure to sunlight.

Description of UVR sources used for tanning: Prior to the mid- 1970s, the source of UVR was usually an unfiltered, medium- or high-pressure mercury arc lamp which emitted a broad spectrum of radiation, from UVC through to visible and infrared radiation (Diffey & Farr, 1991b). The units often incorporated one or more infrared heaters and were commonly called ‘sunlamps’ or ‘health lamps’ (Anon., 1979). One disadvantage of this type of unit was that the area of irradiation was limited to a region such as the face and so whole-body tanning was tedious. By incorporating several mercury arc lamps into a 'solarium', whole body exposure was achieved. Tanning devices based on mercury arc lamps emit relatively large quantities of UVB and UVC radiation, resulting in a significant risk of burning and acute eye damage. Solaria that incorporate unfiltered mercury arc lamps are therefore now less popular (Diffey, 1990a).

So-called UVB fluorescent lamps (e.g., Westinghouse FS Sunlamp, Philips TL12) emit approximately 55% of their UV energy in the UVB and approximately 45% in the UVA regions (Diffey & Langley, 1986). They were often used in tanning booths, more commonly in the USA than in Europe.

Sunbeds, incorporating high-intensity UVA fluorescent lamps, were developed in the 1970s. These devices consist of a bed and/or canopy incorporating 6-30 fluorescent lamps 150-180 cm in length. The earliest type of UVA lamp used in sunbeds is typified by the Philips TL09, Wotan L100/79 and Wolff Solarium lamps (Diffey, 1987c). The spectral power distribution from this type of lamp is shown in Figure 8a. The emission spectrum comprises the fluorescence continuum, extending from about 315 to 400 nm and peaking at 350-355 nm, together with the characteristic lines from the mercury spectrum down to 297 nm (UVB) (Diffey & McKinlay, 1983). The UVA irradiance at the skin surface from a typical sunbed or suncanopy containing these lamps is between 50 and 150 W/m^2 (Bowker & Longford, 1987; Bruyneel-Rapp *et al.,* 1988).

Fig. 8. Spectral emissions of different lamps used for cosmetic tanning: (a) Philips TL09 (Diffey, 1987c); (b) Philips TL10R (Diffey, 1987c); (c) Wolff Bellarium S (B.L. Diffey, unpublished data); (d) optically filtered high-pressure metal halide lamp (Diffey, 1987c)



In the mid-1980s, another type of UVA fluorescent lamp (Philips TL10R) was introduced especially for cosmetic tanning. The principal features of this type of lamp were a reflector intrinsic to the lamp envelope and a fluorescence spectrum extending from about 340 to 400 nm, peaking at 370 nm (Fig. 8b): note also the presence of characteristic mercury lines in the UVB region. The skin surface irradiance from a sunbed or suncanopy incorporating Philips TL10R lamps is typically around 250 W/m^2 (Diffey, 1987c).

Another type of UV fluorescent lamp that has been used in sunbeds is the so-called 'fast tan' tube. This type of lamp is typified by the Wolff Bellarium S, the spectral power distribution of which is shown in Figure 8(c). The spectrum extends from about 290 to 400 nm and peaks at around 350 nm (Diffey & Farr, 1987).

Optically filtered, high-pressure mercury lamps doped with metal halide additives are also used in cosmetic tanning. The spectral emission lies entirely within the UVA waveband (Fig. 8d), and irradiances at the skin surface of more than 1000 W/m^2 can be achieved. The best known of this type of unit is probably the UVASUN (Mutzhas, 1986).

A summary of the physical and photobiological emissions from these different types of lamps is given in Table 5 (Diffey & Farr, 1991a).

Table 5. Characteristics of different ultraviolet (UV) lamps used for tanning

Lamp	Radiation emission (%)			Contribution to tanning (%)		
	UVA	UVB	UVC	UVA	UVB	UVC
Mercury arc sunlamp	40	40	20	0	35	65
Simulated sunlight lamp	95	5	0	20	80	0
Type I UVA lamp	99	1	0	60	40	0
Type II UVA lamp	> 99.9	< 0.1	0	> 90	< 10	0
Optically filtered high-pressure lamp[a]	100	0	0	100	0	0
Summer UV sunlight[b]	95	5	0	20	80	0

From Diffey & Farr (1991b) unless otherwise specified
[a]From Mutzhas (1986)
[b]From Sliney & Wolbarsht (1980)

Exposure to UVR *sources used for tanning:* Telephone surveys carried out in the Netherlands (Bruggers *et al.,* 1987) and in the United Kingdom (Anon., 1987) in the mid-1980s showed that 7-9% of the adult population in each country had used sunbeds in the previous one to two years. A more recent market survey in the United Kingdom (R. McLauchlan, personal communication), with a sample size of 5800, gave a slightly higher figure, with 10% of the population having used a sunbed during the previous year (1988) and 19% of the sample admitting to having used a sunbed at some time in the past. In these and other surveys in the United Kingdom (Diffey, 1986) and the USA (Dougherty *et al.,* 1988), women accounted for 60-85% of users, about half of the subjects being young women aged between 16 and 30. The commonest reason given for using tanning equipment was to acquire a pre-holiday tan (Anon., 1987; R. McLauchlan, personal communication); other reasons included perceived health benefits, reduction of stress and improved relaxation, protection of the skin before going on holiday, sustaining a holiday tan and treatment of skin diseases such as psoriasis and acne (Diffey, 1986; Dougherty *et al.,* 1988).

In the Dutch survey (Bruggers *et al.,* 1987), about half of the users interviewed used tanning equipment at home and the other half used facilities at commercial premises, such as tanning salons, hairdressers, sports clubs and swimming pools. Most people had used UVA equipment; 24% had used either UVB mercury arc sunlamps or solaria incorporating these lamps. A more recent survey in the United Kingdom (McLauchlan, 1989) confirmed the Dutch finding that the amount of use at home and at commercial premises was approximately the same. A survey carried out at commercial establishments in the United Kingdom indicated that all the equipment used emitted primarily UVA radiation, mostly from fluorescent UVA lamps and 10% from optically filtered high-pressure metal halide lamps (Diffey, 1986). Sales of tanning appliances in the United Kingdom increased rapidly during the 1980s, but by the end of the decade there appeared to be a steady, or possibly reduced, level of sales (Diffey, 1990a).

The mean number of tanning sessions per year in the Dutch study was 23 (Bruggers *et al.,* 1987). In the United Kingdom, half-hour sessions were the most popular (Diffey, 1986). Each tanning session with UVA equipment normally results in an erythemally-weighted

Exposure of about 0.8 MED (150 J/m^2), whereas exposure to mercury arc lamps results in about 2 MED per session (400 J/m^2). In the Dutch survey, it was estimated that the median annual exposure was 24 MED (4.8 kJ/m^2) (Bruggers *et al.,* 1987).

(ii) *Medical and dental applications*

UVR has both diagnostic and therapeutic applications in medicine and dentistry. The diagnostic uses are confined largely to fluorescing of skin and teeth, and the UVR source is normally an optically filtered medium-pressure mercury arc lamp producing radiation mainly at 365 nm (so-called 'Wood's lamps') (Caplan, 1967). Radiation exposure is limited to small areas (< 15 cm in diameter), and the UVA radiation dose per examination is probably no more than 5 J/cm^2. The therapeutic uses of UVR, which result in considerably higher doses, are mainly in the treatment of skin diseases and occasionally the symptomatic relief of pruritus.

Phototherapy: The skin diseases that are most frequently treated with UVR are psoriasis and eczema. Phototherapy of psoriasis at hospital may include the use of tar and related derivatives and other substances, such as anthralin, on the skin (Morison, 1983a; see also IARC, 1987a).

The first treatment of psoriasis with an artificial source of UVR is credited to Sardemann, who used a carbon arc lamp of the type developed by Finsen at around the turn of the century. These lamps were unpopular in clinical practice because they emitted noise, odour and sparks, and they were superseded by the development of the medium-pressure mercury arc lamp. In the 1960s, a variety of metal halides were added to mercury lamps to improve emissions in certain regions of the UV and visible spectra. Fluorescent lamps were developed in the late 1940s; since then, a variety of phosphor and envelope materials have been used to produce lamps with emissions in different regions of the UV spectrum, such that, today, there exists a wide range of lamps for the phototherapy of skin diseases (Diffey & Farr, 1987).

Lamp systems can be classified into one of five categories in terms of suitability for phototherapy (Diffey, 1990b):

Type A: a single, medium-pressure mercury arc or metal halide lamp;

Type B: one or more vertical columns containing five or six optically filtered high-pressure metal halide lamps;

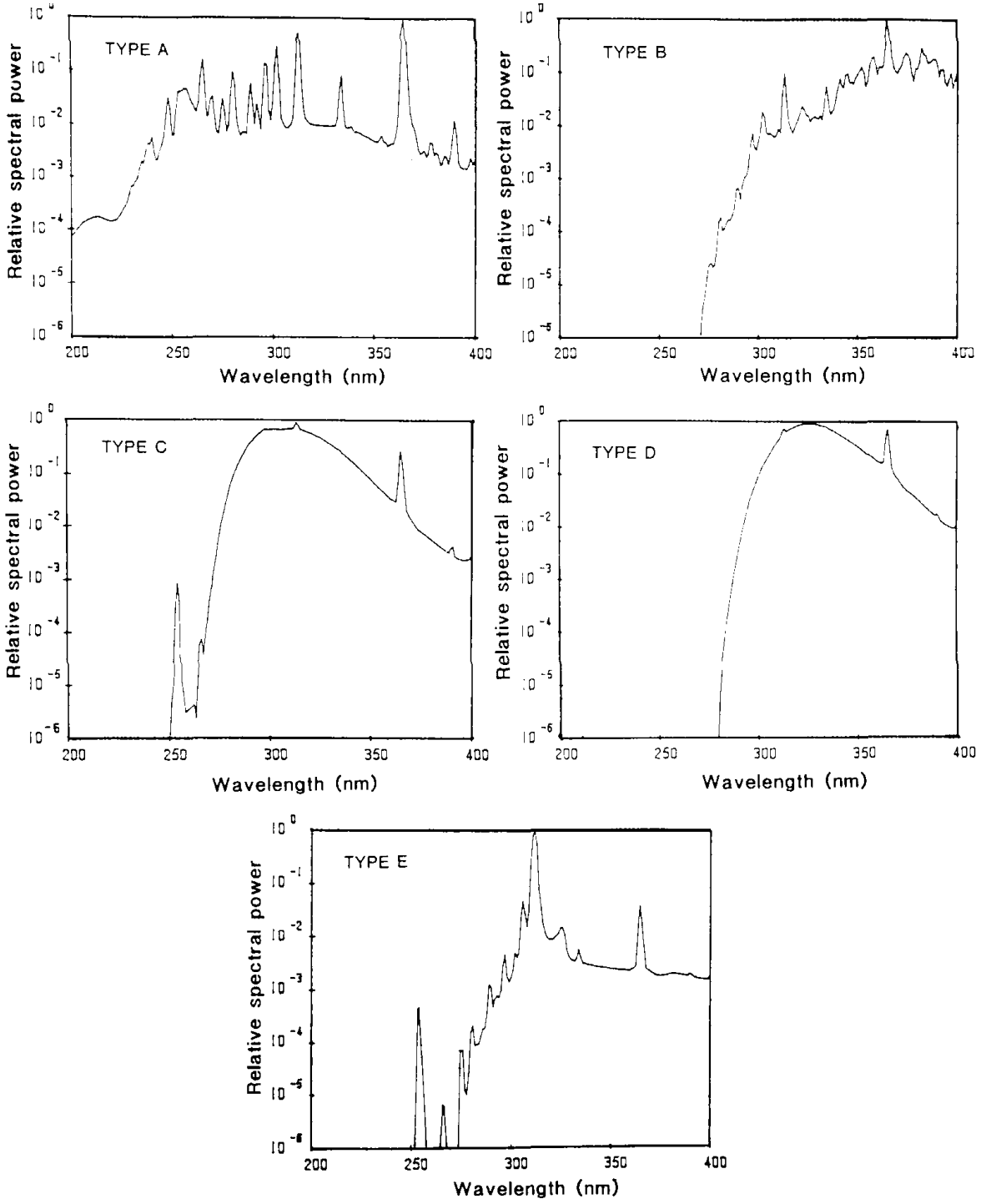
Type C: a canopy or cubicle containing fluorescent sunlamps which emit predominantly UVB but also significant amounts of radiation at wavelengths below 290 nm (e.g., Westinghouse FS sunlamp, Philips TL12 and Sylvania UV21 lamps);

Type D: a canopy, sunbed or cubicle incorporating fluorescent lamps which emit predominantly UVB radiation and negligible amounts of radiation at wavelengths below 290 nm (e.g., the Wolff Helarium);

Type E: a newly developed fluorescent lamp that emits a narrow band of radiation around 311-312 nm (Philips TL01).

The spectral power distributions characteristic of each of these five types of lamp are shown in Figure 9. The therapeutic radiation for psoriasis lies principally within the UVB waveband (Parrish & Jaenicke, 1981), and the cumulative UVB dose required for clearing

Fig. 9. Spectral power distributions of different types of phototherapy lamp (Diffey, 1990b). Type A: unfiltered medium-pressure mercury arc lamp; type B: optically filtered iron iodide lamp; type C: fluorescent sunlamp (Philips TL12); type D: Wolff Helarium lamp; type E: narrow-band UVB fluorescent lamp (Philip.s TL0l)



psoriasis is typically 100-200 MED (Diffey, 1990a), usually delivered over a course consisting of 10-30 exposures over 3-10 weeks (van der Leun & van Weelden, 1986).

Annual doses received by 90% of patients given UMB phototherapy for psoriasis range from about 60 to 670 MED, with a typical dose in a single course being between 200 and 300 MED (Slaper, 1987).

Psoralen photochemotherapy (see also IARC, 1980, 1986a, 1987b): This form of treatment, known colloquially as PUVA, involves the combination of photoactive drugs, psoralens (P), with long-wave UVR (UVA) to produce a beneficial effect. Psoralen photochemotherapy has been used to treat many skin disease in the past decade, although its principal success has been in the management of psoriasis (Parrish *et al.,* 1974), a disorder characterized by an accelerated cell cycle and rate of DNA synthesis. Psoralens may be applied to the skin either topically or systemically; the latter route is generally preferred, and the psoralen most commonly administered is 8-methoxypsoralen. The patient is usually exposed to UVA radiation from banks of fluorescent lamps with the spectral power distribution shown in Figure 8a. Values for UVA irradiance in clinical treatment cubicles have been found to range from 16 to 140 W/m^2 (Diffey *et al*., 1980; Diffey, 1990b), although an irradiance of 80 W/m^2 is probably typical. The UVA dose per treatment session is usually in the range 1-l0 J/cm^2 (Diffey *et al.,* 1980).

Generally, approximately 25 treatments over a period of 6-12 weeks, with a cumulative UVA dose of 100-250 J/cm^2, are required to clear psoriatic lesions (Melski *et al.,* 1977; Henseler *et al*., 1981*).* PUVA therapy is not a cure for psoriasis, and maintenance therapy is often needed at intervals of between once a week to once a month to prevent relapse (Gupta & Anderson, 1987).

Neonatal phototherapy for hyperbilirubinaemia: Phototherapy is sometimes used in the treatment of neonatal jaundice or hyperbilirubinaemia. The preferred method of treatment is to irradiate the baby for several hours a day for up to one week with visible light, particularly blue light (Sisson & Vogl, 1982). The lamps used for phototherapy, although intended to emit only visible light, may also have a UV component: One commercial neonatal phototherapy unit was found to emit not only visible light and UVA but also radiation at wavelengths down to 265 nm (Diffey & Langley, 1986).

Fluorescence in cutaneous and oral diagnosis: Wood's light—a source of UVA obtained by filtering optically a mercury arc lamp with 'blackglass'—is used by dermatologists as a diagnostic aid in skin conditions that produce fluorescence (Caplan, 1967; Diffey, 1990a). As irradiation of the oral cavity with a Wood's lamp can produce fluorescence under certain conditions, this has been used in the diagnosis of various dental disorders, such as early dental caries, the incorporation of tetracycline into bone and teeth, dental plaque and calculus (Hefferren *et al.,* 1971).

Polymerization of dental resins: Pits and fissures in teeth have been treated using an adhesive resin polymerized with UVA. The resin is applied with a fine brush to the surfaces to be treated and is hardened by exposure to UVA radiation at a minimal irradiance of 100 W/m^2 for 30 s or so (Eriksen *et al.,* 1987; Diffey, 1990a).

(iii) *Occupational exposures*

Artificial sources of UVR are used in many different ways in the working environment. In some cases, the UV source is well contained within an enclosure and, under normal circumstances, presents no risk of exposure to personnel. In other applications of UVR, it is inevitable that workers are exposed to some radiation, normally by reflection or scattering from adjacent surfaces. Occupational exposure to UVR is also a consequence of exposure to general lighting in the workplace.

Industrial photoprocesses: Many industrial processes involve a photochemical component. The large-scale nature of these processes often necessitates the use of high-power (several kilowatts) lamps such as high-pressure metal halide lamps (Diffey, 1990a).

The principal industrial applications of photopolymerization include the curing of protective coatings and inks and photoresists for printed circuit boards. The curing of printing inks by exposure to UVR is now widespread; as the cure takes only a fraction of a second, UV drying units can be installed between printing stations on a multicolour line, so that each colour is dried before the next is applied. Another major use of UV curing has been for metal decorating in the packaging industry (Phillips, 1983). UVA is also used to inspect printed circuit boards and integrated circuits in the electronics industry (Pauw & Meulemans, 1987).

Artificial sources of UVR are used to test the weathering capability of materials such as polymers. Xenon-arc lamps are often the light source because their emission spectra is similar to the spectrum of terrestrial sunlight, although some commercial weathering chambers incorporate carbon-arc lamps, high-pressure metal halide lamps or fluorescent sunlamps (Davis & Sims, 1983).

Sterilization and disinfection: Radiation with wavelengths in the range 260-265 nm is the most effective for this use, since it corresponds to a maximum in the DNA absorption spectrum. Low-pressure mercury discharge tubes are thus often used as the radiation source, as more than 90% of the radiated energy lies in the 254 nm line. These lamps are often referred to as 'germicidal lamps', 'bactericidal lamps' or simply 'UVC lamps' (Diffey, 1990a).

UVC radiation has been used to disinfect sewage effluents, drinking-water, water for the cosmetics industry and swimming pools. Germicidal lamps are sometimes used inside microbiological safety cabinets to inactivate airborne and surface microorganisms (Diffey, 1990a). The combination of UVR and ozone has a very powerful oxidizing action and can reduce the organic content of water to extremely low levels (Phillips, 1983).

Welding (see also IARC, 1990): Welding equipment falls into two broad categories: gas welding and electric arc welding. Only the latter process produces significant levels of UVR, the quality and quantity of which depend primarily on the arc current, shielding gas and metals being welded (Sliney & Wolbarsht, 1980).

Welders are almost certainly the largest occupational group with exposure to artificial sources of UVR. It has been estimated (Emmett & Horstman, 1976) that there may be as many as half a million welders in the USA alone. The levels of UV irradiance around electric arc welding equipment are high; effective irradiance (relative to the action spectrum of the American Conference of Governmental Industrial Hygienists) at 1 m at an arc current of 400 A ranged from 1 to 50 W/m^2 (Table 6), and the unweighted UVA irradiance ranged from 3 to 70 W/m^2, depending on the type of welding and the metal being welded (Cox,

1987; Mariutti & Matzeu, 1987). It is not surprising therefore that most welders at some time or another experience 'arc eye' or 'welder's flash' (photokeratitis) and skin erythema. The effective irradiance at 0.3 m from many types of electric welding arcs operating at 150 A is such that the maximum permissible exposure time for an 8-h working period on unprotected eyes and skin varies from a few tenths of a second to about 10 s, depending on the type of welding process and the material used (Cox, 1987).

Table 6. Limits of exposure to ultraviolet radiation and radiation effectiveness

Wavelength (nm)	Exposure limit (J/M^2)	Relative spectral effectiveness (S_λ)[a]
180	2500	0.012
190	1600	0.019
200	1000	0.030
205	590	0.051
210	400	0.075
215	320	0.095
220	250	0.120
225	200	0.150
230	160	0.190
235	130	0.240
240	100	0.300
245	83	0.360
250	70	0.430
254b	60	0.500
255	58	0.520
260	46	0.650
265	37	0.810
270	30	1.000
275	31	0.960
280[b]	34	0.880
285	39	0.770
290	47	0.640
295	56	0.540
297[b]	65	0.460
300	100	0.300
303[b]	250	0.120
305	500	0.060
308	1200	0.026
310	2000	0.015
313[b]	5000	0.006
315	1.0×10^4	0.003
316	1.3×10^4	0.0024
317	1.5×10^4	0.0020
318	1.9×10^4	0.0016
319	2.5×10^4	0.0012

Table 6 (contd)

Wavelength (nm)	Exposure limit (J/m^2)	Relative spectral effectiveness (S_λ)[a]
320	2.9×10^4	0.0010
322	4.5×10^4	0.00067
323	5.6×10^4	0.00054
325	6.0×10^4	0.00050
328	6.8×10^4	0.00044
330	7.3×10^4	0.00041
333	8.1×10^4	0.00037
335	8.8×10^4	0.00034
340	1.1×10^5	0.00028
345	1.3×10^5	0.00024
350	1.5×10^5	0.00020
355	1.9×10^5	0.00016
360	2.3×10^5	0.00013
365[b]	2.7×10^5	0.00011
370	3.2×10^5	0.000093
375	3.9×10^5	0.000077
380	4.7×10^5	0.000064
385	5.7×10^5	0.000053
390	6.8×10^5	0.000044
395	8.3×10^5	0.000036
400	1.5×10^6	0.000030

From American Conference of Governmental industrial Hygienists (1991); wavelengths chosen are representative, and other values should be interpolated at intermediate wavelengths.

[a]For explanation, see pp. 46-47

[b]Emission lines of a mercury discharge spectrum

In a survey of electric arc welders in Denmark, 65% of those questioned had experienced erythema; however, as no indication of the frequency of skin reactions was reported, it is not possible to estimate annual exposure (Eriksen, 1987). Monitoring of the exposure to UVR of non-welders working in the vicinity of electric arc welding apparatuses showed that their daily exposure dose exceeded the maximum permissible exposure limits by almost an order of magnitude (Barth *et al.,* 1990).

Phototherapy: Although there is a trend to the use of enclosed treatment cubicles, some of the lamps used to treat skin disease (see the section on medical and dental applications) are unenclosed, emit high levels of UVR and can present a marked hazard to staff; at 1 m from these lamps, the recommended 8-h occupational exposure limits can be exceeded in less than 2 min (Diffey & Langley, 1986).

In a study of the exposure of staff in hospital phototherapy departments (Larko & Diffey, 1986), annual exposure to UVR could be estimated from the number of occasions per year on which staffhad experienced at least minimal erythema (Diffey, 1989b). Estimated annual

occupational exposures to UVR were 15,92 and 200 MED, corresponding to a frequency of erythema of once per year, once per month and once per week, respectively.

Operating theatres: UVC lamps have been used since the 1930s to decrease the levels of airborne bacteria in operating theatres (Berg, 1987). The technique requires complete protection of the eyes and skin of staff and patients; for this and other reasons, filtered air units are often preferred.

Research laboratories: Sources of UVR are used by most experimental scientists engaged in aspects of photobiology and photochemistry and in molecular biology. These applications, in which the effect of UV irradiation on biological and chemical species is of primary interest to the researcher, can be differentiated from UV fluorescence by absorption techniques where the effect is of secondary importance (Diffoy, 1990a).

UV photography: There are two distinct forms of UV photography: reflected or transmitted UV photography and UV fluorescence photography. In both applications, the effective radiation lies within the UVA waveband (Lunnon, 1984).

UV lasers: High-power lasers which emit in the UV region, used in nuclear and other research laboratories, are far less common than those that emit in the visible or infrared regions of the electromagnetic spectrum.

Nitrogen lasers emit at a wavelength of 337 nm (Phillips, 1983), and instruments with a peak power output of up to 2.3 MW per pulse are available. Nitrogen lasers can be used in conjunction with fluorescent dyes to produce spectral emissions of 360-900 nm, with a power pulse of 200-480 kW. If frequency doubling crystals are used in conjunction with a nitrogen laser, UV emissions down to 260 nm are possible.

An alternative laser source of UVR is the excimer laser. (The term 'excimer' denotes a homonuclear molecule which is bound in an electronically excited state but is dissociative in the ground state [Phillips, 1983].) The wavelength of the pulsed UVR from this type of laser depends on the excimer molecules, such as ArF, F_2, XeCl and KrF, which emit at 193, 157, 308 and 248 nm, respectively (Phillips, 1983; Bos & de Haas, 1987). On the basis of worst-case assumptions, the estimated annual risk for skin cancer for workers exposed to UV lasers in medical applications is equivalent to about one additional day of sunbathing, and that for workers exposed to UV lasers in laboratories is comparable to the risk for outdoor workers (Sterenborg *et al.*, 1991).

Quality assurance in the food industry: Many contaminants of food products can be detected by UV fluorescence techniques. For example, the bacterium *Pseudomonas aeruginosa,* which causes rot in eggs, meat and fish, can be detected by its yellow-green fluorescence under UVA irradiation. One of the longest established uses of UVA fluorescence in public health is to demonstrate contamination with rodent urine, which is highly fluorescent (Ultra-Violet Products, Inc., 1977).

Insect traps: Many flying insects are attracted by UVA radiation, particularly in the region around 350 nm. This phenomenon is the principle of electronic insect traps, in which a UVA fluorescent lamp is mounted in a unit containing a high-voltage grid. The insect, attracted by the UVA lamp, flies into the unit and is electrocuted in the air gap between the high-voltage grid and a grounded metal screen. Such units are commonly found in areas where food is prepared and sold to the public (Diffey, 1990a).

Sunbed salons and shops: The continuing popularity of UVA sunbeds and suncanopies for cosmetic tanning has resulted in the establishment of a large number of salons and shops selling sunbeds for use at home. Some shops may have 20 or more UVA tanning appliances, all switched on, thus exposing members of the public and staff to high levels (> 20W/m^2) of UVA radiation (Diffey, 1990a).

Discotheques: UVA 'blacklight' lamps are sometimes used in discotheques to induce fluorescence in the skin and clothing of dancers. The levels of UVA emitted are usually low (< 10 W/m^2) (Diffey, 1990a).

Offices: Signatures can be verified by exposing a signature obtained with colourless ink to UVA radiation, under which it fluoresces. UVA exposure of office staff is normally to hands, and irradiance is low (< 10 W/m^2) (Diffey, 1990a).

(iv) General lighting

Fluorescent lamps used for general lighting in offices and factories emit small quantities of both UVA and UVB. A UVA irradiance of 30 mW/m^2 (Diffey, 1990a) and a UVB irradiance of 3 mW/m^2 (McKinley & Whillock, 1987) were found for bare fluorescent lamps with a typical illuminance of 500 lux. These UV levels give rise to an annual exposure of indoor workers to no more than 5 MED, and this dose can be reduced appreciably by the use of plastic diffusers (McKinley & Whillock, 1987). A study of the personal doses of UVR received by workers in the car manufacturing industry who were engaged in inspecting paintwork of new cars under bright fluorescent lamps indicated a similar annual exposure (Diffey *et al*., 1986). Most plastic diffusers reduce erythemally effective irradiance to 0.2% or less of that of the bare lamp. An exception is clear acrylic diffusers, which absorb only about 20% of the erythemally effective radiation. The absorption of UVA radiation by diffusers is less effective, transmission ranging from 1% for opal polycarbonate to 74% for clear acrylic (McKinley & Whillock, 1987). Spectroradiometric measurements of the UV levels from indoor fluorescent lamps carried out in the USA, however, indicated much higher annual doses for people exposed occupationally for 2000 h per year: The annual estimated exposure dose ranged from 8 to 30 MED for an illuminance level of 500 lux from bare lamps (Cole et al., 1985).

Desk-top lights which incorporate tungsten-halogen (quartz) lamps may result in exposure to UVR of the hands and arms, if the lamps are used in excess of recommended occupational exposure levels (McKinley et *al.,* 1989). Experimental studies have shown that erythema can be induced in susceptible individuals after a 15-min exposure at 10 cm from a 100-W tungsten-halogen source, principally by the UVB component of the emission (Cesarini & Muel, 1989). Tungsten-halogen lamps are also used for general lighting (e.g., spotlights, indirect lighting, floor lamps) in some countries.

(c) *Regulations and guidelines*

(i) *Cosmetic use*

The most comprehensive guidelines for the use of sunlamps and sunbeds in cosmetic tanning are those published by the international Electrotechnical Commission (1987,1989). The guidelines classify tanning appliances into one of four types according to the effective irradiance at short ($\lambda \leq 320$ nm) and long ($320 < \lambda \leq 400$ nm) UV wavelengths (Table 7).

Table 7. Classification of tanning appliances

Type	Effective irradiance (W/m^2)	
	$\lambda \leq 320$ nm	$320 < \lambda \leq 400$ nm
1	< 0.0005	≥ 0.15
2	0.0005-0.15	≥ 0.15
3	< 0.15	< 0.15
4	≥ 0.1	< 0.15

From International Electrotechnical Commission (1989)

Effective radiance is defined as:

$$\sum_{250}^{400} E_\lambda \times S_\lambda \times \Delta_\lambda$$

where E_λ is the spectral irradiance (W/m^2 x nm) at wavelength λ (nm) at the shortest recommended exposure distance; Δ_λ is the wavelength interval used in the summation; and S_λ is the relative erythemal effectiveness recently adopted by the Commission Internationale de l'Eclairage (McKinley & Diffey, 1987), specified as shown in Table 8. The guidelines recommend that the exposure time for the first session on untanned skin should correspond to an effective dose not exceeding 100 J/m^2; this is approximately equivalent to 1 MED for subjects with sun-reactive skin type I. The annual exposure should not exceed an effective dose of 25 kJ/m^2 (International Electrotechnical Commission, 1989).

Table 8. Specifications of relative erythemal effectiveness

Wavelength (λ; nm)	Relative erythemal effectiveness ($S\lambda$) (weighting factor)
$\lambda < 298$	1
$298 < \lambda < 328$	$10^{0.094(298-\lambda)}$
$328 < \lambda \leq 400$	$10^{0.015(139-\lambda)}$

From McKinlay & Diffey (1987); International Electrotechnical Commission (1989)

Although these guidelines form the basis of several national standards on sunlamp and sunbed use, it should be noted that variations exist; for example, in the Netherlands, Norway and Sweden, certain UV appliances are not permitted. Regulations concerning the use of tanning appliances are in force in only a few countries, but many others have published advice on sunbed use, including information on adverse effects, as well as guidelines on manufacturing standards.

(ii) Occupational exposure

Guidance on the maximal limits of exposure to UVR as a consequence of occupation is given by the International Non-ionizing Radiation Committee of the International Radiation

Protection Association. These exposure limits, which apply only to incoherent (i.e., non-laser) sources, represent conditions under which it is expected that nearly all individuals may be repeatedly exposed without adverse effects and are below levels which would be used for medical or cosmetic exposure to UVR. The limits for occupational exposure to UVR incident upon the skin or eye were considered separately for the UVA spectral region (315-400 nm) and the actinic UV spectral region (UVC and UVB, 180-315 nm). In 1984, the limit provided an equal spectral weighting between 315 and 400 nm, a maximal 1000-s radiant exposure of 10 KJ/m^2 and a maximal irradiance of 10 W/m^2 for longer periods (International Non-ionizing Radiation Committee of the International Radiation Protection Nssociation, 1985). Studies of skin and ocular injury resulting from exposure to UVA led the Committee to issue revised exposure limits in 1988: For the UVA spectral region (315-400 nm), the total radiant exposure incident upon the unprotected eye should not exceed 1.0 J/cm^2 (10 kJ/m^2) within an 8-h period, and the total 8-h radiant exposure incident upon the unprotected skin should not exceed the values given in Table 6. Values for the relative spectral effectiveness S_λ are given up to 400 nm to expand the action spectrum into the UVA region for determining the exposure limit for skin exposure. For the actinic UV spectral region (UVC and UVB, 180-315 nm), the radiant exposure incident upon the unprotected skin or eye within an 8-h period should not exceed the values given in fable 6 (International Non-ionizing Radiation Committee of the International Radiation Protection Association, 1989).

'I'he effective irradiance (E_{eff}) in W/m^2 of a broad-band source weighted against the peak of the spectral effectiveness curve (270 nm) is determined according to the formula:

$$E_{eff} = \Sigma\, E_\lambda \times S_\lambda \times \Delta_\lambda$$

where E_λ is the spectral irradiance (W/m^2 x nm) from measurements, S_λ is the relative spectral effectiveness (Table 6) and Δ_λ is the band-width (nm) of the calculation or measurement interval (International Non-ionizing Radiation Committee of the International Radiation Protection Association, 1985).

The maximal permissible exposure time in seconds for exposure to UVR incident on the unprotected skin or eye within an 8-h period is computed by dividing 30 J/m^2 by the value of E_{eff} in W/m^2 (American Conference of Governmental Industrial Hygienists,]991). A worker receiving the maximal permissible exposure of 30 J/m^2 per 8-h day will, in the course of a working year, have a cumulative dose of 60-70 MED (Diffey, 1988), a value comparable with the natural exposure of non-occupationally exposed indoor workers (Diffey, 1990a).

Occupational exposure limits to lasers were also defined by the International Non-Ionizing Radiation Committee of the International Radiation Protection Association in 1989, at 3 mJ/cm^2 and 40 mJ/cm^2 over 8 h for argon-fluoride and xenon-chloride lasers, respectively (Sliney, 1990).

CONTINUE

2. Studies of Cancer in Humans

2.1 Solar radiation

2.1.1 *Nonmelanocytic skin cancer*

Nonmelanocytic skin cancer is classified into two major histological types: basal-cell carcinoma and squamous-cell carcinoma. Basal-cell carcinoma is the commoner type in white populations. No information was available to the Working Group on other types of nonmelanocytic skin cancer.

(a) *Case reports*

In general, case reports were not considered, owing to the availability of more informative data.

(i) *Studies of xeroderma pigmentosum patients*

Xeroderma pigmentosum is a rare autosomal-recessive genetic disease in which there is an excision repair defect, as observed in cultured skin fibroblasts damaged by UVR (Cleaver, 1968). Patients display cellular and clinical hypersensitivity to UVR (Kraemer, 1980). The disease is present in about one in 250 000 people in the USA and Europe (Cleaver & Kraemer, 1989), and as many as 1 in 100 000 (Takebe *et al.,* 1987) or even 1 in 40 000 (Cleaver & Kraemer, 1989) people may be affected in Japan.

In a survey of 830 cases located through published case reports (Kraemer *et al.,* 1987), 45% had malignant skin neoplasms. Most of the patients were young, and the median age of development of the first skin cancer in the 186 patients for whom information was available was eight years: this observation presumably represents a substantial excess over the expected number. Only 259 neoplasms were specifically categorized as basal- or squamous-cell carcinoma in the published reports. Of these 97% were on constantly exposed sites (face, head and neck) by comparison with 80% of similar tumours in the US general population. [The Working Group recognized that data collected from previously published case reports is not uniform and may not be typical of a true incidence or prevalence series.]

(ii) *Studies of transplant recipients*

Australian renal transplant recipients were reported to have an increased risk for nonmelanocytic skin cancer (Hardie *et al.,* 1980). Among 875 male and 669 female Australasian recipients, aged 35-64, 47 squamous-cell carcinomas and 27 basal-cell carcinomas were observed among males and 27 squamous-cell and 15 basal-cell carcinomas were observed among females (Kinlen *et al.,* 1979). The rates/10^5 person-years for squamous-cell carcinoma were 2680 in males and 1710 in females, or 3.0 and 5.9 times the rates observed among residents of the same age distribution surveyed in Geraldton, Western Australia (Kricker *et al.,* 1990). For basal-cell carcinoma, the rates for 1540 (males) and 940 (females) were 1.154 and 1.150 times the Geraldton rates, respectively.

By February 1980, a registry in Denver, Colorado (USA), had received data on 906 organ transplant recipients who had developed 959 types of cancer: 42% arose in the skin, of which 47% were squamous-cell carcinomas (Penn, 1980). While several studies from areas with lower solar radiation are available (Boyle *et al.,* 1984), neither singly nor collectively do they contain enough observations to permit a comparable calculation.

(b) *Descriptive studies*

Nonmelanocytic skin cancer is often not recorded in cancer registries (e.g., in the USA and in most parts of Australia), and when it is registered case ascertainment is likely to be incomplete since many patients are treated in consulting rooms, frequently without histological verification (Doll *et al.,* 1970). Thus, descriptive studies of the incidence of nonmelanocytic skin cancer can be difficult to perform because of the absence of routinely collected data or difficult to interpret because of incomplete registration. Studies in Australia and the USA have relied upon special surveys, while in the United Kingdom and the Nordic countries data from cancer registries have been used. Studies of mortality rates are also difficult to interpret because nonmelanocytic skin cancer is rarely fatal, and many deaths are incorrectly attributed to skin cancer (Muir *et al*., 1987).

A number of features of the occurrence of nonmelanocytic skin cancer as revealed by descriptive studies have been taken as evidence that exposure to the sun is a major cause of the disease. These include features presumed to be related to sun exposure such as sex, anatomical site, latitude of residence (or annual dose of UVB radiation), migration from places of low insolation to places of high insolation, occupation and features related to sensitivity to the sun such as race (i.e., degree of skin pigmentation).

(i) *Host factors*

The occurrence of nonmelanocytic skin cancer according to host factors such as race provides indirect evidence that sunlight is a cause. In most white populations, nonmelanocytic skin cancer occurs more commonly in men than in women (Muir *et al.,* 1987). The highest incidence rates have been recorded among Australians, who are largely of British (Celtic) descent (Giles *et al.,* 1988). Populations with greater skin pigmentation have low rates of nonmelanocytic skin cancer, for instance, in South Africa (Oettlè, 1963) and Singapore (Shanmugaratnam *et al.,* 1983).

Albinism is an inherited disorder of melanin metabolism, with a decrease or complete absence of melanin. Large numbers of skin cancers (mostly squamous-cell carcinomas) have been reported in albinos (Luande *et al.,* 1985; Kromberg *et al.,* 1989).

(ii) *Anatomical distribution*

The majority of cases of skin cancer recorded in cancer registries (Haenszel, 1963 [USA]: Whitaker *et al.,* 1979 [United Kingdom]; Swerdlow, 1985 [United Kingdom]: Levi *et al*., 1988 [Switzerland]; Østerlind *et al*., 1988a [Denmark]; Moanetal., 1989 [Norway]) and in special surveys in the USA (Haenszel, 1963; Scotto *et al*., 1983) occurred on the head and neck. In contrast, in two studies in Australia—one of incidence (Giles *et al*., 1988) and the other of prevalence (Kricker *et al*., 1990)—the proportions of cancers on the head and neck were lower. [The Working Group noted that the contrasting results may be due to time differences.] In the incidence survey, 43% of squamous-cell carcinomas and 66% of

basal-cell carcinomas were on the head and neck. In the prevalence survey, about one-third of all basal-cell carcinomas were on the head and neck, whereas the trunk accounted for about half of these lesions. The density of tumours was five times greater in men and eight times greater in women on usually exposed sites than on sites which were sometimes exposed. Squamous-cell carcinomas occurred almost exclusively on exposed sites. The site distributions of both types of nonmelanocytic skin type are generally similar in the two sexes (Østerlind *et al.,* 1988a; Moan *et al.,* 1989; Kricker *et al.,* 1990).

A distinctive feature of the site distribution of basal-cell carcinoma is a virtual absence on the dorsa of the hands and infrequent occurrence on the forearms, compared with the distribution of squamous-cell carcinoma (Haenszel, 1963; Silverstone & Gordon, 1966; Levi *et al.,* 1988; Magnus, 1991). Basal-cell carcinoma also occurs frequently on parts of the face that receive comparatively little sun exposure (Urbach *et al.,* 1966).

[The Working Group noted that cancers on the head and neck may be more likely to be diagnosed than cancers at other sites.]

(iii) *Geagraphical variation*

Nonmelanocytic skin cancer incidence and mortality have long been known to increase with increasing proximity to the equator. Gordon and Silverstone (1976) demonstrated a negative correlation between incidence of nonmelanocytic skin cancer in various countries and latitudes by tabulating the incidence according to latitudinal zones. Much of the early evidence came from surveys conducted in the USA. In the first of these, Dorn (1944a,b,c) reported the results of the US First National Cancer Survey conducted in 10 urban areas in 1937-38. [Nonmelanocytic] skin cancer incidence was greater among whites living in the south than in the north of the country. Blum (1948) subsequently reanalysed these data, substituting latitude for place of residence, and showed a strong inverse relationship between incidence of mostly nonmelanocytic skin cancer and latitude. No other cancer, with the exception of the buccal cavity (including the lip), showed a similar latitude gradient.

Auerbach (1961), using data from the US Second National Cancer Survey conducted in 1947-48 in the same areas as the previous survey, calculated that the age-adjusted rates for skin cancer doubled for each 3 °48 ' (approximately 265 miles) of latitude towards the equator; similar gradients were seen for men and women and in all age groups. Haenszel (1963) reanalysed data from this survey for four southern and four northern cities. The inverse gradient with latitude was present for both basal-cell and squamous-cell carcinoma. In addition, there was some evidence that the gradient was strongest for head, neck and upper limbs (sites which are usually exposed).

A similar latitude gradient was seen in the US Third National Cancer Survey (Scotto *et al*., 1974). Inverse latitude gradients have also been reported in Australia (Silverstone & Gordon, 1966; Giles *et a*l., 1988) and in the Nordic countries (Teppo *et al*., 1980; Moan *et al*., 1989; Magnus, 1991).

Several authors have correlated nonmelanocytic skin cancer incidence (or mortality) with estimates of UVR. Green *et al*. (1976) reported a positive correlation between estimates of annual UV dose and of incidence rates in the USA, the United Kingdom, Canada and Australia. Estimates of UV dose were derived from models relating latitudinal and seasonal ozone distributions, adjusted for cloud cover. [The Working Group noted that

no allowance was made in the analysis for different methods of case ascertainment. It is not clear how well the predicted values were correlated with actual levels of UVR.]

A positive correlation, stated to be stronger than that for latitude, was seen between UVR, as measured by Robertson-Berger meters, and the incidence of nonmelanocytic skin cancer in four cities in the US Third National Cancer Survey (Scotto *et al.,* 1982). Scotto *et al.* (1983) examined incidence data collected in eight cities in 1977-78 and again showed an inverse relationship with latitude and a positive correlation with measurements of UVR. The gradient was steeper for squamous-cell than for basal-cell carcinoma.

Moan *et al.* (1989) examined nonmelanocytic skin cancer incidence in six regions of Norway from 1976 to 1985, excluding the area around Oslo to reduce bias due to possible differences in reporting and diagnosis. Two measures of UVR, one weighted according to the action spectrum for erythema and the other according to the action spectrum for mutagenesis in cells in the basal layer of the skin, were derived from atmospheric models. Similar, positive relationships between UVR and nonmelanocytic skin cancer incidence were obtained with each method.

Elwood *et al.* (1974) conducted a study of mortality from nonmelanocytic skin cancer in the contiguous states of the USA and in all of the provinces of Canada fit 1950-67. The correlation between latitude and mortality was as strong as that between mortality and an index of UVR derived from a model relating erythemal dose according to latitude with adjustments for cloud cover.

(iv) *Migration*

Studies of migrants to Australia (and other countries with high exposure to the sun) offer the opportunity to examine, indirectly, the effect of exposure to the sun. Most migrants to Australia come from higher latitudes which have lower levels of exposure to the sun than Australia. The effect of exposure to the sun is most readily examined in migrants from the British Isles to Australia, from whom most Australians are descended.

Armstrong *et al.* (1983) found that the age-adjusted mortality rate among men born in England or Wales was 0.55 (95% confidence interval (CI), 0.43-0.71) times that in Australian-born men. There was little evidence that rates in migrants increased with duration of residence in Australia, although the numbers of deaths were small and the rates unstable.

Giles *et al.* (1988) found age-adjusted incidence rates of 402 per 100 000 person-years among immigrants from the British Isles and 936 in the Australian-born population.

(v) *Occupation*

Death certificates for 1911-44 in England and Wales were used in an analysis of cancer of the skin, excluding melanomas, in male agricultural workers, miners and quarriers and professionals (Atkin *et al.,* 1949). During part of the period (1911-16), cancers of the penis, scrotum and skin were classified together, and the numbers of cancers of the skin alone were estimated from the proportions occurring in the later period. The standardized mortality ratios (SMRs) were greater for those engaged in agriculture (142.4 [137.4-147.6]) than for those in mining (94.4 [88.8-100.3]), and lowest of all for professionals (47.5 [42.6-52.9]).

Whitaker *et al.* (1979) examined occupations among cases of squamous-cell carcinoma reported to the Manchester Regional Cancer Registry, United Kingdom, in 1967-69. The occupations of 23% of cases were not ascertained. In men, standardized registration ratios

(SRRs) were elevated for textile workers (238;$p < 0.001$) and farmers (243;$p < 0.001$). The SRR was also high for female farmers (690;$p < 0.001$). Male fishermen, chemical workers and paper/printing workers had high SRRs for squamous-cell carcinoma of the arm, and building workers for squamous-cell carcinoma of the ear.

The association between occupation and nonmelanocytic skin cancer was examined in England and Wales in 1970-75 in a 10% sample of all male incident cases for which occupation was recorded (Beral & Robinson, 1981). Individuals were assigned, on the basis of stated occupation, to one of three groups: outdoor workers, indoor office workers and other indoor workers, according to the classification of occupations of the Office of Population Censuses and Surveys. The SRRs for men aged 15-64 were 110 [95% CI, 109-116] for outdoor work, 97 [92-103] for office work and 92 [86-89] for other indoor work. Since place of work may be confounded with social class, the analyses were repeated for men aged 15-64 years in social class III; the SRRs were ll2 [102-122] for outdoor work, 111[100-123] for office work and 85 [78-92] for other incioor work.

Vågerö *et al.* (1986) linked cancer incidence data in Sweden from 1961 to 1979 with census data from 1960 to determine the occupations of cases of nonmelanocytic skin cancer. Occupations were classified into three main groups: office workers, other indoor workers and outdoor workers. SRRs standardized for age, county of residence and social class, were slightly higher for outdoor workers (106; 95% CI, 101-112) than for office workers (103; 96-110) and other indoor workers (95; 91-100). The authors noted that registration may have been more complete among high socioeconomic groups.

(c) *Cross-sectional studies*

Design features of cross-sectional studies of exposure to the sun are summarized in Table 9, and the results are shown in Table 10.

A population-based survey of the prevalence of nonmelanocytic skin cancer [types not separated] was conducted in County Galway, Ireland (O'Beirn *et al.,* 1970). Exposed areas of skin were examined for the presence of cancers. In the 26 cases found, there was no significant association with frequent severe sunburn for basal-cell or squamous-cell skin cancer; among males, there was a positive relationship between cumulative hours of exposure to sunlight and the prevalence of nonmelanocytic skin cancer.

Silverstone and Gordon (1966) and Silverstone and Searle (1970) reported the results of three surveys in Queensland, Australia. Exposed areas of the skin were examined, and subjects were asked to report previously treated nonmelanocytic skin cancer [types not separated]. Women performing home duties were classified as indoor workers. Outdoor occupation showed a weakly positive association with past and present incidence in men and a negative association in women.

Holman *et al.* (1984a) conducted a population-based survey of 1216 subjects in western Australia. After controlling for age, cutaneous sun damage (as assessed by microtopography) was strongly related to a past history of nonmelanocytic skin cancer.

Engel *et al.* (1988) analysed data on basal-cell epithelioma (carcinoma) from the First National Health and Nutrition Examination Survey in the USA (1971-74). Dermatologists diagnosed skin cancers and assessed actinic skin (solar) damage, but histological confirmation of the diagnosis was not obtained routinely. Strong associations between the

prevalence of basal-cell epithelioma and solar skin damage were seen in both men and women.

Green *et al.* (1988a) conducted a survey of the prevalence of nonmelanocytic skin cancer [types not separated for calculation of RR] in Queensland, Australia. Information about exposure to the sun was obtained from questionnaires; dermatologists diagnosed skin cancers and assessed signs of actinic damage (solar lentigines, telangiectasia of the face, solar elastosis of the neck and solar keratoses). After adjustment for age, sex, skin colour and ability to tan, outdoor occupation and number of sunburns were both weakly associated with increased prevalence. Stronger associations were seen for cutaneous indicators of sun exposure, particularly for solar lentigines on the hands and telangiectasia on the face. Recreational exposure was not associated independently with nonmelanocytic skin cancer.

In a later report (Green, 1991), the occurrence of nonmelanocytic skin cancer was positively correlated with grade of cutaneous microtopography.

In a subsequent study (Green & Battistutta, 1990), subjects were asked to report nonmelanocytic skin cancer treated between 1 December 1985 and 30 November 1987, around the survey in 1986. Meclical records were searched to confirm the diagnoses. Subjects who had had a skin cancer diagnosed at the prevalence survey were excluded. Outdoor occupation, outdoor leisure activities and number of sunburns showed little association with basal-cell carcinoma in an analysis including past history of skin cancer. All three variables were related to incidence of squamous-cell carcinoma. [The Working Group noted that the exclusion of subjects found to have skin cancer during the prevalence survey makes interpretation of these results difficult. The inclusion of past history of skin cancer in the analysis would have weakened any association with exposure to the sun.]

Vitasa *et al.* (1990) conducted a survey of the occurrence of nonmelanocytic skin cancer among men engaged in traditional fishing practices ('waterman') in Maryland, USA. Subjects were examined by dermatologists and interviewed about their history of exposure to the sun. Estimates of individual annual and lifetime doses of UVB radiation were made by weighting the ambient UVR by a history of occupation and outdoor activities and by taking into account relative doses recorded by film dosimeters on the fierce. Patients with squamous-cell carcinoma aged 15-60 had had an 11% higher annual dose of UVB radiation and those with basal-cell carcinoma had had an 8% lower annual dose than that of age-matched watermen without cancers. The effect of cumulative UVB radiation was examined after adjustment for age, eye colour, childhood freckling and skin reaction to sunlight, all of which were positively associated with occurrence of both types of nonmelanocytic skin cancer. Cumulative UVB radiation dose was not associated with basal-cell carcinoma but was positively associated with squamous-cell carcinoma. The latter association was significant in a comparison of the top quarter of cumulative UVB *versus* the bottom three-quarters but not in a comparison of exposures above and below the median. [The Working Group noted that the results for the two types of cancer are not necessarily incompatible, both because of the small number of cases and the fact that the diagnosis was confirmed histopathologically in only 62%.]

Table 9. Design features of cross-sectional studies of sun exposure and nonmelanocytic skin cancer

Reference	Place	Period of diagnosis	Population	Sample size	Response rate	Cases	Histological confirmation
O'Beirn *et al*. (1970)	County Galway, Ireland	1960s	Population-based	1338	Approx. 81%	13 BCC; 13 SCC on exposed sites only	Incomplete; 57% had biopsies
Silverstone & Gordon (1966); Silverstone & Searle (1970)	Queensland, Australia	1961-63	Population-based	About 2200	87%	221 BCC or SCC on exposed surfaces	Incomplete
Holman *et al*. (1984a)	Busselton, Western Australia	1981	Population-based	1216		102, type not stated	No
Engel *et al*. (1988)	USA	1971-74	Population-based	20 637	74%	BCC, number not stated	Incomplete [small proportion]
Green *et al*. (1988a)	Nambour, Australia	1986	Population-based	2095	70-78%	42 BCC or SCC [90% of subjects examined on head/neck/hands/forearms only]	Yes
Green & Battistutta (1990)	Nambour, Australia	1985-87	Population-based	1770	84%	66BCC; 21 SCC self-reported (confirmed from medical records)	Incomplete
Vitasa *et al*. (1990)	Maryland, USA	1985-86	Male fishermen > 30 years old	838	70%	33 BCC; 35 SCC	Incomplete

BCC, basal-cell carcinomas; SCC, squamous-cell carcinoma

Table 10. Summary of results of cross-sectional studies of nonmelanocytic skin cancer

Reference	Index of exposure	Categories	Odds ratio (95% CI)	Comments
O'Beirn *et al*. (1970)	Sunlight hours (lifetime)	< 30 000 h	1.00	Mean aged > 60 years; calculated from raw data [p = 0.02]
		> 50 000 h	[8.10 (1.2-348.2)]	
Silverstone & Searle (1970)	Occupation	Indoors	1.0	Men, chi-square = 1.4 [$p > 0.1$]; calculated from raw data, no adjustment
		Outdoors	[1.29]	
	Occupation	Indoors	1.0	Women, chi-square = 0.3 [$p >$ 0.1]; calculated from raw data, no adjustment
		Outdoors	[0.6]	
Holman *et al*. (1984a)	Cutaneous microtopography	Grades 1-3	1.0	$p = 0.004$, trend adjusted for age
		Grade 4	3.9	
		Grade 5	3.6	
		Grade 6	9.2	
Engel *et al*. (1988)	Solar skin damage	None	1.0	BCC, men, age-adjusted prevalence ratio, $p < 0.01$
		Any	[8.0]	
		None	1.0	
		Any	[6.0]	
Green *et al*. (1988a)	Occupational exposure	Indoors	1.00	Adjusted for age, sex, skin colour and propensity to sunburn
		Indoors and outdoors	1.01 (0.44-2.31)	
		Outdoors	1.76 (0.77-4.05)	
	Painful sunburns	None	1.00	Adjusted for age, sex and other signs of actinic damage
		1	0.77 (0.22-2.61)	
		2-5	1.09 (0.41-2.95)	
		≥ 6	1.66 (0.59-4.64)	
	Solar lentigines on hands	None	1.00	Adjusted for age, sex and other signs of actinic damage
		1-10	1.61 (0.78-3.35)	
		11-20	1.43 (0.43-4.77)	
		≥ 6	3.78 (1.06-13.41)	
	Telangiectasia on face	None	1.00	Adjusted for age, sex and other signs of actinic damage
		Mild	1.63 (0.58-4.57)	
		Moderate	2.74 (0.89-8.40)	
		Severe	3.67 (0.79-17.11)	

Table 10 (contd)

Reference	Index of exposure	Categories	Odds ratio (95% CI)	Comments
Green *et al*. (1988a) (contd)	Actinic elastosis on neck	None	1.00	Adjusted for age, sex and other signs of actinic damage
		Mild to moderate	1.42 (0.53-3.80)	
		Severe	1.75 (0.56-5.45)	
	Solar keratoses on face	None	1.00	Adjusted for age, sex and other signs of actinic damage
		1-5	1.55 (0.67-3.59)	
		6-20	1.86 (0.69-5.04)	
		21-50	3.00 (0.54-16.69)	
		≥ 51	2.72 (0.73-10.15)	
Green & Battistutta (1990)	BCC	Mainly indoors	1.0	Adjusted for age, sex, skin colour and past history of skin cancer
	Occupational exposure	Indoors and outdoors	1.5 (0.8-2.9)	
			1.3 (0.6-2.8)	
	Leisure exposure	Mainly indoors	1.0	Adjusted for age, sex, skin colour and past history of skin cancer
		Indoors and outdoors	1.0 (0.4-2.2)	
		Mainly outdoors	0.6 (0.3-1.3)	
	No. of painful sunburns	None	1.0	Adjusted for age, sex, skin colour and past history of skin cancer
		1	0.5 (0.2-1.4)	
		2-5	0.6 (0.3-1.5)	
		≥ 6	1.0 (0.4-2.5)	
	SCC	Mainly indoors	1.0	Adjusted for age, sex, skin colour and past history of skin cancer
	Occupational exposure	Indoors and outdoors	4.4 (0.9-20.9)	
		Mainly outdoors	5.5 (1.1-28.2)	
	Leisure exposure	Mainly indoors	1.0	Adjusted for age, sex, skin colour and past history of skin cancer
		Indoors and outdoors	2.0 (0.2-19.9)	
		Mainly outdoors	3.9 (0.5-30.9)	
	No. of painful sunburns	0-1	1.0	Adjusted for age, sex, skin colour and past history of skin cancer
		2-5	3.3 (0.9-12.3)	
		≥ 6	3.0 (0.7-12.2)	

Table 10 (contd)

Reference	Index of exposure	Categories	Odds ratio (95% CI)	Comments
Vitasa *et al*. (1990)	SCC	Below median	1.0	Proportionate odds ratios; adjusted for age, eye colour, freckling and sunburn reaction
	Cumulative UVB dose to face	Above median	2.05 (0.84-5.01)	
		Below 75 percentile	1.0	
		Above 75 percentile	2.53 (1.18-5.40)	
	BCC	Below median	1.0	Proportionate odds ratios; adjusted for age, eye colour, freckling and sunburn reaction
	Cumulative UVB dose to face	Above median	0.69 (0.31-1.53)	
		Below 75 percentile	1.0	
		Above 75 percentile	1.11 (0.50-2.44)	

BCC, basal-cell carcinoma; SCC, squamous-cell carcinoma; unless otherwise specified, all analyses are for the two types together

(d) *Case-control studies*

Design features of the case-control studies of exposure to the sun and the occurrence of nonmelanocytic skin cancer are summarized in Table 1l. Most of the studies employed hospital- or clinic-based controls, which introduces potential for selection bias. The results are summarized in Table 12. The methods of analysis and of measurements of exposure to the sun, particularly in the earlier studies, were crude. Neither sensitivity to the sun, usually measured as the ability to tan or propensity to burn, nor pigmentary characteristics (such as skin colour and hair colour), which are likely to be confounding variables, were taken into account in most of the analyses.

The hospital-based study of Lancaster and Nelson (1957) in Sydney. Australia, was primarily a case-control study of melanoma (described in detail on p. 100). It can also be considered to be a case-control study of nonmelanocytic skin cancer, however, because it included two control groups—one of patients with basal-cell carcinoma, squamous-cell carcinoma or solar keratosis and the second of patients with leukaemia or cancer at a site other than the skin. All groups were matched by age and sex. Among males, long duration of occupational exposure to the sun was associated with an increased risk for nonmelanocytic skin cancer or solar keratosis. A summary of total exposure to the sun was devised by assigning scores to a number of factors considered to be related to exposure to the sun. Risk was highest among subjects judged to have excessive exposure to the sun. [The Working Group noted that the proportion of cases who had a solar keratosis is not stated, that no account was taken of matching in the analyses, and that the effect of exposure to the sun was not adjusted for sensitivity to the sun.]

Gellin *et al*. (1965) conducted a study in a single hospital in New York, USA, on 861 patients with basal-cell carcinoma and 1938 non-cancer dermatolcygical patients attending the same clinic. Since 95% of cases and 43% of controls were 40 years old and over, the study was limited to these patients, resulting in 771 cases and 783 controls. The skin cancer patients spent more time outdoors per day than did control patients and were significantly more likely than controls to have light hair, fair complexion, blue eyes and an inability to tan. [The Working Group noted that the analyses were not adjusted for age, sex or sensitivity to the sun, and that confounding by age is likely because controls were younger than cases.]

Urbach *et al.* (1974) conducted a hospital-based study in Philadelphia, USA, and compared exposure to the sun of 392 patients with histologically confirmed basal-cell carcinoma, 59 patients with histologically confirmed squamous-cell carcinoma and 281 outpatients receiving treatment for a skin disease other than cancer. Controls were matched to cases by age and sex. Among male patients, those with basal-cell or squamous-cell carcinoma had more cumulative hours of exposure than did controls. Skin cancer patients also reported more sunburns. [The Working Group noted that the analyses were not adjusted for ability to tan, age or sex (apart from the sex-specific analysis).]

Vitaliano (1978) subsequently reanalysed the data of Urbach *et al.* (1974) and showed that, after adjustment for complexion (dark *versus* pale), ability to tan and age (< 60, ≥ 60), the cumulative time spent outdoors was related to both types of nonmelanocytic skin cancer. For basal-cell carcinoma, the odds ratio for $\geq 30\,000$ h of exposure relative to $< 10\,000$ h was 3.19; for squamous-cell carcinoma it was 22.8. [The Working Group noted that confi-

dence intervals were not given. Part of the apparently stronger effect for squamous-cell carcinoma could be due to confounding by age: the controls were matched by age to the basal-cell carcinoma cases, who were younger than the squamous-cell carcinoma cases.]

A hospital-based case-control study was conducted in Montreal, Canada (Aubry & MacGibbon, 1985), in which patients with histologically confirmed squamous-cell carcinoma were identified in hospitals in 1977-78. Two patients with other conditions were matched as controls to each case by age, sex and hospital. Information on exposure to the sun was obtained from a postal questionnaire. Among 306 eligible cases, 94 (31%) replied, as did 186 (30%) of the eligible controls; 92 cases and 174 controls completed the questionnaire. Most of the controls who replied had been seen for seborrheic keratoses (61%) or intradermal naevi (16%). Scores for nonoccupational and occupational exposures were estimated, and the two scores were divided into thirds for analysis, which was based on logistic regression. The odds ratios, adjusted for each other and for host factors, were 1.08 and 1.64 for the middle and upper thirds of occupational exposure and 1.93 and 1.58 for the same levels of nonoccupational exposure, respectively. [The Working Group noted the low response rate and that the complexity of the recreational exposure to sun indices and the nature of the control group make the results difficult to interpret.]

O'Loughlin *et al.* (1985) conducted a case-control study in a hospital in Dublin, Ireland. Patients with histologically confirmed nonmelanocytic skin cancer [types not separated] were compared w ith age- and sex-matched patients who had cancers of other organs. There was no statistically significant difference between cases and controls in eight measures of exposure to the sun summarized in a single index of exposure and either type of nonmelanocytic skin cancer. [The Working Group noted that the measures of exposure to the sun were crude and likely to be subject to considerable misclassification. No adjustment was made for sensitivity to the sun.]

Herity *et al.* (1989) conducted a case-control study in the same hospital in Dublin of 396 histologically confirmed nonmelanocytic skin cancers in 1984-85. An equal number of age- and sex-matched patients with other cancers, attending the same hospital, were used as controls. More cases than controls lived in rural areas ($p = 0.007$), and cases reported more frequently spending more than 30 h outdoors per week, but the difference was nonsignificant. For other indices of exposure to the sun, there was little difference between cases and controls. [The Working Group noted that results were not adjusted for reaction to sunlight.]

In a case-control study (reported as an abstract) conducted in 1983-84 in Alberta, Canada (Fincham & Hill, 1989), 225 men with basal-cell carcinoma and 181 men with squamous-cell carcinoma were compared with 406 age-matched male controls. Sunburn in adult life gave an odds ratio of 2.33 ($p < 0.05$) for all nonmelanocytic skin cancer; for basal-cell carcinoma, childhoood sunburn gave an odds ratio of 2.48 ($p < 0.05$) and peeling an odds ratio of 1.85 ($p < 0.05$).

A population-based case-control study was conducted in Saskatchewan, Canada (Hogan *et al.,* 1989), which included all patients diagnosed with basal-cell carcinoma in the Province in 1983. Two controls, matched by year of birth, sex and municipality of residence, were selected for each case from a universal Provincial health insurance plan. Replies to mailed questionnaires were received from 55.5% of the cases and 43.7% of the

controls. A number of measures of exposure to the sun were associated with incidence of basal-cell carcinoma. In a stepwise logistic regression analysis, occupation as a farmer, history of severe sunburn and working outdoors for more than 3 h per day in winter were independently associated with basal-cell carcinoma, after adjustment for freckles in childhood, family history of skin cancer, 'Celtic' mother, skin colour and hair colour. [The Working Group noted that the measures of exposure were crude and that the estimates do not appear to have been adjusted for the matching variables. The low response rate makes interpretation of the results difficult.]

On the basis of a population-based survey in Western Australia in 1987 of skin cancer among residents aged 40-64 years of age (Kricker *et al*., 1990), Kricker *et al.* (1991a) conducted a case-control study of 226 confirmed cases of basal-cell carcinoma and 45 of squamous-cell carcinoma; two sets of 1015 controls with no lesions, who had completed an interview, were available for each type of cancer. The response rate among those eligible to participate was identical for cases and controls: 89%. Separate analyses were undertaken for basal-cell carcinoma and squamous-cell carcinoma using unconditional logistic regression analysis. Risks for both cancers were higher in native-born Australians than in migrants, and the risk for basal-cell carcinoma decreased with increasing age at arrival in Australia. Only four of the subjects with squamous-cell carcinoma had been born outside Australia—an insufficient number to examine the effects of age at arrival. Indicators of sun damage to the skin (facial telangiectasia, solar elastosis of the neck, facial solar lentigines and number of solar keratoses), assessed by dermatologists during the prevalence survey, were examined in models adjusted for age, sex, ethnicity and migrant status and including all other sun damage indicators except solar keratoses, which were considered to be preneoplastic lesions and thus inappropriate for inclusion in models concerned with etiology. Cutaneous microtopography, an objective measure of actinic skin damage, graded without knowledge of the person's skin cancer status, and solar elastosis of the neck had significant residual effects for basal-cell carcinoma, while solar elastosis and facial telangiectasia had significant residual effects for squamous-cell carcinoma. The independently significant indicators of sun damage were analysed in models which included adjustment for age, sex, ethnicity and migrant status as well as measures of sun sensitivity. Solar elastosis of the neck remained an independent predictor of risk of basal-cell carcinoma (odds ratios, > 1.50;$p = 0.003$) and squamous-cell carcinoma (odds ratios, > 2.00;$p = 0.04$).

A subsequent analysis of individual SUIT exposure was published as an abstract (Kricker *et al.*, 1991b). A positive association was found between nonmelanocytic skin cancer and life-time potential for exposure to the sun, but no evidence of increasing risk for either basal-cell carcinoma or squamous-cell carcinoma with increasing total hours of actual exposure to the sun as recalled by subjects. Risk for basal-cell carcinoma on the trunk was increased substantially in association with maximal exposure of the trunk to the sun, but there was no consistent pattern of association of site-specific basal-cell or squamous-cell carcinoma with exposure of the head and neck or limbs. Neither basal-cell nor squamous-cell carcinoma showed evidence of an association with sun exposure on working days; however, there was persuasive evidence of increased risk for both types of skin cancer with intermediate and high levels of accumulated exposure to the sun on non-working days.

Moreover, there was evidence of an association, stronger for basal-cell carcinoma than for squamous-cell carcinoma, with a measure of intermittent exposure to the sun.

Gafá *et al.* (1991) conducted a case-control study of nonmelanocytic skin cancer in Sicily, Italy, in which 133 cases identified from a population-based registry (response rate, 94%) were compared with 266 sex- and age-matched controls. For each case, one control was selected randomly from among patients with non-neoplastic diseases at the same hospital as the case, and a second control was selected randomly from among friends or relatives of the case. After adjustment for family history of skin cancer, 'cancer-related cutaneous disease', skin colour and skin reaction to sunlight, sun exposure for at least 6 h per day and residence for at least 10 years at more than 400 m above sea level were significantly related to risk for nonmelanocytic skin cancer. In crude analyses in which the two types of cancer were separated, sun exposure for at least 6 h per day without a hat was strongly associated with risk for squamous-cell carcinoma [site unspecified] (odds ratio, 6.4; 95% CI, 1.9-21.1) but not for basal-cell carcinoma (1.4, 0.7-2.6). [The Working Group noted that the nature of the control group, the assessment of exposure and the failure to account for age in the analysis make the results difficult to interpret. The crude analysis of the type-specific results, the lack of data on the site of the tumours and the small numbers may explain the different results for the two types.]

(e) *Cohort studies* (Tables 13 and 14)

In a study in Chicago, IL (USA), Robinson (1987) investigated the incidence of second nonmelanocytic skin cancer among a group of 1000 patients who had had basal-cell carcinoma. Among 978 who were followed for five years after the initial diagnosis, 22% developed a second basal-cell carcinoma at the end of the first year and 36% within five years. There was no significant correlation between developing a second cancer and frequent exposure through sunbathing or outdoor leisure activities, work or currently living in an area with heavy exposure to the sun, or according to estimated number of hours of daily exposure to the sun. Among those with skin types I and II (always burn easily and never or minimally tan) who reported frequent sun exposure, there was an increased risk of second cancer ($p < 0.03$). [The Working Group noted that the methods of assessing exposure and the methods of analysis were not described, and that no numbers were reported. Risk factors for second cancers might not be the same as for the first.]

Marks *et al.* (1989) conducted a longitudinal series of examinations of the head, neck, forearms and hands of a population in Maryborough, north-central Victoria, Australia, for one week annually between 1982 and 1986. The incidence rates of squamous-cell and basal-cell carcinoma were higher in outdoor workers than in indoor workers. In an analysis of the two types combined, occupation was not significantly associated after adjustment for age, sex and reaction to sunlight ($p = 0.09$). [The Working Group noted that no account was taken of lesions that might have been removed between surveys.]

Hunter *et al.* (1990) conducted a study of basal-cell carcinoma in a cohort of female nurses in the USA. A total of 771 cases were identified from responses to follow-up questionnaires sent to the women two and four years after the initial exposure questionnaire was given. In a sample of 29 women, the diagnosis was confirmed for 28; confirmation of the diagnosis was not obtained routinely. Residents of California and Florida had the highest

Table 11. Design features of case-control studies of sun exposure and nonmelanocytic skin cancer

Reference	Place	Periods of diagnosis	Cases		Controls	
			No.	Source	No.	Source
Lancaster & Nelson (1957)	Sydney, Australia	Unknown	173 BCC, SCC or solar keratosis	Major hospitals	173	Other cancers, same hospital
Gellin *et al*. (1985)	New York, USA	1955-59	771 BCC ≥ 40 years old	One skin hospital	783 ≥ 40	Other diagnoses, same skin clinic
Urbach *et al*. (1974)	Philadelphia, USA	1967-69	392 BCC 59 SCC	One skin and cancer clinic	281	Other diagnoses, same clinic
Aubry & MacGibbon (1985)	Montréal, Canada	1977-78	92 SCC	12 hospitals	174	Skin conditions, same hospitals
O'Loughlin *et al*. (1985)	Dublin, Ireland	Unknown	63 SCC 58 BCC	One hospital	121	Other cancers, same hospital
Herity *et al*. (1989)	Dublin, Ireland	1984-85	396 BCC and SCC	One hospital	396	Other cancers, same hospital
Hogan *et al*. (1989)	Saskatchewan, Canada	1983	538 BCC	Population	738	Population
Kricker *et al*. (1991a)	Geraldton, Australia	1987	226 BCC 45 SCC	Population	1015 1015	Population
Gafá *et al*. (1991)	Ragusa, Sicily, Italy	1987-88	133 BCC and SCC	Cancer registry	133 133	Non-neoplastic disesases, same hospital; friends or relatives

BCC, basal-cell carcinoma; SCC, squamous-cell carcinoma

Table 12. Summary of results of case-control studies of nonmelanocytic skin cancer

Reference	Exposure	Categories	Odds ratio (95% CI)	Comments
Lancaster & Nelson	Years of occupational exposure	< 5	1.0	[$p < 0.001$, trend; p and odds ratio calculated from raw data]
		5-10	[1.9]	
		> 10	[4.2]	
	Total sun exposure	Minimal	1.0	[$p = 0.13$; p and odds ratio calculated from raw data]
		Moderate	[1.8]	
		Excessive	[2.4]	
Gellin *et al*. (1965)	Hours per day outdoors	0-2	1.0	BCC [$p < 0.001$]
		3-5	[4.9 (3.8-6.3)]	
		≥ 6	[7.7 (5.6-10.6)]	
Urbach *et al*. (1974)	Cumulative hours (x 1000)	< 30	1.0	BCC
		30-50	[3.5 (20.-6.6)]	
		> 50	[9.3 (3.2-37.4)]	
		< 30	1.0	SCC
		30-50	[4.0 (1.7-9.6)]	
		> 50	[11.1 (2.8-53.6)]	
Aubry & MacGibbon (1985)	Non-occupational exposure score	Low	1.0	SCC [$p = 0.07$] for continuous variable, adjusted for occupation and host factors
		Medium	1.23	
		High	1.58	
	Occupational score	Low	1.0	SCC [$p = 0.008$], for continuous variable, adjusted for non-occupational score and host factors
		Medium	1.08	
		High	1.64	
	Use of sunlamps	Never	1.0	SCC [$p = 0.008$], adjusted for sun exposure and host factors
		Ever	13.4 (1.38-130.48)	
O'Loughlin *et al*. (1985)	Outdoor occupation	No	1.0	Not significant (McNemar's test) [odds ratio calculated from raw data ignoring matching]
		Yes	[1.5]	
	Hours per week outdoors	< 10	1.0	Not significant
		≥ 10	[1.4]	
	Sunbathing > 4 h per day on vacations	No	1.0	Not significant
		Yes	[1.0]	
Herity *et al*. (1989)	Living in rural area > 30 h outdoors/week		[1.4]	$p = 0.007$
			[1.1]	$p = 0.7$

Table 12 (contd)

Reference	Exposure	Categories	Odds ratio (95% CI)	Comments
Hogan *et al*. (1989)	Farmer	No	1.0	BCC, adjusted for each other, plus freckles, family history of skin cancer, Celtic mother, skin colour, hair colour
		Yes	1.29 [1.12-1.46]	
	Severe sunburn	No	1.0	BCC
		Yes	1.19 [1.04-1.35]	
	Working outdoors > 3 h per day winter	No	1.0	BCC
		Yes	1.13 [1.01-1.27]	
Kricker *et al*. (1991a)	BCC			$p < 0.001$, adjusted for other variables below and for ethnicity, ability to tan, freckling as a child and number of moles on back
	Age at migration (years)	Australian	1.0	
		born	1.37 (0.55-3.42)	
		< 10	0.32 (0.18-0.59)	
		< 10		
	Solar elastosis of the neck	None	1.00	$p = 0.003$, comments as above
		Mild	1.85 (0.80-4.26)	
		Moderate	2.75 (1.16-6.50)	
		Severe	3.96 (1.58-9.93)	
	Cutaneous microtopography	Grades 1-3	1.0	$p = 0.10$, comments as above
		Grade 4	2.01 (1.00-4.07)	
		Grade 5	2.42 (1.17-5.01)	
		Grade 6	2.15 (0.99-4.70)	
	SCC		1.0	$p = 0.13$, adjusted for variables below plus ability to tan, skin colour, freckling as a child
	Migrant to Australia	No	0.46 (0.15-1.38)	
		Yes		
	Permanent colour	No	1.0	$p = 0.03$, comments as above
	difference between neck and adjacent skin	Yes	2.58 (1.03-6.47)	
	Telangiectasia of face	None/mild	1.0	$p = 0.10$, comments as above
		Moderate	2.22 (1.06-4.67)	
		Severe	1.88 (0.72-4.90)	
	Solar elastosis of the neck	None/mild	1.00	$p = 0.04$, comments as above
		Moderate	2.31 (1.00-5.34)	
		Severe	3.33 (1.23-9.04)	

Table 12 (contd)

Reference	Exposure	Categories	Odds ratio (95% CI)	Comments[a]
Gafá *et al.* (1981)	Residence > 400 m above sea level	No	1.0	Adjusted for family history of skin cancer, cutaneous-related conditions, skin colour, skin reaction to sunlight and sun exposure
		Yes	2.0 (1.2-3.2)	
	Sun exposure ≥ 6 h/day	No	1.0	Adjusted for family history of skin cancer, cutaneous-related conditions, skin colour, skin reaction to sunlight and residence > 400 m above sea level
		Yes	1.9 (1.2-3.1)	

BCC, basal-cell carcinoma; SCC, squamous-cell carcinoma; unless otherwise specified, analyses are for the two types together

incidence rates. There was a trend of increasing incidence with increasing number of sunburns. With respect to time spent outdoors during the summer, nurses who spent more than 8 h per week outside and who used sunscreens had the highest incidence rates. The rates in women who spent the least time outdoors were similar to those who spent more time outdoors and did not use sunscreens. [The Working Group noted that the high incidence rate in nurses using sunscreens, despite control for reaction to sunlight, might be due partly to confounding.]

Table 13. Design feature of cohort studies of sun exposure and nonmelanocytic skin cancer

Reference	Place	Period of diagnosis	Population	Sample size	Response rate	Cases	Histological confirmation
Robinson (1987)	Chicago, IL, USA	Not stated	Patients with previous BCC	1 000	98%	BCC, approx. 350	Not stated
Mark *et al*. (1989)	Maryborough, Australia	1982-86	Population-based	1 981	74%	35 SCC; 113 BCC on light-exposed surfaces only	Yes
Hunter *et al*. (1990)	USA	1980-84	Female nurses	73 366	74%	771 BCC (self-reported)	Not routinely [records of 28 out of sample of 29 confirmed]

BCC, no. of people with basal-cell carcinoma; SCC, no. of people with squamous-cell carcinoma

(f) *Collation of results*

The results discussed in this section come from cross-sectional studies by Holman *et al.* (1984a), Angel *et al.* (1988), Green *et al.* (1988a) and Vitasa *et al*. (1990), a case-control study by Kricker *et al*. (1991a) and cohort studies by Marks *et al*. (1989) and Hunter et al. (1990), all of which included information pertinent to the association between nonmelanocytic skin cancer and different aspects of sun exposure. Other studies described individually were not considered to provide useful information because of various methodological deficiencies. No data were available on short periods of residence and intermittent exposure, issues which are addressed for melanoma of the skin.

(i) *Total sun exposure: potential exposure by place of residence*

Consistent with descriptive data in a case-control study, migrants to Australia had a lower risk for squamous-cell carcinoma than did native-born Australians, after adjustment for host factors related to risk for nonmelanocytic skin tumours. Late age at arrival in Australia was associated with a lower risk for basal-cell carcinoma (Kricker *et al.,* 1991a).

(ii) *Biological responses to total sun exposure*

Cross-sectional studies and a case-control study are consistent in showing a strong relationship between cutaneous indicators of sun damage and both types of nonmelanocytic skin cancer. In most studies, the indicators of damage and diagnoses of skin cancer were made by the same examiner, but cutaneous microtopography, graded without knowledge of outcome, also showed strong associations.

Table 14. Summary of results of cohort studies of nonmelanocytic skin cancer

Reference	Exposure	Categories	RR (95% CI)	Comments
Marks *et al*. (1989)	Occupation	*BCC*		
		Indoors	1.0	Adjusted for age, $p = 0.03$
		Outdoors	1.6	
		SCC		
		Indoors	1.0	Adjusted for age, $p = 0.109$
		Outdoors	1.7	
Hunter *et al*. (1990)	Severe sunburns on face or arms			BCC
		None	1.0	Adjusted for age; p (trend) = 0.001
		1-2	1.40 (1.13-1.75)	
		3-5	1.78 (1.42-2.25)	
		≥ 6	2.91 (2.37-3.58)	
	Severe sunburns on face or arms	None	1.0	Adjusted for age, time period, region, time spent outdoors, sunscreen habit, hair colour, childhood tendency to sunburn; p (trend) < 0.001
		1-2	1.18 (0.94-1.48)	
		3-5	1.34 (1.05-1.71)	
		≥ 6	1.90 (1.50-2.40)	
	Time spent outdoors during summer (h/week)	≥ 8 (sunscreen)	1.0	Adjusted for age
		≥ 8 (no sunscreen)	0.59 (0.50-0.69)	
		< 8	0.71 (0.58-0.88)	
	Time spent outdoors during summer (h/week)	≥ 8 (sunscreen)	1.0	Adjusted for age, time period, region, number of sunburns, hair colour, childhood tendency to sunburn
		≥ 8 (no sunscreen)	0.70 (0.60-0.82)	
		< 8	0.73 (0.59-0.90)	

[a]BCC, basal-cell carcinoma; SCC, squamous-cell carcinoma

(iii) *Total sun exposure assessed by questionnaire*

No effect of time spent outdoors during summer was seen in a cohort study of basal-cell carcinoma (Hunter *et al.,* 1990). In a cross-sectional study of fishermen, cumulative exposure to UVB radiation was positively associated with the occurrence of squamous-cell carcinoma but not of basal-cell carcinoma (Vitasa *et al., 1990).* The different results may be attributable in part to small numbers and incomplete histopathological confirmation of diagnoses.

(iv) *Occupational exposure*

In two studies from Australia, outdoor occupation was not significantly associated with the prevalence of the two types of carcinoma combined (Green *et al.,* 1988a) or with the incidence of squamous-cell carcinomas (Marks *et al.,* 1989).

(v) *Sunburn*

A cohort study of basal-cell carcinoma in the USA showed a trend of increasing risk with increasing number of sunburns after adjustment for various factors, including tendency to sunburn (Hunter *et a/.,* 1990). Number of sunburns showed a nonsignificant positive association with risks for basal-cell and squamous-cell carcinoma of the skin after adjustment for various constitutional variables, including propensity to burn (Green *et a/.,* 1988a).

2.1.2 *Cancer of the lip*

Assessment of the carcinogenicity of solar radiation for the lip is complicated by the fact that carcinoma at this site is actually diagnosed as a mixture of cancers of the external lip and cancers of the buccal membranes (oral cavity). Use of alcohol and tobacco are known causes of the latter tumours (IARC, 1985, 1986b, 1988).

While there are wide variations in the apparent incidence of cancer of the lip with latitude, evaluation of the association is difficult because of inconsistency in the definitions of the boundaries of the lip. 'Cancer of the lip' is defined as cancer of the vermilion border and adjacent mucous membranes and thus excludes cancers of the skin of the lip (WHO, 1977). Most are squamous-cell carcinomas and are located on the lower lip (Keller, 1970; Lindqvist, 1979), which is more heavily exposed to sunlight than is the upper lip (Urbach *et a/.,* 1966).

In general, case reports were not considered, because of the availability of more informative data. One case report from Nigeria described the occurrence of two lip tumours in albinos (Onuigbo, 1978).

(a) *Descriptive studies*

The incidence of lip cancer is 4-10 times higher in men than in women in most white populations, and higher in whites than in populations of darker skin complexions living in the same geographical areas (Muir *et a/.,* 1987).

(i) *Geographical variation*

The incidence of lip cancer is higher in rural than in urban areas, in particular among men (Doll, 1991).

Mortality from and incidence of lip cancer are substantially lower in migrants to Australia than in native-born Australians (Armstrong *et al.*, 1983; McCredie & Coates,

1989). Groups of migrants to Israel all show lower risks for lip cancer than the locally born population (Steinitz *et al*., 1989).

(ii) *Occupation*

As reviewed by Clemmesen (1965), several observations during the nineteenth century pointed to an increased risk of lip cancer among people in outdoor occupations, in particular farmers and farm labourers. In England and Wales, increased risks for lip cancer were reported among agricultural labourers, fishermen, other dock workers and railwaymen employed outdoors (Young & Russell, 1926). Atkin *et al.* (1949) studied the occupations of 1537 men in England and Wales who died from lip cancer between 1911 and 1944. They reported that mortality from cancer of the lip was 13 times higher among men employed in agriculture than in men with professional jobs. Excess risks for lip cancer have also been observed in farmers in western Canada (Gallagher *et al*., 1984) and in Denmark (Olsen & Jensen, 1987; Lynge & Thygesen, 1990).

(b) *Case-control studies*

Keller (1970) compared 301 men with lip cancer admitted to veterans' hospitals in the USA between 1958 and 1962 with two groups of white age-matched controls admitted to the same hospitals, comprising 301 oral cancer controls and 265 general controls. Altogether, 59.9% of the lip cancer cases, 37.1 % of the cancer controls and 40.6% of the general controls had been born in the south of the USA. Farming was recorded as the occupation of 27% of the lip cancer cases but of only *to* of cancer controls and 47 of the general controls [crude odds ratios, 4.0 and 8.4, respectively]. Any type of outdoor work was recorded for 39% of cases of lip cancer, for 20% of cancer controls and for 12% of the general controls [crude odds ratios, 2.6 and 4.8, respectively]. Risk estimates were not adjusted for smoking, another risk factor identified in the study.

Spitzer *et al.* (1975) obtained information by personal interview on 339 men with squamous-cell carcinoma of the lip registered with the Newfoundland (Canada) Cancer Registry between 1961 and 1971 and 199 male controls chosen from the electoral register, matched for age and geographical location in nine census divisions; the overall response rate was 93%. An association was found between lip cancer and outdoor work (odds ratio, 1.52;$p < 0.05$); an odds ratio of 1.50 ($p < 0.05$) was found for occupation as a fisherman for at least eight full seasons, after adjustment for outdoor work, pipe smoking and age. No positive association was found for specific fishing activities, such as use of mouth as a third hand or of cast nets.

Lindqvist (1979) obtained information by mailed questionnaires from 171 cases (149 men, 22 women; 74% response rate) of epidermoid carcinoma of the lip registered with the Finnish Cancer Registry in 1972-73 and from a control group of 124 patients (56 men, 68 women; 77% response rate) registered with squamous-cell carcinoma of the skin of the head and neck. Risk estimates were adjusted for age. Odds ratios for men working outdoors ranged from 2.2 to 3.2 according to the calendar period during which the subjects had worked outdoors. The odds ratio was significantly increased only for those who both worked outdoors and smoked. [The Working Group noted that the choice of head and neck skin cancer patients as controls would lead to an underestimate of the odds ratio for outdoor work.]

Dardanoni *et al.* (1984) obtained information by personal interviews from 53 men with lip cancer registered in the Ragusa Cancer Registry in Italy and from 106 male controls matched for age and municipality of residence and admitted to the same hospitals for non-neoplastic diseases. An association was found between lip cancer and working or spending at least 6 h each day outdoors (odds ratio, 4.9; $p < 0.001$). After control for socio-economic level, the odds ratio was 1.7 ($p < 0.001$). [The Working Group noted that the latter *p* value is inconsistent with the number of subjects.]

2.1.3 *Malignant melanoma of the skin*

Melanoma of the skin is divided into three major histological types. The majority of melanomas in white-skinned populations (of European origin) are superficial spreading and nodular melanomas. Lentigo maligna melanoma—also known as Hutchinson's melanotic freckle—occurs later in life than the other types, and more specifically on exposed sites; however, the body site and evidence of sun damage in surrounding skin may influence its pathological classification (McGovern *et al.,* 1980). Acral lentiginous melanoma has not been studied epidemiologically; it is rare in white-skinned populations, although it comprises a substantial proportion of melanomas in Japan (Elwood, 1989a).

(a) *Case reports*

In general, case reports were not considered, owing to the availability of more informative data.

In a survey of 830 cases of xeroderma pigmentosum located through published case reports (Kraemer *et al.,* 1987), melanomas were reported in 37 patients (5%). As the median age at last follow-up of these cases was only 19 years, this observation is likely to represent a substantial excess over the number expected, although the exact nature of the study population precludes an accurate comparison. Site was specified for 29 of the 37 cases; 65% of these were on the face, head and neck (normally constantly UVR-exposed sites) as compared with 19.4% on this site among affected members of the US general population. [The Working Group recognized that data collected from previously published case reports are not uniform and may be atypical of a true incidence or prevalence series. Furthermore, no information is available on the relationship between solar exposure and the occurrence of malignant cutaneous melanoma in these patients.]

(b) *Descriptive studies*

(i) Sex distribution

The sex distribution of melanoma, adjusted for age, varies widely between populations. In many, it occurs as often as or more commonly in women than in men (Lee & Storer, 1980; Lee, 1982), in contrast to other types of skin cancer which are uniformly commoner in men (Muir *et al.,* 1987).

(ii) *Age distribution*

Age distributions of melanoma in human populations vary with sex (Lee, 1982). They cannot easily be interpreted because they represent a variable combination of the different patterns of melanomas at different sites as well as a combination of time trends and trends in the experience of birth cohorts.

(iii) *Anatomical distribution*

Melanoma is proportionately commonest on the back and face in men and on the legs in women (Crombie, 1981); however, the incidence of melanoma per unit of body area is similar on fully exposed sites, such as the face, and on partially exposed sites, such as the lower limbs in women and the back in men. The frequency on body sites that are usually covered, such as the buttocks, is much lower (Elwood & Gallagher, 1983).

(iv) *Ethnic origin*

Melanoma is predominantly a disease of white-skinned populations. Rates in dark-skinned populations are much lower, the age-standardized incidence rate in India being 0.2 per 100 000 compared to around 30 in Queensland, Australia. In Los Angeles, USA, rates were less than 1 per 100 000 in Japanese and Chinese subjects and 11-12 in white subjects (Muir *et al.,* 1987: Whelan *et al.,* 1990). The site and histological distribution of melanoma are different in non-white populations and have been little studied epidemiologically. The remainder of this section deals only with melanoma in white populations.

The incidence of melanoma is substantially lower among Hispanics than among other whites in the USA. For example, the incidence among Hispanics in New Mexico is less than 2 per 100 000 person years. but in other whites it is about 11 per l00 000 (Muir *et al.,* 1987). In several case-control studies (described in detail below), subjects with a southern or eastern European background had lower risks than those with northern European or British origins (Elwood *et al.,* 1984; Holman & Armstrong, 1984a).

In a Canadian study (Elwood *et al.*, 1984), people with an eastern or southern European background had a crude odds ratio of 0.5 relative to those with an English background. This effect was not changed appreciably after adjustment for constitutional factors of hair, eye and skin colour and the skin's reaction to sun exposure. In contrast, the effect of ethnic origin observed in Western Australia was substantially reduced after adjustment for pigmentation characteristics (Holman & Armstrong, 1984a).

(v) *Geographical variation*

Armstrong (1984) showed that the relationship between melanoma incidence in Caucasians and latitude of residence decreases from around 35 ° to a minimum around 55° and then rises with latitude due to high rates in Scandinavian and Scottish populations. This pattern is likely to be due to both latitudinal and pigmentation factors. Within countries, inverse relationships of incidence or mortality with latitude have been seen in England and Wales (Swerdlow, 1979), Norway (Magnus, 1973), Sweden (Eklund & Malec, 1978) and Finland (Teppo *et al.,* 1978).

In the first comprehensive analysis of the geography of melanoma in whites, Lancaster (1956) noted that mortality from the disease was higher in Australia and South Africa than in the parts of Europe from which their populations originated: that mortality in Australia, New Zealand and the USA increased with proximity to the equator; but that within Europe it was higher in Norway and Sweden in the north than in France and Italy in the south. These patterns are also evident in more recent data (Armstrong, 1984).

Geographical variation in relationship to ambient UV irradiation levels: Several studies have compared melanoma incidence and mortality rates in different areas of North America to estimated or measured levels of ambient UVR, and Elwood (1989b) estimated the change

in rate for a 10% change in UVR level (Table 15). [The Working Group noted that these studies did not assess any other component of the solar spectrum.]

Elwood *et al.* (1974) showed, using mortality data for US states and Canadian provinces, that the correlation coefficients with latitude were 0.79 for men and 0.72 for women. A variation in latitude of 2 °, which is equivalent to 138 miles, was associated with a change in death rates from melanoma of about 10%. Annual UV flux at erythema-producing wavelengths was calculated from information on latitude and meteorological data on cloud cover. This calculated index of exposure was very strongly correlated with latitude (correlation coefficient, 0.89), so melanoma mortality rates were strongly related to this index; a 10% increase in received UVR dosage would be expected to give an increase of 3.7-4.5% in the death rate from melanoma at latitude 50 °, and 6.8-10.3% at latitude 30 ° (Table 15). These values were somewhat higher for men than for women; for example, 4.4% in men compared with 3.0% in women at latitude 50 ° using the exponential model.

Fears *et al.* (1976) related melanoma incidence to latitude and to a calculated measure of UVR. Their data cover a slightly narrower range of latitude, and they calculated that a 10% increase in UVR would cause an increase in melanoma mortality of 7-12%, the higher figure applying to more southerly latitudes, which already have higher rates. Incidence rates vary more rapidly with latitude than do mortality rates, and therefore they predicted that a 10% increase in UVR would be likely to give a 14-24% increase in the incidence of melanoma (see Table 15).

Estimates using calculated UVR levels: Fears *et al.* (1977) used measurements from Robertson-Berger meters for four areas and a power model, in which the calculated percentage changes are not dependent upon the initial latitude. These calculations showed considerably stronger effects, with an estimated 25% increase in incidence for a 10% increase in solar UVR (see Table 15).

Scotto and Fears (1987) used annual UVR counts from Robertson-Berger meters in seven areas of the USA (Detroit, Seattle, Iowa, Utah, San Francisco, Atlanta and New Mexico) and data on melanoma from incidence registries (the Surveillance Epidemiology and End Results system). They fitted a power model and presented analyses by sex and by body site of the melanoma divided into trunk and lower limb *versus* head, neck and upper limb. They obtained data on covariates, including ethnic origin, pigmentation characteristics, hours spent outdoors during weekdays and during weekends and use of suncreens, suntan lotion and protective clothing, from telephone interviews with at least 500 households in each area. Data on the melanoma patients were not available, however. The results predict greater increases for females than for males, unlike the earlier work. The overall effects of a 10% increase in UVR are a 5.5% increase for trunk and lower limb turnouts and a 9% increase for head, neck and upper limb tumours, averaged over the two sexes. Adjustment for the various covariates reduces the predicted increases to a 3.5 % increase for trunk and lower limb tumours, and 5.5% for head, neck and upper limb turnouts (see Table 15).

Pitcher and Longstreth (1991) used data on melanoma mortality over a 30-year period and calculated UV flux on the basis of satellite data from the US National Aeronautics and Space Administration, including measurements of ozone concentrations at high atmospheric

Table 15. Estimates by Elwood (1989b) of percentage increase in frequency of melanoma among whites with a 10% increase in solar ultraviolet radiation, based on differences with latitude in Canada and the USA

Ultraviolet radiation level derived from[a]	Model	50 ° latitude		30 ° latitude		Reference on which estimates based
		Incidence	Mortality	Incidence	Mortality	
Calculation of erythema-weighted index	Linear		4.5		6.8	Elwood *et al*. (1974)[b]
	Exponential		3.7		10.3	
Calculation of erythema-weighted index	Exponential	14.0	7.0	23.5	12.0	Fears *et al*. (1976)[c]
RB meter (1974)	Power	25.0		25.0		Fears *et al*. (1977)[d]
RB meter (1978-81)	Power					Scotto & Fears (1987)[e]
	Trunk and lower limb					
	Crude	5.5		5.5		
	Adjusted	3.5		3.5		
	Head, neck and upper limb					
	Crude	9.0		9.0		
	Adjusted	5.5		5.5		
	Total					
	Crude	6.7		6.7		
	Adjusted	4.2		4.2		
Calculation of erythema-weighted estimate from NASA including satellite ozone column measurements	Power					Pitcher & Longstreth (1991)[f]
	Annual		3.2		3.2	
	Peak		7.0		7.0	
	Exponential					
	Annual		2.1		4.5	
	Peak		5.8		8.2	

Both sexes (simple average of sex-specific results)

[a]RB, Robertson-Berger; NASA, National Aeronautics and Space Administration

[b]Mortality data, USA and Canada 1950-67 by state/province; 58 areas

[c]Incidence data. Third National Cancer Survey (1969-71) for nine areas; US mortality by state. Calculation based on latitude equivalent to change in ultraviolet radiation

[d]Incidence data, Third National Cancer Survey (1969-71) for four areas

[e]Incidence data, Surveillance Epidemiology and End Results Program for seven areas. Crude results take account only of age; adjusted results are controlled for ethnic origin, hair or skin colour, suntan lotion use and hours spent outdoors; total, for comparison, is based on 67% trunk and lower limb and 33% head, neck and upper limb tumours

[f]Mortality data by US county 1950-79; estimates of changes in mean annual dose and in peak doses (clear day in June); estimates using DNA action spectrum were also made and were 1-8% higher than those shown.

conditions. The models fitted are complex, as they are fitted for the two sexes, for three different places covering a range of latitudes, and separately for changes in the annual UV flux and changes in the peak levels in clear summer conditions. Larger effects were again found for males than for females, and a larger effect when using the peak measurements than when using the annual measurements. The overall estimates of the percentage increase in melanoma mortality associated with a 5% decrease in ozone level, on the assumption that this is roughly equivalent to a 10% increase in solar UVR, ranged from 2.1 to 7.0 at 50 ° N and from 3.2 to 8.2 at 30 °N (see Table 15).

[The Working Group noted that, despite the sophistication of some of the mathematical models, these results are derived from population-based descriptive data and not from individual measurements and are restricted to North America.]

(vi) Migration

The most informative data on risk in migrants come from Australia, New Zealand, Israel and the USA. Native residents of Australia (McCredie & Coates, 1989; Khlat *et al.,* 1992) and New Zealand (Cooke & Fraser, 1985), mostly of British origin, experienced incidence and mortality rates of melanoma roughly twice those of British immigrants. Native Israelis had a risk at least twice that of immigrants to Israel from Europe for at least 30 years after immigration (Steinitz *et al.,* 1989).

The higher incidence in white immigrants to Hawaii from the US mainland compared with white natives has been attributed to a difference in skin colour (Hinds & Kolonel, 1980). Non-Hispanic migrants to Los Angeles County (California, USA) from higher latitudes in the USA are still substantially protected against melanoma of all histological types decades after migration. Similar relative protection is enjoyed by native residents of more northerly US communities in comparison with co-resident migrants from the south-western USA (Mack & Floderus, 1991).

(vii) *Socioeconomic status and occupation*

Melanomas are much commoner in higher socioeconomic groups, as shown in data from the United Kingdom since 1949-51. In the United Kingdom, the distribution of melanoma in married women by social class (categorized by their husbands' social class) is similar to that of men, indicating that this is a social rather than a specific occupational factor (Lee, 1982). In the USA, the risk increases with income for men aged 30-69; at age 70 and above, the trend is reversed, suggesting a role for long-term exposure to the sun (Kirkpatrick *et al.,* 1990). In case-control studies, the effect of socioeconomic status is weakened after adjustment for measures of exposure to the sun (Gallagher *et al.,* 1987; Østerlind *et al.,* 1988b).

Assessment of outdoor exposure on the basis of routine data on job descriptions showed that melanoma is commoner in indoor than in outdoor workers, even within the same socioeconomic group (Lee & Strickland, 1980; Lee, 1982). Cutaneous melanoma incidence rates during 1972-76 in New Zealand showed no pattern according to outdoor workplace (Cooke *et al.,* 1984). An analysis of 3991 cases of cutaneous melanoma registered during 1971-78 in England and Wales and of 5003 cases registered during 1961-79 in Sweden suggested an elevated incidence in professional occupations. The incidence among farmers was close to that expected (Vågerö *et al.,* 1990).

Garland *et al.* (1990) reported 176 incident cases of melanoma among US Navy personnel. The rate for indoor occupation was higher than that for outdoor workers.

(c) *Case-control studies*

Elements of each case-control study described below are given in Table 16.

(i) *Australia*

Lancaster and Nelson (1957) carried out a case-control study on 173 patients aged over 14 years treated for malignant melanoma in hospitals in Adelaide, Melbourne and Brisbane, and 173 hospital controls with cancers other than of the skin, matched for sex and age. Information was obtained by interviews [response rate not given], and analysis was done by single factor cross-tabulations only. Unmatched crude odds ratios were calculated by the Working Group. Skin [odds ratio, 1.95 for fair *versus* olive and medium], hair colour [odds ratio, 1.7 for fair and red *versus* black and brown], eye colour [odds ratio, 1.75 for blue and green-gray *versus* brown and hazel] and skin reaction to sunlight [2.9; 95% CI, 1.9-4.5 for red *versus* brown reaction] were significantly associated with risk for malignant melanoma. Among the other factors studied were birth outside Australia [0.8; 0.4- 1.6], 10 years' or more occupational exposure to sunlight in males [1.4; 0.7-2.7], sunbathing [1.5; 0.9-2.4] and moderate [1.2; 0.5-3.1] and excessive [2.3; 0.8-6.3] total exposure to the sun compared to minimal exposure. There were only eight cases and 11 controls in the latter category of sun exposure.

Beardmore (1972) studied 468 cases of histologically confirmed malignant melanoma and 468 sex- and age-matched hospital controls (including patients with skin cancer) at one hospital in Brisbane. Information was obtained by interview [response rate and method of evaluation of hair, skin and eye colour not given]. Hair, skin and eye colour and skin reaction to sunlight were not associated with risk for malignant melanoma. Comparison of exposure to sunlight from mainly outdoor occupations to that from mainly indoor occupations resulted in a crude odds ratio of [1.42; 95% CI, 1.03-1.97]; a similar comparison for recreational activities gave a crude odds ratio of [1.03: 0.75-1.42]. Fewer cases than controls had a history of treatment for keratosis and/or skin cancer or currently had keratosis and/or skin cancer [crude odds ratios, 0.51, 0.38-0.69; and 0.16, 0.12-0.22, respectively].

In the Western Australia Melanoma study (Holman & Armstrong, 1984a,b), 511 cases aged 10-79 years and 511 population controls matched for sex, age and area of residence were interviewed at home using a questionnaire based on that of the Western Canada study, which included objective measurements and naevi counts. The study also included a review of pathology slides. Analyses were presented for superficial spreading, nodular and lentigo maligna melanomas and for a fourth, unclassifiable group. Response rates were 76% for cases and 62% for controls, and adjustment was made for chronic and acute skin reaction to sunlight, hair colour, ethnic origin and age at arrival in Australia using a multiple logistic regression model. Hair colour, acute and chronic reaction to sunlight, number of naevi and family history of melanoma were significantly associated with risk; skin and eye colour were significantly associated in a crude analysis only. Duration of residence in Australia was strongly, positively associated with risk for all melanomas and for all sub-types except for unclassifiable melanoma. After control for ethnic origin, the odds ratios for superficial spreading melanoma were 1.2 (95% CI, 0.25-5.5) for people arriving in Australia at age 0-4, 1.7 (0.34-8.0) for those arriving at age 5-9, 0.74 (0.17-3.3) for those arriving at age 10-14, 0.25 (0.05-1.4) for those arriving at age 15-19 years or older (< 30 years) and 0.38

(0.19-0.78) for those arriving at age $\geq$ 30 years (p for trend, < 0.0001) compared to those born in Australia. A lifetime residential history was used to calculate the mean annual hours of bright sunlight based on place of residence as a measure of potential exposure to the sun. An analysis restricted to native-born Australians showed positive associations for all melanomas and for each subtype except nodular melanoma. An analysis dichotomizing exposure at an annual mean of > 2800 h sunlight at different ages showed that the highest risk ratio for all melanomas and for the superficial spreading subtype were for high exposure at ages 10-24. Cutaneous microtopography was used to measure skin damage; a positive association was found with all melanomas, being strongest for lentigo maligna melanoma.

In a further analysis by individual habits of exposure to the sun (Holman *et al*., 1986a), no significant association was seen for total outdoor exposure. Analysis by recreational outdoor exposure, expressed as a proportion of total exposure, at ages 10-24 years showed no significant association. For superficial spreading melanoma, analysis by specific activity showed positive associations with boating (p = 0.04) and fishing (p = 0.07) and weaker, nonsignificant associations with swimming and sunbathing at ages 15-24 or 0-9 years before diagnosis. For other types of melanoma, no clear positive association was found; regular swimmers had a lower risk of lentigo maligna melanoma (trend test significant). Occupational exposure was analysed on the basis of whether the site of the melanoma was usually covered by clothing and compared to that of a referent group for whom the site was usually covered: subjects for whom the site was exposed showed a significant positive association. In comparison with the same referent group, patients who had never worked outdoors had significantly increased risks for all melanomas. The type of bathing suit usually worn by females in summer was assessed, and a positive association was found for wearing bikinis or for nude bathing, which was significant for all trunk melanomas and for superficial spreading melanoma on the trunk. When previous sunburns were classified by severity, no significant trend was observed for all melanomas; but there was a positive trend for lentigo maligna melanoma (p = 0.06) and a significant negative association for nodular melanoma.

In the smaller Queensland Melanoma study (Green, 1984; Green *et al*., 1985a), 183 patients with histologically confirmed melanoma, other than lentigo maligna melanoma or acral lentiginous melanoma, and 183 population controls matched for sex, age and area of residence were interviewed at home using a standardized questionnaire, which included objective measurements and naevi counts. The response rates were 97% and 92%, respectively. Adjustment was made using a multiple logistic regression model. Hair colour, acute sun reactions and naevi were significantly associated with risk. Skin colour, eye colour, chronic sun reaction, freckling and family history of melanoma were significant in a crude analysis only. Hours of occupational and recreational exposure to the sun from 10 years of age across three categories gave risks of 1, 3.2 (95% CI, 0.9-12.4) and 5.3 (0.9-30.8) after adjustment for naevi, hair colour and propensity to sunburn. Average levels of exposure to UVB radiation were also allocated by residential history but showed no association with risk for melanoma. People born in Queensland had moderately higher risks than those who arrived there later in life or who had lived somewhere else at any time. Melanoma patients had more kerotoses or skin cancers on their faces (odds ratio, 2.8; 1.1-7.2). Sunburn (Green et al., 1985a) was defined as pain persisting longer than 48 h, with or without blistering, and was recorded as the number of episodes in each decade. Risk increased with the number of

severe sunburns and was 1.9 and 5.0 in the two higher categories on matched analysis, decreasing to 1.5 (0.7-3.2) and 2.4 (1.0-6.1), respectively, when adjusted for naevi and exact age. An additional analysis of 49 cases of lentigo maligna melanoma and 49 controls showed no association with sunburn (Green & O'Rourke, 1985; Green *et al.,* 1986).

In a more detailed review of these data (Green *et al.,* 1986), no association was observed with occupational exposure to the sun. Analyses of recreational hours spent on the beach in the sun were made for lifetime exposures, exposures at 10-19 years of age and exposures in the five years prior to diagnosis; no strong or consistent association was seen in either crude or adjusted analyses. Associations with total accumulated hours of exposure to the sun (calculated by adding occupational and total recreational exposures) showed a positive trend for lifetime exposure and exposure at ages 10-19 (odds ratio, 4.4; 95% CI, 1.8-184.5), but no association was seen for exposure during the previous five years. Analysis of levels of UVR by lifetime residential history showed no major association and no site-specific association.

(ii) *Europe*

In a case-control study of residents of Oslo, Norway (Klepp & Magnus, 1979), 78 malignant melanoma patients over 20 years of age were compared with 131 unmatched hospital controls with other cancers. Both cases and controls with advanced disease were excluded. Information was obtained by questionnaire [response rate not given]. Hair and eye colour were recorded independently by the interviewer and subject but were not associated with risk for the disease, whereas skin reaction to sunlight and freckling were. A nonsignificant odds ratio of [1.5] was found for men working outdoors for more than 3-4 in/day; the odds ratio for taking sunbathing holidays in southern Europe was 2.4 ($p = 0.05$). No significant association was seen with degree of exposure of different body sites, classified from 'as often as possible' to 'hardly ever'.

Adam *et al.* (1981) conducted a population-based case-control study in the United Kingdom of 111 female cases of malignant melanoma aged 15-49 traced from registries and 342 female controls randomly selected from general practitioners' lists and matched for age and marital status. Information was obtained by postal questionnaire; response rates were 66% for cases and 68% for controls. Hair colour and skin reaction to sunlight, but not skin colour, were significantly associated with risk for malignant melanoma. Slightly more cases than controls reported deliberately tanning their legs or trunk, either at home or abroad. No difference was reported in the amount of work, leisure or total time spent outdoors. [The Working Group noted that the study concentrated on oral contraceptive use and that information on exposure to the sun was very limited.]

MacKie and Aitchison (1982) conducted a case-control studyin western Scotland of 113 malignant melanoma patients aged 18-76 years and 113 sex- and age-matched hospital controls with conditions not related to the skin. Cases of lentigo maligna melanoma were excluded. Information about exposure to the sun within the previous five years was obtained by questionnaire [response rate not given] and included occupational and recreational exposure ($\geq$ 16 h *versus* < 16 h outdoor exposure per week) and history of severe sunburn, defined as either ‘blistering sunburn’ or ‘erythema persisting for a week or longer’. Other factors included in the multivariate analysis were social class and skin type. A significant negative association was observed for recreational exposure and for

occupational exposure to the sun in males. A significant positive association was observed for severe sunburn. No significant difference was observed for the number of continental holidays taken or total number of days spent in sunnier climates.

Sorahan and Grimley (1985) studied 58 patients aged 20-70 years with cutaneous malignant melanoma (other than lentigo maligna melanoma) in two hospitals in the United Kingdom and 182 hospital controls with diseases other than of the skin and 151 unmatched controls from electoral rolls. The response rates were 64% for cases and 60% for each control group. Information was obtained by postal questionnaire, and analyses were adjusted using a multiple logistic regression model. A significant positive association was observed for number of bouts of painful sunburn ever experienced, with an odds ratio reaching 7.0 for five or more bouts compared to none. A significant positive association was also seen with the number of holidays ever spent abroad in a hot climate, reaching 6.5 for 21 holidays or more, compared to none. Both associations were weakened, and the latter became nonsignificant, after adjustment for propensity to sunburn, number of moles and history of sunburn.

In another study in the United Kingdom (Elwood *et al.,* 1986), 83 histologically confirmed cases over 18 years of age and 83 hospital controls (in- and out-patients), matched for sex, age and area of residence, were interviewed at home using a questionnaire which included objective measurements and naevi counts. The responses were validated by replies to a postal questionnaire. The response rates were 74% for cases and 92% for controls. Adjustment was made using a multiple logistic regression model. Skin reaction to sunlight, freckling and naevi were significantly associated with risk. A history of sunburn causing pain for two days or more gave a significant odds ratio of 3.2 (95% CI, l.7-5.9). Past outdoor occupational exposure showed a significantly reduced odds ratio of 0.2 (0.1-0.9) for the second highest category but a nonsignificant odds ratio of 1.7 (0.3-8.6) for the highest category and no overall trend.

In northern Italy, Cristofolini *et al.* (1987) compared 103 patients aged 21-79 under treatment for cutaneous malignant melanoma at one hospital with 205 hospital controls with diseases other than skin tumours. Subjects were interviewed [response rate not given] and assessed by a dermatologist. Adjustment was made using a multiple logistic regression model. Hair and skin colour and family history were significantly associated with risk, but eye colour, freckling and number of naevi were not. A history of frequent sunburn as an adult gave an odds ratio of 1.2 (95% CI, 0.7-2.1) and that of severe sunburn in early life an odds ratio of 0.7 (0.4-1.2). Heavy or frequent exposure to sunlight during the previous 20 years, categorized as yes or no, gave a significantly reduced odds ratio of 0.6 (0.4-0.95). Outdoor compared to indoor occupation gave a nonsignificant odds ratio of 0.9 (0.5-1.7), and a history of carcinoma of the skin gave a risk ratio of 0.4 (0.02-2.9), based on small numbers. Melanoma at exposed sites showed positive associations with heavy sun exposure (1.44; 0.8-2.8) and outdoor occupation (1.8; 0.9-3.7), while melanoma at normally unexposed sites showed a significant negative association with heavy exposure to the sun (odds ratio, 0.25; 95% CI, 0.13-0.47).

In a study of melanoma in eastern Denmark (Østerlind *et al.*, 1988b,c; Østerlind, 1990), 474 cases of melanoma, excluding lentigo maligna melanoma patients, aged 20-79 were compared with 926 population controls and matched for sex and age. Subjects were inter-

viewed at home using a questionnaire which included objective measurements and naevi counts, and adjustment was made using a multiple logistic regression model. Response rates were 92% for cases and 82% for controls. The number of sunburns (defined as those causing pain for two days or longer) before age 15, from age 15 to 24 and over the previous 10 years were all significantly associated with risk: crude odds ratios for the maximal categories, 3.7 (95% CI, 2.3-6.1), 2.4 (1.6-3.6) and 3.0 (1.6-5.4), respectively. Adjustment for sex and host factors, including naevi, freckles and hair colour, reduced the risk ratios, but they remained significant. Adjustment for sunburns before age 15 rendered the associations with later sunburn weak and nonsignificant. Joint analysis of sunburns and naevi suggested independent, additive risks. Significantly increased risks were seen with residence near the coast before age 15 or for more than 30 years. Specific recreational activities were investigated and categorized by the number of years of regular participation, adjusted for sex and host factors, including number of naevi, and for other activities. Significant positive associations were observed with sunbathing, boating, winter skiing and swimming, the latter becoming nonsignificant after adjustment. Regular participation in gardening, ball games, golf, horseback riding or hiking was not associated with risk for melanoma. A positive trend was seen with vacations spent in beach resorts in southern Europe (odds ratio, 1.7; 95% Cl, 1.2-2.4), which was weakened after adjustment for sunbathing and sunburn (1.4; 1.0-2.1). Socioeconomic status showed a strongly positive association in men, which became nonsignificant when adjusted for sunburn and recreational exposure to the sun. Occupational exposure outdoors for at least six months was associated with a significantly reduced odds ratio of 0.7 (0.5-0.9) in men; the protective effect was most pronounced in men who started working outside at an early age and continued for at least 10 years. No association was seen with skin grading categories defined by microtopography.

In a study in northern Italy (Zanetti *et al.*, 1988), 208 cases of histologically confirmed malignant melanoma were identified from the regional tumour registry and were compared with 416 controls chosen from the National Social Service Registry. Response rates were 87% for cases and 68% for controls. An increased risk was observed with light hair colour, tendency to burn and a history of sunburn in childhood. No significant effect of region of origin was observed. Exposure to the sun was assessed by activity: for outdoor work, a nonsignificant increased risk was seen with the maximal duration of exposure (2 33 years) in men, but the overall trend was nonsignificant. Outdoor sports, assessed by years of participation, showed an increased risk at the maximal level in men and women (significant for men). A significantly increased risk was found for men participating in sports categorized as involving the greatest exposure to the sun. A nonsignificantly increasing trend in men was observed for total number of weeks' holiday, but little effect was seen in women; a significant positive trend was observed in men, but not for women, for the number of weeks spent at the seaside in childhood. Similar exposure in adult years resulted in a nonsignificant positive trend.

Garbe *et al.* (1989) studied 200 malignant melanoma patients at a dermatological follow-up clinic in Berlin, Germany, in 1987 and 200 controls from the same clinic who had any other skin disease (response rate, 90%). Subjects of non-German origin were excluded, as were those seeking consultation for pigmented naevi or who had been treated previously

by UVR (10%). Occupational exposure to the sun, assessed as none, sometimes or nearly all the time, showed a strongly increased risk up to an odds ratio of 5.5 (1.2-25.3). No significant relationship was found with duration of leisure-time exposure to the sun or number of sunburns [The Working Group noted that little detail was given about exposure and that the control group consisted of patients with other skin disease.]

Weiss *et al.* (1990) studied 1079 cases of malignant melanoma reported to the German Dermatological Society Registries in 1984-87 and 778 hospital controls from the same clinics. Positive associations were seen with occupational exposure to the sun, which increased with the number of years of exposure. No association was seen with exposure to the sun during leisure time or with sunbathing. [The Working Group noted that this study appears to overlap with that of Garbe *et al.* (1989) and that the data were presented with relative risks but with no test of significance.]

Beitner *et al.* (1990) studied 523 incident cases of malignant melanoma seen at a hospital in Stockholm, Sweden (representing 64% of all cases registered in Stockholm County), and 505 controls selected from the population register for Stockholm County. Cases completed a questionnaire while waiting at the clinic, and controls received the questionnaire by mail (response rates, 99.6% and 96.2%, respectively). A significant positive effect was seen for the number of sunbathing sessions each summer, with a history of erythema after sunbathing and with sunbathing vacations abroad. Residence in countries around the Mediterranean or in a sub-tropical or tropical climates for more than one year during the previous 10 years gave a significant odds ratio of 1.9 [95% CI, 1.0-3.6]. There was no increase in risk with sunbathing during winter vacations at high altitudes. Outdoor workers had a significantly reduced risk of 0.6 (0.4-1.0) after adjustment for age, sex and hair colour.

Elwood *et al.* (1990) studied 195 cases of superficial spreading or nodular melanoma in people aged 20-79 from five pathology laboratories in the United Kingdom and 195 controls chosen from among all in- and out-patients in the region. Cases and controls underwent an interview and a limited examination by an interviewer in their homes (participation rate—cases and controls, 73%; voluntary response rate—cases, 91%: controls, 78%). Risk was significantly increased with sunburn at age 8-12 (odds ratio, 3.6; 1.4-11.2), but no significant increase was observed with sunburn at age 18-22 or with sunburn received 18-20 or five years prior to diagnosis. No other sun exposure variable was reported.

Grob *et al.* (1990) compared 207 consecutive white patients, 18-81 years old, with histologically confirmed invasive melanoma (at least level 2: lentigo melanoma and acral lentiginous melanoma excluded) seen in one dermatology clinic in Marseilles, France, with 295 controls. Controls under 65 years of age were chosen from among subjects interviewed after reportedly random selection and examined at a public health centre; those over 65 were chosen from among out-patients with non-cancer and non-dermatological conditions. Patients and controls were examined and interviewed by the same dermatologist. Multiple logistic model analysis was used. The risk for melanoma was increased significantly in association with annual outdoor leisure exposure during the previous two years (odds ratio, 8.4; 95% Cl, 3.6-19.7), outdoor occupation (6.0; 2.1-17.4) and total lifetime sun exposure (odds ratio for maximum category, 3.4; 1.6-7.1). There was a nonsignificant association with sunburns in recent years (1.7; 0.63-4.6) after adjustment for number of naevi, maximal depth of suntan, hair colour, social level, complexion and age. [The Working Group found

the study difficult to interpret because of the nature of the control group and the relative recency of measurements of exposure to the sun.]

In a report designed to produce a risk prediction model, MacKie *et al*. (1989) studied 280 cases of invasive cutaneous malignant melanoma (level 2 or deeper) from Scottish melanoma registries. Controls were 280 hospital patients with non-dermatological diseases. Response rates were 76% for cases and unknown for controls. An increased risk was observed for history of severe sunburn (adjusted odds ratio, 7.6 (95% CI, 1.8-32.0) for men and 2.3 (0.95.6) for women). A significant positive association for tropical residence was noted for men, which became nonsignificant after adjustment. [The Working Group noted that, apart from tropical residence, no data were presented on exposure to the sun.]

(iii) North America

Gellin *et al*. (1969) studied 79 patients, aged 30-79, with histologically confirmed malignant melanoma at one hospital in New York, USA, and compared them with 1037 hospital controls with skin conditions other than cancer. Information was obtained by interview and examination [response rate not given]. The odds ratios for duration of daily outdoor activity were [2.8 (95% CI, 1.3-5.8)] for 6 h or more and [4.1 (2.5-6.8)] for 3-5 h, compared to 0-2 h. [The Working Group noted that the controls had skin diseases.]

Paffenbarger *et al.* (1978) reported on cases found by follow-up of subjects first examined when entering Harvard University in 1916-50 and the University of Pennsylvania in 1931-40. Out of a total of 50 000 male subjects and 1.71 million person-years of observation, 45 deaths from melanoma were observed and each compared to four controls born in the same year, who were classmates and who had survived as long as the case subjects. Of the many factors investigated, only outside remunerative work was associated with a significant risk for melanoma (odds ratio, 3.9; $p = 0.01$). Within the cohort, students from New England had a 50% lower risk for melanoma than other students, presumably owing to more northerly residence.

Lew *et al.* (1983) carried out a study in Massachusetts on 111 cases of cutaneous malignant melanoma, aged 23-81, followed at one hospital and 107 controls who were friends of cases, matched by age and sex. Information was obtained by interview at the clinic; response rates were 99% for cases and 90% for controls, and analysis was made using a logistic regression model. Cases showed poorer tanning ability, and a significant association was observed with blistering sunburn during adolescence (odds ratio, 2.1; 95% CI, 1.2-3.6) and with 30 days or more vacation in sunny, warm places during childhood (2.5; 1.1-5.8). The association with history of sunburn persisted after controlling for tanning ability. [The Working Group noted that the nature of the controls and the simplicity of the analyses presented make interpretation of the results difficult.]

Rigel *et al.* (1983) analysed data on 114 melanoma patients (out of a total of 328) seen in a referral centre in New York between 1978 and 1981, and on 228 controls who were staff and patients at the centre. Significantly increased risks were seen with > 2 h per day sun exposure 11-20 years previously (odds ratio, 2.5;$p = 0.005$) and outdoor *versus* indoor recreation (2.4; $p = 0.01$). [The Working Group noted that the selection of subjects and the nature of the control group make these results difficult to interpret.]

In the Western Canada Melanoma case-control study (Elwood *et al.,* 1984, 1985a,b), carried out in four Canadian provinces, 595 cases of malignant melanoma, aged 20-79, and 595 population controls, matched for sex, age and province of residence, were questioned by trained interviewers at their homes (response rates: cases, 83%; controls, 48-59%). Cases of lentigo maligna melanoma and acral lentiginous melanoma were excluded. Analyses were made using a multiple logistic regression model. Significant positive associations were found after adjustment for host factors and ethnic origin for frequent recreational (odds ratio, 1.7; 95% CI, 1.1-2.7) and holiday exposure (1.5; 1.0-2.3) and with the number of sunny vacations per decade (1.7; 1.2-2.3). No overall trend was observed for occupational exposure, but a significantly increased risk was associated with moderate occupational exposure, defined as seasonal or short-term occupational exposure. Maximal occupational exposure was associated with a significantly reduced odds ratio in men (0.5 [CI not given]) but not in women (1.5 [CI not given]). Analysis of total annual exposure to the sun from all sources showed no overall trend (odds ratio, 1.0-1.6 in various categories above the minimal exposure referent group). Severe or frequent sunburn in childhood resulted in a nonsignificant odds ratio of 1.3, after adjustment for host factors and sun sensitivity. From variables relating to sunburn on vacation and the usual degree of suntan in winter and summer, positive associations were observed for increasing sunburn and with decreasing usual tan. Cross-tabulation of sunburn with tendency to sunburn (skin type) did not change the significant positive effect of tendency to burn, but the odds ratio for sunburn fell from 1.8 in the maximal category to 1.4 ($p > 0.2$) after adjustment for sun reaction. Similarly, cross-tabulation of usual degree of suntan against skin type gave little difference in the positive association with reaction to the sun, but a weakening of the association with usual degree of suntan was seen which became nonsignificant. A multivariate analysis including history of sunburn, usual degree of suntan, skin type and host factors showed significance for the two latter factors, nonsignificant positive effects of holiday sunburn and a significant negative effect of usual degree of suntan. These results are interpreted as showing a primary association with tendency to burn easily or to tan poorly rather than with history of either sunburn or suntan. For men, a significant negative association was seen with outdoor occupation, but this weakened and became nonsignificant when adjusted for recorded exposure to the sun. Similarly, the crude odds ratio for upper compared to lower socioeconomic groups was 3.8 (2.0-7.4) but was reduced to 2.3 (1.0-5.1) after adjustment for host factors and for occupational, recreational and holiday sun exposure (Gallagher *et al.,* 1987).

Elwood *et al.* (1987) made an analysis separating superficial spreading melanoma, nodular melanoma and lentigo maligna melanoma in the western Canada study, based on 415,128 and 56 cases, respectively. Recreational exposure, holiday exposure and the number of sunny vacations per decade were positively and significantly (trends) associated with superficial spreading melanoma (odds ratios, 1.4, 2.0 and 2.2; 95% CI, 1.0-2.0, 1.4-2.9 and 1.5-3.3, respectively); recreational exposure was also positively associated with nodular melanoma (2.4; 1.3-4.5), but neither holiday exposure nor the number of sunny vacations showed an association. None of these measures of intermittent exposure was significantly associated with lentigo maligna melanoma. Occupational exposure showed no significant association with any of the three types. History of sunburn showed positive but

nonsignificant associations with superficial spreading and lentigo maligna melanomas but not with nodular melanoma.

Brown *et al.* (1984) identified 120 men who had been aged 18-31 during the Second World War from among 1067 patients seen at a melanoma clinic in New York City in 1972-80 and sent them questionnaires (response rate, 74%). Controls were 65 age-matched subjects attending the same dermatology department with skin diseases other than melanoma [response rate unknown]. Within the total of 74 cases and 49 controls who had been in the armed services, the odds ratio for service in the tropics as compared to service in the USA or Europe was [7.7; 95% CI, 2.5-23.6].

In a hospital-based study in Buffalo, NY, USA (Graham *et al.*, 1985), 404 cases of cutaneous malignant melanoma referred to the Roswell Park Memorial Institute, aged from under 30 to over 65, were compared with 521 controls with other neoplasms at the same institute, using questionnaires completed on admission. There was a weak negative trend with total number of hours of exposure to the sun, which was significant in men; a similar trend was observed for average annual exposure to the sun. Occupational exposure to the sun gave a nonsignificant reduction in risk in men in the highest exposure group after adjustment for tendency to burn. Multivariate analysis showed a negative association with cumulative exposure to the sun, which was significant in men when adjusted for tendency to burn, freckling and light complexion. Results specific to recreational or holiday exposure to the sun were not presented.

Dubin *et al.* (1986) compared 1103 cases of melanoma seen at the New York University Medical Center from 1972 to 1982 (mostly in 1977-79) to 585 controls interviewed in 1979-82 at the skin clinic for conditions excluding cancer. Both cases and controls were interviewed by physicians; response rates were 98% for cases and 78% for controls. In order to complete the data on risk factors, a postal questionnaire was sent requesting information on exposures to fluorescent lights and to the sun and on skin colour (response rates, 45% of cases and 30% of controls). Mostly outdoor compared to mostly indoor work gave an odds ratio of 2.5 (95% CI, 1.4-4.4) and mostly outdoor compared with mostly indoor recreation gave an odds ratio of 1.7 (1.2-2.3), although mixed indoor and outdoor recreation gave a significantly reduced risk of 0.6 (0.5-0.8). Overall exposure to the sun (three categories) showed no trend. A history of the presence of solar keratosis gave a significant risk ratio of 5.0 (2.3-10.5). Quantitative total sun exposure was assessed for 623 cases and all 585 controls: there was no significant trend with total hours of exposure to the sun per day 0-5, 6-10 or 11-20 years before diagnosis. [The Working Group noted that the cases and controls were not interviewed over the same period.]

In a study based on a subset of the above (Dubin *et al.*, 1989), 289 cases and 527 controls were interviewed using the same method (response rates, 100% of eligible cases; 70% of controls [19% of potential controls were excluded because of diagnosis of a lesion known to be caused by exposure to the sun]). Mostly outdoor occupation gave a nonsignificant elevated risk. Mostly outdoor recreation was associated with a significantly elevated risk in light tanners but a nonsignificant elevated risk in dark tanners (interaction nonsignificant). Overall exposure to the sun was associated with significantly increased risks in all groups. A history of sunburn was associated with a significantly increased risk in light tanners and

in all subjects but had a nonsignificant protective effect in dark tanners (interaction significant).

When analysed by age group, a history of sunburn gave a positive association at age 20-39, a weak association at 40-59 and a negative association at 60 or over (interaction significant). Prior skin cancer or solar keratosis had a significant effect, which was stronger in men than in women (interaction nonsignificant).

In a study in San Francisco, Holly *et al.* (1987) compared 121 patients with nodular or superficial spreading melanoma at a university melanoma clinic with 139 controls from a medical screening clinic or from an orthopaedic clinic at the same centre. Response rates were 'over 95%'. Sunburn score, based on the number of blistering sunburns during school and young adult years, showed a significant odds ratio of 3.8 (95% CI, 1.4-10.4) after controlling for naevi, hair colour and previous skin cancers. A positive association was seen with previous skin cancer (3.8; 1.2-12.4).

Weinstock *et al.* (1989) reported a case-control study within a cohort of US nurses (see Hunter *et al.,* 1990, p. 86). Data on 130 cases and 300 controls (response rates to post-diagnosis questionnaire, 85% and 81%, respectively) were analysed using multivariate models. Following adjustment for skin sensitivity, significant positive effects were seen for sunburn at ages 15-20 (odds ratio, 2.2; 95% CI, 1.2-3.8), but not at age ≥ 30 (1.3; 0.7-2.3), and for residence at a southern latitude at age 15-20 (2.2; 1.1-4.2), but not at age 2 30 (1.6, 0.9-2.8). No direct recording of exposure to the sun was reported.

A further analysis (Weinstock *et al*., 1991a) assessed the use of swimsuits in these subjects. There was a significant positive association of melanoma risk with the frequency of use of swimsuits of any type in sun-sensitive women (odds ratio, 6.4; 95% CI, 1.7-23.8) but not in sun-resistant women (0.3; 0.1-1.0). After controlling for type of swimsuit and sensitivity factors, melanoma risk was increased with increasing hours per day of outdoor swimsuit use (any type) after age 30, but no association was seen with intensity of exposure or with the number of winter vacations in warm and sunny locations. The use at age 15-20 of a bikini compared to high backline, one-piece swimsuits, gave an odds ratio for all melanomas of 1.9 (1.0-3.7) and for trunk melanoma specifically of 0.8 (0.3-2.6); the risks were 3.5 [CI not given] among sun-sensitive women and 1.3 [CI not given] among less sun-sensitive women, but the interaction was not significant.

In a case-control study of patients attending a pigmented lesion clinic in Boston, USA (Weinstock *et al.*, 1991b), 186 had cutaneous melanoma; the 239 controls had other dermatological diagnoses, the most frequent of which were common naevus and solar keratosis. Data were obtained from medical records and from a self-administered questionnaire completed before clinical examination and were analysed by a multivariate method. Significantly increased risks for melanoma were associated with lack of tan after repeated exposures as a teenager (odds ratio, 2.3; 95% CI, 1.0-4.9). A nonsignificant trend towards increased risk was observed for residence in southerly areas. [The Working Group noted that the paper dealt primarily with dysplastic naevi and the results on melanoma are not given in detail, and that the controls also had dermatological conditions.]

Table 16. Case-control studies of melanoma in which exposure to the sun and/or artificial ultraviolet radiation was assessed

Place	Period of diagnosis	No. of cases	Source of cases	Melanoma type	No. of controls	Type of control	Reference
Australia							
East Australia	NS	173	3 hospitals	All types	173	Other cancers	Lancaster & Nelson (1957)
Queensland, Australia	1963-69	468	1 hospital	All types	468	Hospital patients, including skin cancers	Beardmore (1972)
Western Austraia	1980-81	511	Population	All types	511	Population	Holman & Armstrong (1984a,b)
Queensland, Australia	1979-80	183	Population	No LMM	183	Population	Green (1984); Green *et al*. (1985a)
Europe							
Oslo, Norway	1974-75	78	1 hospital	All types	131	Other cancers, same hospital	Klepp & Magnus (1979)
United Kingdom	1971-76	111	Population	All types	342	General practice lists	Adam *et al*. (1981)
Western Scotland	1978-80	113	Hospital	No LMM	113	Hospital, non-skin	MacKie & Aitchison (1982)
Birmingham, UK	1980-82	58	2 hospitals	No LMM	333	Hospital and population	Sorahan & Grimley (1985)
Nottingham, UK	1981-84	83	Population (2 hospitals)	All types	83	Matched hospital	Elwood *et al*. (1986)
Trento, Italy	1983-85	103	1 hospital	All types	205	Hospital	Cristofolini *et al*. (1987)
East Denmark	1982-85	474	Population	No LMM	926	Matched population	Østerlind et al. (1988a,b); Østerlind (1990)
Turin, Italy	1984-86	208	Population	All types	416	Population	Zanetti *et al*. (1988)
Berlin, Germany	1987	200	1 hospital	All types	200	Skin clinic patients	Garbe *et al*. (1989)

Table 16 (contd)

Place	Period of diagnosis	No. of cases	Source of cases	Melanoma	No. of controls	Type of control	Reference
Scotland	1987	280	Population	Invasive MM at least type 2	280	Hospital, excluding skin	MacKie *et al*. (1989)
Germany	1984-87	1079	6 dermatology clinics	All types	778	Skin clinic patients	Weiss *et al*. (1990)
Stockholm, Sweden	1978-83	523	1 hospital	All types	505	Matched population	Beitner *et al*. (1990)
Midlands, Uk	1984-86	195	Population	SSM and NM	195	Hospital in-/out-patients	Elwood *et al*. (1990)
Southeast France	1986-88	207	Hospital	Invasive, all types	295	Health centre	Grob *et al*. (1990)
North America							
New York, USA	1955-67	79	1 hospital	All types	1037	Other skin diseases, non-cancer	Gellin *et al*. (1969)
Boston, MA, USA Philadelphia, PA, USA	NS	45	Cohort of university alumni	All types	180	Classmates	Paffenbarger *et al*. (1978)
Boston, MA, USA	1978-79	111	1 hospital	All types	107	Friends of cases	Lew *et al*. (1983)
New York, USA	1978-81	114	1 hospital	All types	228	Patients and staff	Rigel *et al*. (1983)
New York, USA	1972-80	74	1 melanoma clinic	All types	49	Skin clinic patients	Brown *et al*. (1984)
Western Canda	1979-81	595	Population	SSM, NM or UCM	595	Population	Elwood *et al*. (1984, 1985a,b)
Buffalo, NY, USA	1974-80	404	Hospital patients	All types	521	Cancer patients	Graham *et al*. (1986)
New York, USA	1972-82	1103	3 hospitals	All types	585	Skin clinic patients	Dubin *et al*. (1986)
Western Canada	1979-81	415 128 56	Population	SSM NM LMM	415 128 56	Population	Elwood *et al*. (1987)
San Francisco, CA, USA	1984-85	121	1 melanoma clinic	NM and SSM	139	Clinic patients	Holly *et al*. (1987)

Table 16 (contd)

Place	Period of diagnosis	No. of cases	Source of cases	Melanoma type	No. of controls	Type of controls	Reference
New York, USA	1979-82	289	3 hospitals	All types	527	Non-cancer skin patients	Dubin *et al*. (1989)
USA	1976-84	130	Nurses cohort	AM excluded	300	Nurses cohort	Weinstock *et al*. (1989)
Boston, MA, USA	1982-85	186	1 hospital	All types	239	Skin clinic patients	Weinstock *et al*. (1991b)

NS, not specified; SMM, superficial spreading melanoma; NM, nodular melanoma; UCM, unclassifiable melanoma; LMM, lentigo maligna melanoma (or Hutchinson's melanotic freckle); AM, acral lentiginous melanoma

(d) *Collation of results*

The studies summarized above show that a range of host characteristics are related to melanoma risk, including ethnic origin, skin, hair and eye pigmentation, and, importantly, a tendency to sunburn or suntan, often expressed clinically as skin type. These factors can be assumed to reflect genetic sensitivity to cutaneous effects of sun exposure and, in addition to the indirect evidence of a role of exposure to the sun in melanoma that they provide, should be considered as confounders in a relationship between sun exposure and melanoma. The numbers of acquired benign naevi and of dysplastic naevi have been shown to be very strong risk factors for melanoma in several studies; the density of freckling on the skin has also been shown to be a risk factor. Because there is evidence that these outcomes are themselves related to sun exposure, and in the case of naevi may be intermediate steps in the genesis of melanoma, they should not be considered confounding factors (Armstrong, 1988). Most of the studies relied on a wide range of questions to assess different aspects of sun exposure. Armstrong (1988) developed a useful classification of such questions, dividing them into those that assess potential exposure, such as place of residence and time of migration, those that record actual exposure and those that record response to exposure, such as questions on sunburn and suntanning.

(i) *Total sun exposure: potential exposure by place of residence* (Table 17)

Consistent with the descriptive studies, Holman and Armstrong (1984b) showed that the risk in migrants arriving in Australia before age 10 (odds ratio, 0.89; 95% CI, 0.44-1.80) is as high as that of the Australian born (1.00), and the risk in those arriving at age 10 or above is much less (0.34. 0.16-0.72 for age 10-29; 0.30; 0.08-1.13 for age 2 30). These data are an improvement on descriptive data as they allow control for ethnic background and pigmentation. In the same study, an association was seen with annual hours of bright sunlight averaged over all places of residence.

In the USA, two case-control studies (Graham *et al.,* 1985; Weinstock *et al*., 1989) showed increased risks for people who had lived at southerly latitudes.

Increased risks in people who have lived near the coast were seen in Denmark (Østerlind *et al.,* 1988b) and in Queensland, Australia (Green & Siskind, 1983). It was assumed in the Danish study that coastal residence would involve more exposure to the sun. In Queensland, living near the coast is not related to annual ambient UVR, which varies with latitude, so that peak summer UV irradiance is higher in the interior than on the coast (Green & Siskind, 1983). The observations are thus due either to different behavioural patterns with geographical location or to differences in exposure to UVR.

(ii) Biological response to total sun exposure

It has been assumed that a history of nonmelanocytic skin cancer, solar keratoses, actinic turnouts or changes on cutaneous microtopography are all indicators of cumulative sun damage. Positive associations are seen with these measures in studies in Australia and in the USA, although Østerlind *et al.* (1988b) in Denmark saw no relationship with microtopographical change (Table 17).

Table 17. Results of case-control studies on melanoma: place of residence, biological markers

Place	Direction of association	OR[a]	95% CI	*p* value	Measurement of exposure	Reference
Potential exposure by place of residence						
Australia	Up	5			Residence near coast; mortality rate/100 000 (incidence rate/100 000, 37)	Green & Siskind (1983)
Australia	Down	0.3	(0.1-1.1)	< 0.001	Age at arrival in Australia; OR given for age ≥ 30 years; *p* value for trend	Holman & Armstrong (1984b)
Australia	Up	2.8	(1.8-4.8)	< 0.001	Mean annual hours of bright sunlight at places of residence; *p* for trend	Holman & Armstrong (1984b)
USA	Up	1.4	(0.9-2.0)	> 0.05	Ever resided below 40 ˚N latitude	Graham *et al*. (1985)[b]
Australia	Down	0.3	(0.1-1.4)	> 0.05	Length of residence in Australia; risk associated with migration to Australia	Green *et al*. (1986)
Denmark	Up	1.7	(1.1-2.7)	0.006	Residence near coast; crude OR	Østerlind *et al*. (1988b)
USA	Up	2.2	(1.1-4.2)	0.02	Residence in southerly latitude at age 15-20, OR for 12.6 ˚	Weinstock *et al*. (1989)
Biological markers of cumulative sun exposure						
Australia	Up	2.7	(1.4-5.0)	0.003	Cutaneous microtopography; *p* for trend	Holman & Armstrong (1984b)
Australia	Up	3.7	(2.1-6.6)	<0.001	History of nonmelanocytic skin cancer	Holman & Armstrong (1984b)
Australia	Up	3.6	(1.8-7.3)	< 0.001	Actinic tumours on face	Dubin *et al*. (1986)
USA	Up	5.0	(2.3-10.5)	< 0.01	History of solar keratosis	Green & O'Rourke (1985)
USA	Up	3.8	(1.2-12.4)	0.03	History or nonmelanocytic skin cancer, adjusted	Holly *et al*. (1987)
Denmark	Flat	1.1	(0.7-1.8)	> 0.05	Cutaneous microtopography; crude OR	Østerlind *et al*. (1988b)

[a]Odds ratio for maximal category

[b]Results calculated by Armstrong (1988)

(iii) *Total sun exposure assessed by questionnaire*

The results of studies in which total sun exposure was assessed using questionnaires, either over lifetime or at different periods of life, have been mixed (Table 18). Positive associations were seen by Green (1984) in Queensland, Australia; no consistent overall association was seen in western Canada, and in Western Australia the association was negative. The results of the other studies are similarly mixed. This inconsistency, in contrast to the results noted above by place of residence and by biological response, could be due either to the difficulty of assessing total sun exposure by questionnaires (Armstrong, 1988) or to different effects of differing patterns of exposure to the sun.

(iv) *Short periods of residence implying high potential exposure*

Several case-control studies have reported, usually as incidental findings, that subjects who have had a short period of residence in tropical or sub-tropical environments have an increased risk for melanoma (Table 19).

(v) *Occupational exposure*

Regular outdoor occupational exposure is probably the most convenient measure of relatively constant sun exposure and has been assessed with differing degrees of detail, from simple questions on ever/never or a basic amount of outdoor exposure, to detailed assessments involving assessments of clothing habits, geographical location of work and so on. The results appear to be inconsistent (Table 20). The more detailed studies, however, show more consistency, with a significant negative association, particularly in men, who constitute most of the highly exposed subjects (Table 21).

An overall irregular pattern was seen in western Canada, probably because individuals with relatively little occupational exposure are those who perform outdoor work seasonally or for short periods, often in early life, so that this exposure may be an indication of intermittent rather than constant exposure (Elwood *et al.,* 1985b). Such results are consistent with the effects of a short period of residence in a sunny place, as reviewed earlier. Paffenbarger *et al.* (1978) also showed that students who recorded outdoor work before college [presumably summer employment] had a significantly increased risk of melanoma in later life.

(vi) *Intermittent exposure*

To assess the effects of intermittent exposure, investigators have asked questions about specific activities that would be likely to represent relatively severe intermittent exposure, such as sunbathing, or asked particularly about holidays in sunny places, or used more complex questionnaires to attempt to assess total intermittent exposure through recreational or holiday activities. Most of these studies show positive associations, but few show large effects (Table 22).

In general, the more detailed studies show reasonably consistent positive results. For example, in western Canada, significant positive associations were seen with recreational and holiday sun exposures in activities involving reasonably intense sun exposure, such as beach activities (Elwood *et al.,* 1985b). In Denmark, rather similar relative risks of 1.5-1.9 were seen with regular participation in activities such as sunbathing, boating, skiing, swimming and vacations in sunny places (Østerlind *et al.,* 1988b). Significant positive associations with sunbathing were seen in the Swedish study of Beitner *et al*. (1990). In the study of Zanetti *et al.*

Table 18. Results of case-control studies on melanoma: total sun exposure assessed by questionnaire

Place	Direction of association	OR[a]	95% CI	*p* value	Measurement of exposure	Reference
USA	Up	2.5	NA	< 0.001	Sun exposure 2 h/day, 11-20 years previously	Rigel *et al*. (1983)
Australia	Up	5.3	0.96-30.8	NA	Total sun exposure throughout life > 50 000 h, adjusted	Green (1984)
Canada	Weakly up	1.2	0.7-2.0	> 0.1	Hours of sun exposure per year, *p* for trend	Elwood *et al*. (1985b)
USA	Down	0.6	0.4-0.9	< 0.05	Total sun exposure throughout life	Graham *et al*. (1985)[b]
USA	Weakly up	1.1	0.6-2.1	>0.05	Hours of sun exposure 0-5 years previously, > 5 h/day	Dubin *et al*. (1986)
USA	Down	0.85	0.5-1.4	> 0.05	Hours of sun exposure 11-20 years previously, > 5 h/day	Dubin *et al*. (1986)
USA	Weakly up	1.1	0.8-1.6	> 0.05	Lifetime sun exposure	Dubin *et al*. (1986)
Australia	Down	0.7	0.4-1.1	0.13	Mean total outdoor hours/week in summer, > 23 h/week; *p* for trend	Holman *et al*. (1986a)
Italy	Down	0.7	0.4-1.1	> 0.05	Heavy or frequent exposure in previous 20 years	Cristofolini *et al*. (1987)
France	Up	3.4	1.6-7.1	< 0.05	Total lifetime outdoor sun exposure, adjusted	Grob *et al*. (1990)

[a]Odds ratio for maximal category
[b]Results calculated by Armstrong (1988)

Table 19. Evidence of melanoma risk with short periods of residence implying high potential exposure

Place	Direction of association	Odds ratio	95% CI	p value	Measurement of exposure	Reference
USA	Up	[7.7	2.5-23.6]	0.0002	US service: tropics versus USA/Europe	Brown *et al*. (1984)
UK	Up	1.8	0.6-5.1	> 0.05	≥ 1 year living in tropics, subtropics	Elwood (1986)
Scotland	Up	2.6 (males)	1.3-5.4	< 0.05	≥5 years living in tropics, subtropics; crude OR	MacKie et al. (1989)
		1.8 (females)	0.8-4.0	> 0.05		
Sweden	Up	1.9	1.0-3.6	< 0.05	Living in Mediterranean, tropics, subtropics > 1 year in last 10 years	Beitner *et al*. (1990)

Table 20. Results of case-control studies on melanoma: occupational exposure

Place	Direction of association	OR[a]	95% CI	*p* value	Measurement of exposure	Reference
USA	Up	3.9	NR	0.001	Outdoor work recorded at college medical examination; prospective	Paffenbarger *et al*. (1978)
Norway	Up	1.4	0.6-3.5	0.37	At least 3-4 h of outdoor work a day	Klepp & Magnus (1979)[b]
Scotland	Down	0.5	0.2-1.2	> 0.05	Hours of outdoor occupation a week	MacKie & Aitchison (1982)[b]
USA	Up	1.2	NR	> 0.05	Outdoor occupation *versus* indoor	Rigel *et al*. (1983)
Canada	Irregular	0.9	0.6-1.5	< 0.01	Hours of outdoor occupation a week in summer	Elwood *et al*. (1985b)
USA	Down	0.7	0.3-1.3	> 0.05	Lifetime hours of outdoor occupation	Graham *et al*. (1985)
USA	Up	2.5	1.4-4.4	< 0.05	Mostly outdoors; multiple logistic OR = 2.4, p < 0.05	Dubin *et al*. (1986)
UK	Irregular	1.7	0.3-8.6	0.5	Lifetime hours of outdoor occupation	Elwood *et al*. (1986)
Australia	Down	0.5	NR	0.04	Mean hours of outdoor occupation a week in summer	Holman *et al*. (1986a)
Denmark	Down	0.7	0.5-0.9	< 0.05	Outdoor occupation *versus* indoor	Østerlind *et al*. (1988b)
Italy	Irregular	2.1	0.6-6.8	0.32	Outdoor occupation	Zanetti *et al*. (1988)
Germany	Up	5.5	1.2-25.3	< 0.05	Outdoor occupation; adjusted OR = 11.6 (2.1-63.3)	Garbe *et al*. (1989)
Sweden	Down	0.6	0.4-1.0	NR	Outdoor occupation, yes/no	Beitner *et al*. (1990)
France	Up	6.0	2.1-17.4	< 0.05	Outdoors occupation *versus* indoor	Grob *et al*. (1990)

NR, not reported

[a]Odds ratio for maximal category

[b]Calculated by Armstrong (1988)

Table 21. Results of case-control studies on different types of melanoma and occupational exposure

Place	Type of melanoma	Odds ratio	95% CI	*p* value	Measurement of exposure	Reference
Canada	Excluding LMM and ALM	0.5	[0.3-1.0]	NR	> 32 h outdoor occupation a week in summer (men)	Elwood *et al*. (1985b)
Queensland, Australia	Excluding LMM and ALM	No association			Outdoor occupation	Green *et al*. (1986)
Western Australia	SSM	0.5	NR	0.04 for trend	Top quartile, hours of outdoor occupation a week in summer	Holman *et al*. (1986a)
Denmark	Excluding LMM and ALM	0.7	0.5-0.9	< 0.05	Outdoor occupation (men)	Østerlind *et al*. (1988b)

LMM, lentigo maligna melanoma; ALM, acral lentiginous melanoma; SSM, superficial spreading melanoma; NR, not reported

Table 22. Results of case-control studies on melanoma: intermittent exposure

Place	Direction of association	OR[a]	95% CI	*p* value	Measurement of exposure	Reference
Norway	Up	2.4	1.0-5.8	0.06	Sunbathing holidays in southern Europe in previous 5 years	Klepp & Magnus (1979)[b]
UK	Up	1.5	0.9-2.5	0.16	Spent some time deliberately tanning their legs	Adam *et al*. (1981)[b]
	Up	1.6	1.0-2.5	0.05	Spent some time deliberately tanning their trunk	Mackie & Aitchison (1982)[b]
Scotland	Down	0.4	0.2-0.9	< 0.05	Hours a week in outdoor recreation	Lew *et al*. (1983)
USA	Up	2.5	1.1-5.8	< 0.05	Days of vacation in a sunny warm place in childhood	Rigel *et al*. (1983)
USA	Up	2.4	NR	0.01	Outdoor versus indoor recreation	Elwood *et al*. (1985b)
Canada	Up	1.7	1.1-2.7	< 0.01	Hours of high exposure in recreational activities per week in summer	
	Up	1.5	1.0-2.3	< 0.01	Hours of high and moderate exposure in recreational activities per day in summer vacations	
	Up	1.7	1.2-2.3	< 0.001	Number of sunny vacations per decade	
UK	Up	5	NR	> 0.05	Number of holidays abroad in hot climate; adjusted	Sorahan & Grimley (1985)
USA	Irregular	1.7	1.2-2.2	< 0.01	Recreation type; multiple logistic OR, 1.0	Dubin *et al*. (1986)
Australia	Irregular	1.9	0.5-7.4	0.62	Recreational hours spent in sun on beach over whole life; crude RR	Green *et al*. (1986)
Australia	Up	1.3	0.9-1.9	0.25	Proportion of recreational outdoor exposure in summer at 10-24 years of age; *p* for trend	Holman *et al*. (1986a)
	Up	2.4	1.1-5.4	0.04	Boating in summer; *p* for trend	
	Up	2.7	1.2-6.4	0.07	Fishing in summer; *p* for trend	
	Irregular	1.1	0.7-1.8	0.66	Swimming in summer; p for trend	
	Up	1.3	0.8-2.2	0.26	Sunbathing in summer at 15-24 years of age; *p* for trend	
Denmark	Up	1.9	1.3-2.9	0.004	Sunbathing; crude RR; *p* for trend	Østerlind *et al*. (1988b)
	Up	1.7	1.1-2.8	0.012	Boating; crude RR; *p* for trend	
	Up	1.5	0.9-2.4	0.006	Skiing; crude RR; *p* for trend	
	Up	1.5	1.2-2.0	0.004	Swimming (outdoors); crude RR; *p* for trend	
	Up	1.7	1.2-2.4	< 0.01	Vacations in sunny resorts; crude RR; *p* for trend	

Table 22 (contd)

Place	Direction of association	OR	95% CI	*p* value	Measurement of exposure	Reference
Italy	Irregular	2.6	1.0-6.9	0.003	Years of outdoor sport (men); *p* for trend	Zanetti *et al*. (1988)
	Up	3.8	1.1-13.0	NR	High-exposure sports (men)	
	Irregular	1.9	0.6-5.8	0.27	Total weeks' vacation (men); *p* for trend	
	Up	3.7	1.4-9.7	0.001	Weeks' vacation near sea; early life (men); *p* for trend	
	Up	1.6	0.7-3.6	0.77	Weeks' vacation near sea; adult life (men); *p* for trend	
	Irregular	2.1	0.6-7.9	0.37	Years of outdoor sport (women); *p* for trend	
	Up	2.3	0.6-9.1	NR	High-exposure sports (women)	
	Irregular	1.1	0.5-2.4	0.56	Total weeks' vacation (women); *p* for trend	
	Up	1.2	0.6-2.5	0.56	Weeks' vacation near sea; early life (women); *p* for trend	
	UP	1.5	0.9-2.7	0.16	Weeks' vacation near sea; adult life (women); *p* for trend	
Germany	No association	NR	NR	NR	Free-time sun exposure	Garbe *et al*. (1989)
Sweden	Up	1.8	1.2-2.6	< 0.05	Number of sunbaths per summer	Beitner *et al*. (1990)
	UP	2.4	1.5-3.8	< 0.05	Sunbathing vacations abroad	
France	UP	8.4	3.6-19.7	< 0.05	Outdoor leisure exposure	Grob *et al*. (1990)

NR, not reported

[a]Odds ratio for maximal category

[b]Calculated by Armstron (1988)

(1988) in Turin, Italy, positive associations were seen with doing an outdoor sport for many years and with number of weeks of holidays spent near the sea. These consistently positive associations contrast with the less consistent pattern seen in Australia. In Western Australia, stronger associations are seen with boating and fishing than with swimming and sunbathing, which would be expected to involve more intense exposure to the sun, and only a weak association was seen with the proportion of outdoor time spent on recreational activities in teenage and early adult years (Holman *et al.*, 1986a). In Queensland, Green *et al.* (1986) found only irregular associations with recreational hours spent at the beach or in other activities with intense exposure to the sun. This finding might be consistent with the concept that, in a sunny environment, recreational activities may involve sufficient frequency or intensity of sun exposure to result in a constant rather than an intermittent dose pattern.

(vii) *Sunburn*

Most of the studies show positive associations between risk for melanoma and a history of sunburn (Table 23). The questionnaires usually defined very severe sunburn as a burn that causes pain lasting for at least two days or blistering. The greater consistency of this relationship compared to that with intermittent exposure may indicate a specific association with sunburn *per se* or that sunburn is simply a more easily remembered measure of intermittent and/or intense exposure to the sun.

A history of sunburn indicates both unusually intense exposure and skin sensitivity, and therefore studies which assess sunburn while controlling for sensitivity through a separate question on tendency to burn are important. Both the western Canada and Western Australia studies when analysed in this way show that the association is primarily with tendency to burn rather than with a history of sunburn (Elwood *et al*., 1985a; Holman *et al.*, 1986a). The studies in Queensland, Demnark and Scotland, however, show strong associations with sunburn history even after controlling for tendency to burn and other measures of skin sensitivity.

Because sensitivity to the sun and sunburn are likely to be highly correlated and both are likely to be measured with a degree of error, it is difficult to distinguish their effects. Similarly, sunburn is likely to be confounded with intermittent exposure of a less intense nature, from which it cannot readily be distinguished because of measurement error (Armstrong, 1988).

The study in England by Elwood *et al.* (1990) assessed sunburn at different ages and showed the strongest association with sunburn at ages 8-12; a stronger association with sunburns at young age was also seen by Weinstock *et al.* (1989) and by Østerlind *et al.* (1988b).

2.1.4 *Malignant melanoma of the eye*

(a) *Case reports*

In general. case reports were not considered, owing to the availability of more informative data.

Kraemer *et al.* (1987) reported on 830 cases of xeroderma pigmentosum, with a median age of 12 years at last observation, located through a survey of published case reports. Ocular abnormalities were found in 328 of 337 patients on whom information was available.

Table 23. Results of case-control studies on melanoma: history of sunburn

Place	Direction of association	OR[a]	95% CI	*p* value	Measurement of exposure	Reference
Scotland	Up	2.8	1.1-7.4	< 0.05	Blistering sunburn or erythema persisting > 1 week	MacKie & Aitchison (1982)
USA	Up	2.1	1.2-3.6	< 0.05	Blistering sunburn during adolescence (yes/no)	Lew *et al*. (1983)
Canada	Up	1.8	1.1-3.0	< 0.01	Vacation sunburn score	Elwood *et al*. (1985a)[b]
Australia	Up	2.4	1.0-6.1	< 0.05	Number of severe sunburns throughout life	Green *et al*. (1985a)
UK	Up	4.2	NR	< 0.01	Bouts of painful sunburn; adjusted	Sorahan & Grimley (1985)
Canada	Up	3.2	1.7-5.9	< 0.001	Sunburn causing pain for ≥ 2 days	Elwood *et al*. (1986)[c]
Australia	Irregular	0.9	0.5-1.5	0.43	Sunburn causing pain for ≥ 2 days, during last 10 years	Holman *et al*. (1986a)[b]
	Up	1.2	0.6-2.3	0.1	Sunburn causing pain for ≥ 2 days, < 10 years of age	
	Up	1.7	1.0-2.9	0.003	Blistering sunburn	
Italy	Down	0.7	0.4-1.2	> 0.05	Severe sunburn in adolescence or early adult life (yes/no)	Cristofolini *et al*. (1987)
	Up	1.2	0.7-2.1	> 0.05	Sunburn as an adult (yes/no)	
USA	Up	3.8	1.4-10.4	NA	Number of blistering sunburns up to adult age, adjusted	Holly *et al*. (1988)
Denmark	Up	3.7	2.3-6.1	< 0.001	Sunburn causing pain for ≥ 2 days, < 15 years of age	Østerlind *et al*. (1988)
	Up	3.0	1.6-5.4	< 0.001	Sunburn causing pain for ≥ 2 days, during previous 10 years	
Italy	Up(men)	4.1	1.8-9.2	< 0.05	Sunburn in childhood (yes/no)	Zanetti *et al*. (1988)
	Up(women)	2.7	1.3-5.6	< 0.05		
Germany	No association	NR	NR	NR	Number of sunburns	Garbe *et al*. (1989)
Scotland	Up(men)	7.6	1.8-3.2	NR	Number of episodes of severe sunburn, and age, adjusted	MacKie *et al*. (1989)
	Up(women)	2.3	0.9-5.6	NR	Number of episodes of severe sunburn, any age, adjusted	

Table 23 (contd)

Place	Direction of association	OR[a]	95% CI	*p* value	Measurement of exposure	Reference
USA	Up	2.2	1.2-3.8	0.01	Number of blistering sunburns at ages 15-20	Weinstock *et al*. (1989)
Sweden	Up	1.7	1.0-2.9	NR	Erythema after sunbathing	Beitner *et al*. (1990)
UK	Up	3.6	1.4-11.2	< 0.05	Moderate sunburn at ages 8-12 (yes/no)	Elwood *et al*. (1990)
	No association	1.0	0.6-2.0	> 0.05	Moderate/maximum sunburn 18-20 yrs (yes/no)	
	Up	1.8	0.9-3.7	> 0.05	Moderate/maximum sunburn 18-20 yrs before diagnosis (yes/no)	
	Up	1.2	0.6-2.3	> 0.05	Moderate/maximum sunburn 5 years before diagnosis (yes/no)	

NR, not reported
[a]Odds ratio for maximal category
[b]Data calculated by Armstrong (1988)
[c]Exposure to fluorescent and other lighting sources

Of these, 88 were reported to have some form of ocular neoplasm, mostly in the limbus, cornea and conjunctive. Five of these patients were reported as having ocular melanoma; only one was specified as being of uveal origin. [The Working Group recognized that data collected from previously published case reports is not uniform and may not be typical of a true incidence or prevalence series. Furthermore, no information is available on the relationship between solar exposure and the occurrence of ocular melanoma in these patients.]

(b) *Descriptive studies*

As there is no separate ICD code for intra-ocular melanoma, descriptive data for cancer of the eye (ICD-9 190) as a whole have been used as a surrogate. Intra-ocular melanoma comprises some 80% of tumours of the orbit of the eye (Østerlind, 1987), and cancer of the eye has been used as a surrogate for adult ocular melanoma in previous studies (Swerdlow, 1983a,b).

(i) *Ethnic origin*

Examination of incidence figures from many parts of the world reveals higher rates of ocular tumours in whites than in blacks or Asians residing at the same latitude and under similar conditions (Waterhouse *et al.,* 1976; Muir *et al.,* 1987).

(ii) *Place of birth and residence*

When rates for whites are evaluated separately, no variation in incidence rates for ocular tumours is seen with decreasing latitude in the northern hemisphere (Table 24). Similarly, no incidence grading was seen among whites in the USA (Table 25). The more northerly states of Australia do not show higher incidence rates for ocular tumours than the southern states (Table 25).

Table 24. Trends in cancer of the eye for whites by latitude and by time period (rates per 100 000 age standardized to UICC 'world population')

Latitude	Area	~1968-72[a]		~1972-77[b]		~1977-82[c]	
		Men	Women	Men	Women	Men	Women
56 °-61 °N	Denmark	1.4	1.2	0.8	0.7	1.0	0.7
	Finland	0.9	1.0	0.9	0.7	1.0	0.7
	Sweden	1.3	1.2	0.9	0.8	0.9	0.6
47 °-55° N	Canada						
	British Columbia	1.0	0.8	0.9	0.6	0.7	0.4
	Alberta	0.8	0.6	0.8	0.9	0.7	0.7
	Saskatchewan	1.3	0.8	1.1	1.0	1.0	0.7
	Manitoba	1.7	0.9	1.2	1.0	0.8	0.8
46 °N	Geneva, Switzerland	0.4	0.2	0.8	1.1	0.6	1.1
38 °N	San Francisco, CA, USA	0.9	0.9	0.9	0.5	0.9	0.8
35 °N	New Mexico, USA	1.0	0.7	1.3	0.7	0.9	0.9
32 °-38 °S	Australia						
	New South Wales	NA	NA	0.8	0.8	0.9	0.5
	South	NA	NA	0.9	1.0	0.7	0.6

Table 24 (contd)

Latitude	Area	~1968-72[a]		~1972-77[b]		~1977-82[c]	
		Men	Women	Men	Women	Men	Women
22 °S	Hawaii, USA	0.4	0.2	1.2	0.2	1.0	0.0
3 °S	Cali, Colombia	0.6	0.2	0.4	0.5	0.5	0.5

NR, not reported
[a]From Waterhouse *et al.* (1976)
[b]From Waterhouse *et al.* (1982)
[c]From Muir *et al.* (1987)

Table 25. Incidence of cancer of the eye (ICD-9 190) in US and Australian whites 1978-82 in various locations by latitude

Latitude	Location	Male rate/ 100 000	Female rate/ 100 000
USA			
47 °N	Seattle	0.9	0.8
42 ºN	Detroit	0.7	0.6
42 ºN	Iowa	1.0	0.7
41 ºN	Connecticut	0.6	0.3
41 ºN	New York City	0.5	0.4
41 ºN	Utah	1.4	1.1
38 ºN	San Francisco Bay Area	0.9	0.8
35 ºN	New Mexico	0.9	0.9
34 ºN	Los Angeles	0.7	0.6
33 ºN	Atlanta	0.7	0.8
22 ºN	Hawaii	1.0	0.0
Australia			
43 ºS	Tasmania	1.2	0.8
38 ºS	Victoria[a]	1.1	0.4
34 ºS	South Australia	0.7	0.6
33 ºS	New South Wales	0.9	0.5
32 ºS	Western Australia	1.6	0.5
28 ºS	Queensland[a]	0.6	0.7

From Muir *et al.* (1987); rates standardized to UICC 'world population'
[a]Data available only for 1982

Schwartz and Weiss (1988) compared the state of birth of 763 white (not of Spanish origin) US patients with uveal melanoma diagnosed between 1973 and 1984 and identified in nine cancer registries with those of the whites covered by the registries as recorded in the 1980 census. Patients with unknown or foreign birthplace or non-uveal ocular melanomas were excluded. Risk estimates were adjusted for age, sex and residence. The odds ratio for subjects born in the southern USA (south of 40 °N) was 1.1 (95% CI, 0.8-1.5). When states

were classified according to average daily global solar radiation, a nonsignificant gradient was observed, only among women (odds ratio for > 15 500 kJ/m^2 *versus* ≤ 12 300 kJ/m^2,1.6; 95% CI, 0.7-3.6).

Mack and Floderus (1991) examined birthplace and residence of patients diagnosed with intra-ocular melanoma among non-latino whites in 1972-82 in Los Angeles County. The proportional incidence ratio was not higher for cases born in California and Arizona than for those born in more northerly areas.

Doll (1991) observed a small rural excess in the incidence of cancer of the eye compared with urban residence, in a number of countries.

(iii) *Occupation*

Four studies of occupational mortality and one of incidence gave inconsistent results with regard to ocular cancer. Two investigations using proportional mortality ratios demonstrated more deaths from ocular cancer than expected among male farmers (Saftlas *et al.,* 1987; Gallagher, 1988), a group likely to have substantial exposure to solar UVR. These findings were not confirmed, however, in two other studies using similar methods (Milham, 1983; Office of Population Censuses and Surveys, 1986).

An investigation of ocular melanoma carried out on data from the cancer registry of England and Wales did not show an elevated incidence in farmers, but an increased risk was seen for professionals (relative risk, 124; 95% CI, 99-153), which was significant for teachers (177; 120-248) (Vågerö *et al.,* 1990).

(iv) *History of skin cancer*

Cancer registry-based studies (Østerlind *et al*., 1985; Tucker *et al*., 1985a; Holly *et al*., 1991) found no or a nonsignificant (Lischko *et al*., 1989) association between the occurrence of cancer of the eye and cutaneous melanoma or nonmelanocytic skin cancer. A single investigation of 400 sequential cases of uveal melanoma (Turner *et al*., 1989) suggested that intra-ocular melanoma patients have an elevated frequency of prior cutaneous melanoma. Thus, although one study indicated a possible association, the overall evidence does not support an association between ocular melanoma and either melanoma or nonmelanocytic skin cancer.

(c) *Case-control studies*

Four case-control studies were evaluated. The first study (Gallagher *et al*., 1985) evaluated all ocular melanomas, while the other three (Tucker *et al*., 1985b; Holly *et al*., 1990; Seddon *et al*., 1990) studied uveal melanomas (excluding conjunctival melanomas).

Gallagher *et al*. (1985) conducted a study of ocular melanoma in patients diagnosed in the four western provinces in Canada between 1 April 1979 and 31 March 1981. Of the 90 ascertained cases, 87 were eligible by age for interview (20-79 years); of these, 65 cases (75%) were actually interviewed. For each case, a single control was randomly selected from the general population, matched by age (± 2 years), sex and province of residence. Response rates for controls were 59°N, for Alberta, Saskatchewan and Manitoba and 48% for British Columbia. Personal interviews were conducted in subjects' homes, and conditional logistic regression was used to control for matching variables and eye, hair and skin colour. No significant association was seen between ocular melanoma and either intermittent (occupational, recreational and holiday) or cumulative exposure to solar UVR.

A strong association was detected between ocular melanoma and blue or grey iris colour (crude odds ratio, 3.0; $p = 0.04$) and blond or red hair colour (crude odds ratio, 7.7; $p = 0.03$). (In a multivariate analysis, these odds ratios became nonsignificant.) A nonsignificantly elevated risk (crude odds ratio, 2.8; $p = 0.08$) for ocular melanoma was also seen for subjects with light skin colour by comparison with subjects with darker skin.

A case-control study conducted by Tucker *et al.* (1985b) evaluated risk factors in 444 white patients with intra-ocular (uveal) melanoma treated at the Wills Eye Hospital in Philadelphia, USA, and 424 controls with detached retinas seen at the same centre. [The Working Group noted that use of a single disease category for the controls could introduce spurious associations with risk factors for that condition.] Response rates were 89% for cases and 85 % for controls. Interviews were conducted by telephone; interviews were with next-of-kin for 17% of the cases and 14% of the controls. Logistic regression models were fitted which included sun-exposure variables, age, sex, eye colour and presence of cataracts, which was included to reduce bias in view of the association between cataracts and detached retina. Sunbathing appeared to increase the risk of intra-ocular melanoma, although no gradient of risk was noted with frequency of exposure (frequent *versus* never, odds ratio, 1.5; 95% CI, 0.9-2.3). A significantly elevated risk was detected for those who engaged in gardening (1.6; 1.0-2.4), but similar associations were not seen for other recreational outdoor activities, such as fishing, camping and hunting. Cases of intra-ocular melanoma also reported increased exposure to the sun during vacations in comparison with controls' with an odds ratio of 1.5 (95% CI, 0.97-2.3) for subjects 'frequently' experiencing increased exposure *versus* subjects never exposed (test for linear trend over four strata, $p = 0.01$). Cases reported less frequent use of eye protection (sunglasses, headgear, visors) when outdoors as compared with controls, but there was no dose-response relationship with frequency of use of these protective devices. A gradient of risk was seen with use of any eye shading when iris melanomas were examined separately, suggesting that eye shading may have been specifically important for lesions at the front of the eye (never *versus* occasional use of eye protection, odds ratio, 4.9; 95% CI, 1.4-13.7). [Numbers of iris melanomas were not given.] Subjects who were born in the southern USA (lower than 40 °N latitude) were found to have a significantly elevated risk of intra-ocular melanoma (2.7; 1.3-5.9) after adjustment for number of years spent in the south and for the presence of cataracts; with adjustment for all other sun-related variables, the odds ratio was 3.2 (95% CI, 1.8-5.7). The association persisted after excluding subjects not living close to Philadelphia. There was no relation between the number of years spent in the south and the risk of intraocular malignant melanoma, after adjustment for having been born in the south. Blue-eyed subjects had the highest risk of intra-ocular melanoma, with gray-green and hazel-eyed subjects at intermediate risk, and brown-eyed subjects at lowest risk (unadjusted odds ratio for brown- *versus* blue-eyed subjects, 0.6; 95 % CI, 0.4-0.8). Cases were more likely than controls to have fair skin and blond or brown hair, although no odds ratios are given and the differences disappeared when eye colour was taken into account. Cases were also more likely to have 25 or more freckles (used as an indirect measure of sun exposure and sensitivity) than controls (odds ratio, 1.4; 95% CI, 1.0-2.0).

A case-control study by Holly *et al.* (1990) involved 407 white cases of uveal melanoma and 870 controls. The cases were diagnosed between January 1978 and February 1987 at

the for Ocular Oncology Unit of the University of California, San Francisco, USA, were aged 20-74 at diagnosis and lived in 11 western states. Controls were selected by random digit dialling and were matched to cases on age and area of residence. Telephone interviews were conducted by interviewers unaware of the study hypotheses, most cases being interviewed within four years of their diagnosis. The response rate was 93% of cases and 77% of eligible controls. No clear association was seen between uveal melanoma and vacation time spent in sunny climates or high proportion of leisure time spent outdoors. Individuals who spent 50% of their leisure time indoors and 50% outdoors had a reduced risk for uveal melanoma (odds ratio, 0.6; 95% CI, 0.4-0.9) when compared to subjects who stayed mainly indoors. Significantly elevated risks were seen in subjects with grey, green, hazel or blue eyes, compared to those with brown eyes, with increasing frequency of large naevi (27 mm) ($p = 0.04$ for trend) and with a propensity to burn rather than tan in the sun.

Seddon *et al.* (1990) compared 197 white patients with uveal melanoma diagnosed in 1984-87, who were resident in the six New England states close to the Massachusetts Eye and Ear Infirmary, with 385 controls obtained through random digit dialling and matched to cases by age (± 8 years), sex and area of residence. All subjects were interviewed by telephone using a standard questionnaire. The response rate was 92% among cases, and 85% of the eligible controls contacted agreed to participate in the study. Matched logistic regression techniques were employed to evaluate potential associations between exposure to UVR and risk of uveal melanoma, adjusting for age, sex, constitutional factors and socio-economic variables. An inverse association with southern birthplace (south of 40 °N latitude) was detected (odds ratio, 0.2; 95% CI, 0.0-0.7) after adjustment for constitutional and other factors. When cumulative lifetime residence in the south was examined, subjects who had lived for more than five years south of 40 ºN had an odds ratio of 2.8 (95% CI, 1.1-6.9) after adjustment for birthplace. Several indices of sun exposure were computed for each subject. The first combined duration of residence in the north or south with self-reported severity of sun exposure (low, medium, high). Subjects in the highest exposure group appeared to have a higher risk of uveal melanoma by comparison with those in the lowest exposure category (1.7; 0.9-3.0) although no dose-response relationship was seen over the three categories of exposure. A further index was obtained by taking average values of solar radiation for each state in which the subject has resided and multiplying this value by the duration of residence within the state and the reported amount of time spent in the sun. No association was seen between this index and risk of uveal melanoma. Individuals who reported having spent a great deal of time working outdoors 15 years prior to diagnosis showed a somewhat lower risk of uveal melanoma than those who worked minimally outdoors or were retired (odds ratio, 0.6; 95% CI, 0.3-1.4) after control for age, skin, eye colour and southern residence. No association was seen with sunbathing, use of sunglasses or visors, or outdoor hobbies all conducted 15 years prior to diagnosis. Use of eye glasses was not related to uveal melanoma risk. Cases reported more cutaneous naevi and lighter skin colour than controls and were more likely to be of northern European or British ancestry than controls. An expanded analysis comparing 387 cases of uveal melanoma with 800 sibling controls was also conducted. There was a gradient of risk with cumulative years of intense sun exposure; the odds ratio for the highest exposure was 2.1 (1.4-3.2).

2.1.5 *Other cancers*

No adequate data were available to the Working Group.

2.2 Artificial sources of ultraviolet radiation

Epidemiological investigations that have attempted to assess exposure to artificial sources of UVR have neither measured actual UVR nor considered the emission spectra. It is presumed that in the studies described below, subjects were exposed to sources that varied in intensity and emission spectra.

2.2.1 *Nonmelanocytic skin cancer*

Three case-control studies, described in detail on p. 84, addressed this issue. In the study in Montreal, Canada, of Aubry and MacGibbon (1985), any use of a sunlamp gave an odds ratio of 13.4 [95% CI, 1.4-130.5] after adjustment for sun exposure and constitutional factors. O'Loughlin *et al.* (1985) in Ireland found that fewer cases than controls reported frequent exposure to 'artificial sunlight' (nonsignificant). In the study of Herity *et al.* (1989) in Ireland, a smaller proportion of cases than of controls reported ever having used sunlamps or sunbeds ($p = 0.2$).

2.2.2 *Malignant melanoma of the skin*[1]

The results of case-control studies of exposure to fluorescent light and melanoma are summarized in Table 26.

Beral *et al.* (1982) conducted a case-control study in Sydney, Australia, of 274 female cases aged 18-54 identified at a melanoma clinic between 1978 and 1980 and 549 hospital and population controls matched by age and, for population controls, residence. The response rate for cases was 71% [response rates for controls not given]. Each job lasting 12 months or longer was recorded, together with information about whether the work had been carried out predominantly indoors or outdoors, whether fluorescent lighting was present, and whether the fluorescent lights were switched on most of the time or less frequently. Among women who always worked indoors, the odds ratio increased with duration of working with fluorescent lights most of the time to a maximum of 2.6 (95% CI, 1.2-5.9) for 20 or more years' exposure. The effect was greater for office workers (odds ratio, 4.3) than for other indoor workers (2.0). Stratification by amount of time spent outdoors, main outdoor activity and amount of clothing worn, history of sunburn, place of birth, hair colour and skin colour did not diminish the association. Among cases exposed to fluorescent lights, there was a relative excess of melanomas on the trunk (a site likely to be covered at work); 24% in exposed cases *versus* 4% in unexposed cases. [The Working Group noted that crude estimates of sun exposure were used.]

Rigel *et al.* (1983) conducted a case-control study in New York, USA, described on p. 106. Cases had had shorter average daily exposure to fluorescent lights (4.9 h) than had

[1] After the meeting, the Secretariat became aware of a study by Walker et al. (1992) on the risk of cutaneous malignant melanoma associated with exposure to fluorescent light.

controls (5.4 h). Among office workers, average daily exposures were similar for cases and controls. The crude odds ratio for any exposure was 0.7 among all subjects and 0.6 among office workers.

English *et al.* (1985) conducted a studyin 1980-81 of the exposure to fluorescent light of 337 cases and 349 age-matched controls who had already participated in a population-based case-control study in Western Australia (see Holman and Armstrong (1984a), p. 100). The response rate was 68% for cases and 91% for controls. Detailed information was obtained from telephone interviews about lifetime hours of residential and occupational exposure, the distance to the nearest light fixture and the presence of diffusers. Neither the duration of occupational exposure, the rate of total exposure (hours/year) nor cumulative total exposure was associated with risk for melanoma. Analyses by body site showed no consistent association with exposure to lights without diffusers. Adjustment for measures of total and intermittent exposure to the sun did not alter the results. Subjects were also asked about exposure to plan printers, laboratory equipment emitting UVR, insect tubes, black lights and photocopiers. No association was seen with any of these sources, although the number of exposed subjects was small. The odds ratio for any use of sunlamps was 1.1 (95% CI, 0.6-1.8), although few subjects had used sunlamps (Holman *et al.*, 1986b).

Sorahan and Grimley (1985) examined fluorescent light exposure in 1980-82 in a case-control study in the United Kingdom, described in detail on p.103. Information on exposure was confined to whether lights were 'mainly on' or 'sometimes on' at work. After adjustment for age and sex, no consistent association was seen for duration of exposure when cases were compared with electoral register controls.

Dubin *et al.* (1986) examined fluorescent light exposure in a subset of subjects in a case-control study in New York, USA, described on p. 108. Subjects were interviewed and/or sent postal questionnaires. In data obtained from interview, but not in data obtained from postal questionnaires, the odds ratios increased with average daily exposure in the five years before interview, after adjustment for age and sex (p value for linear trend, < 0.05). A similar pattern was seen for exposure 6-11 years and 11-20 years previously.

Elwood *et al.* (1986) examined fluorescent light exposure in their case-control study in the United Kingdom in 1981-84, described in detail on p. 103. Subjects were interviewed and later sent postal questionnaires to validate the responses. From the interview data, exposure to undiffused lights at work was associated with an odds ratio of 4.0 (95% CI, 0.8-19.2) for those maximally exposed (p value for trend = 0.2). Control for constitutional factors did not change the results. From the questionnaire data, the odds ratio for maximal exposure (undiffused lights) was 1.9 (95% CI, 0.4-8.4). No association was seen with exposure at home, and no association was seen for use of sunlamps. Subjects were also asked about exposure to particular or unusual light sources, such as vacuum or discharge lamps, insecticidal or germicidal lamps or welding equipment. The odds ratio for exposure to any such source was 2.2 (95% CI, 1.0-4.9). [The Working Group noted that the use of open-ended questions about lighting sources may have introduced recall bias.]

In the Western Canada case-control study in 1979-81 (see Elwood *et al.*, 1984, 1985a,b, p. 107), no association was seen with use of sunlamps ($\chi 2 = 6.1$,5 df) (Gallagher *et al.*, 1986).

Østerlind *et al.* (1988b) examined exposure to fluorescent lighting at work and use of sunlamps and sunbeds in their case-control study in Denmark in 1982-85, described on pp. 103-104. The same proportions of cases and controls reported having been exposed to fluorescent lights at work, and no association was seen with age at first exposure, duration of exposure or type of work place. Past use of sunlamps was also not associated with melanoma, and a smaller proportion of cases than controls had ever used sunbeds (odds ratio, 0.7: 95% CI. 0.5-1.0).

In a case-control study in Scotland (Swerdlow *et al.,* 1988), 180 cases aged 15-84 from three clinics during 1979-84 were compared with 197 age- and hospital-matched patients with various non-malignant diseases. Subjects were interviewed about exposure to fluorescent lights and UV lamps, use of sunbeds, sun exposure and constitutional factors. Controls with skin conditions were excluded from the analysis of UV lamps and sunbeds. No consistent association was seen with exposure to fluorescent lights at home or at work, with or without adjustment for constitutional factors and sun exposure. Significant, positive associations were seen for duration of use of UV lamps and sunbeds (p value for trend, < 0.05). The odds ratio for use for more than one year was 3.4 (95% CI, 0.6-20.3) after adjustment for constitutional factors and sun exposure. Amount of use within five years (1.9; 0.6-5.6) of the interview and more than five years (9.1; 2.0-40.6) before the interview were both positively associated with the risk for melanoma.

MacKie *et al.* (1989) examined use of sunbeds and sunlamps in their case-control study in Scotland described on p. 106. Use was associated with melanoma in men (odds ratio, 2.6; 95% CI, 0.9-7.3) but showed little association in women (1.5; 0.8-2.9). The effect on men largely disappeared after adjustment for sun exposure and constitutional factors.

In the study of Zanetti *et al.* (1988) from Turin, Italy, described in detail on p. 104, an odds ratio of 0.9 (0.4-2.0) was found for use of UVA lamps, although few subjects reported exposure.

A large population-based case-control study on occupational exposures was conducted during 1979-85 in Montreal, Canada (Siemiatycki, 1991). Overall, there were 3730 male cases of cancer aged 35-70, including 124 cutaneous melanoma cases; the participation rate was 82%. Each cancer site was compared with the other cancer sites. Exposure to 293 agents, including arc welding fumes and UVR, was assessed by a team of chemists and industrial hygienists on the basis of each individual's occupational history. Neither arc welding fumes nor exposures to UVR was associated with the risk for cutaneous melanoma (odds ratios, 0.5; 90% CI, 0.3-1.1 and 0.3; 0.1-1.5, respectively).

In a population-based study in southern Ontario, Canada (Walter *et al.,* 1990), 583 cases identified from pathology laboratories and from the cancer registry between 1984 and 1986 were compared with 608 controls randomly sampled from property tax rolls. Participation rates were 90% for cases and 80% for controls. Odds ratios for any use of sunbeds or sunlamps were 1.9 (95% CI, 1.2-3.0) in men and 1.5 (0.99-2.1) in women. Adjustment for constitutional factors did not affect the results. The odds ratios increased with duration of use; for more than 12 months' use, the odds ratios were 2.1 (0.9-5.3) in men and 3.0 (1.1-9.6) in women.

Table 26. Case-control studies of melanoma of the skin and exposure to fluorescent lights

Country	Cases/controls	Odds ratio	95% CI	Definition of exposure	Reference
Australia	274/549	2.6[a,b]	1.2-5.9	Indoor workers, ≥ 20 years' occupational exposure	Beral *et al*. (1982)
		4.3[a,b]	NR	Office workers, ≥ 20 years' occupational exposure	
USA	114/228	0.7	NS	Any exposure	Rigel *et al*. (1983)
		0.6	NS	Any exposure, office workers	
Australia	337/349	1.2[a,b]	0.8-1.9	≥ 35 000 h exposure	English *et al*. (1985)
		1.2[a,b]	0.7-1.9	≥ 1600 h per year	
		1.3[a,b]	0.8-1.9	≥ 22 500 h undiffused lights	
		1.2[a,b]	0.8-1.9	≥ 1300 h per year undiffused lights	
		1.2[a,b]	0.6-2.6	≥ 22 500 h head, neck, upper limbs, undiffused lights	
United Kingdom	58/333	0.6[a]	NR	≥ 20 years, occupational exposure (mainly on)	Sorahan & Grimley (1985)
		0.5[a]	NR	≥ 20 years, indoor workers only (maily on)	
USA	1103/585	2.3[a]	1.0-5.8	≥ 9 h per day, 0-5 years previously (interview)	Dubin *et al*. (1986)
	508/222	0.6[a]	0.3-1.3	≥ 9 h per day, 0-5 years previously (postal questionnaire)	
United Kingdom	83/83	1.4[a,b]	0.4-5.1	≥ 50 000 h occupational exposure (total fluorescent light, postal questionnaire)	Elwood *et al*. (1986)
		4.0[a,b]	0.8-19.2	≥ 50 000 h occupational exposure (undiffused lights, interview)	
	67/66	1.2[a,b]	0.3-5.7	≥ 50 000 h occupational exposure (total fluorescent light, postal questionnaire)	
		1.9[a,b]	0.4-8.4	≥ 50 000 h occupational exposure (undiffused lights, postal questionnaire)	
Denmark	474/926	No association		Duration of exposure, age at first exposure, type of workplace	Østerlind *et al*. (1988b)
Scotland United Kingdom	180/197	1.2[b]	0.7-1.9	Any occupational exposure < 5 years previously	Swerdlow *et al*. (1988)
		0.8[b]	0.4-1.4	Any exposure at home < 5 years previously	
		1.6[b]	0.9-2.6	≥ 5 h per day < 5 years previously at work and at home	
		1.4[b]	0.9-2.3		
		0.8[b]	0.4-1.4	Any occupational exposure > 5 years previously	
				Any residential exposure > 5 years previously	

NR, not reported; NS, not significant

[a]Odds ratio for category with highest level of exposure

[b]Adjusted for sun exposure

2.2.3 *Malignant melanoma of the eye*

In the case-control study carried out in Philadelphia, USA, which is described in detail on p. 128, cases of uveal melanoma were more likely to report use of sunlamps than controls. After adjustment for age, eye colour and a history of cataracts, there was a trend to increasing risk with frequency of use (odds ratio for frequent veesus never, 2.1; 95% CI, 0.3-17.9; test for linear trend over four levels: $p = 0.10$). The odds ratios for those who had ever worked as welders was 10.9 (2.1-56.5) (Tucker *et al.,* 1985b).

In the case-control study from San Francisco, USA, described on pp. 128-129, exposure to artificial UV light or 'black light' [details not given] conferred over three-fold risks for intra-ocular melanoma after adjustment for other significant factors (odds ratio, 3.7; 95% CI, 1.6-8.7). The odds ratios were 2.9 for 1-5 years of exposure and 3.8 for 6 or more years (Holly *et al.*, 1990).

In the case-control study from Boston, USA (Seddon *et al.,* 1990), described on p. 129, exposure to fluorescent lighting was associated with an elevated risk of uveal melanoma (odds ratio, 1.7; 95% CI, 1.1-2.5 for 40 h or more per week as compared to no exposure) in the larger data set, based on case-sibling comparison. In the population-based comparison, the corresponding odds ratio was 1.2 (95% CI, 0.6-2.1). A history of working with welding arcs was reported with similar frequency among cases and controls in both comparisons. Cases reported more frequent use of sunlamps in comparison with both sets of controls. After adjustment for constitutional factors and exposure to the sun, the odds ratios for frequent/occasional use *versus* never were 3.4 (1.1-10.3) in the population comparison and 2.3 (l.2-4.3) in the sibling comparison.

In the large Canadian study on occupational exposure, described on p. 132, 23 cases of ocular melanoma were included. Analysis only of French Canadians revealed four cases of eye melanoma with exposure to arc welding fumes (odds ratio, 8.3; 90% CI, 2.5-27.10) (Siemiatycki, 1991). No increase was found for substantial exposure; no increase in risk was reported for exposure to UVR.

2.3 Premalignant conditions

2.3.1 *Basal-cell naevus syndrome*

Basal-cell naevus syndrome is a hereditary condition (Gorlin, 1987) in which affected family members may show, among other major manifestations, an apparent excess of basal-cell carcinomas. These seem to occur more commonly in sun-exposed parts of the body or in unusual patterns. There is no other evidence that solar radiation plays a role in their development.

2.3.2 *Dysplastic navvus syndrome*

Dysplastic naevus syndrome is a hereditary condition in which affected family members have multiple dysplastic naevi and a greatly increased risk of malignant melanoma (Green *et al.,* 1985b). The distribution of tumours conforms to the usual distribution, and there is anecdotal evidence that solar radiation plays a role in their development (Kraemer Greene, 1985).

2.4 Molecular genetics of human skin cancers

Analysis of mutations in DNA isolated from tumours and believed to be relevant to carcinogenesis can potentially help in making a causal link with exposures to carcinogens. Two important qualifications must, however, be borne in mind. Firstly, the changes detected may have arisen late in tumour development (whether or not the tumour is the result of exposure to UVR) and may not be involved in initiation or other early steps. Secondly, the spectrum of mutations that is seen may be constrained to those changes that can lead to a functional gene product. This qualification applies, for example, to mutations that activate *ras* genes but to only a lesser extent to tumour suppressor gene mutations in which inactivation of gene function is involved.

Experimental studies indicate that UV-induced mutations have a distinctive pattern of base-substitution mutations (see section 4.5):

- Virtually all mutations occur at dipyrimidine sites, especially 5'TC and 5'CC sequences.
- The majority of the base substitution mutations involve cytosiIle with the C IT transition predominating.
- Tandem 5'CC→5'TT mutations occur.

2.4.1 ras *Gene mutations*

Primary melanomas, metastases and cell lines derived from melanomas which developed at body sites characterized as exposed 'rarely', 'intermittently' or 'continuously' to the sun were analysed for the presence of *N-ras* mutations. Of 37 cutaneous melanomas, seven had N-*ras* mutations; all were from 'continuously' exposed sites. All mutations in the N-*ras* gene were at TT or CC sites, which are potential locations for mutagenic UV photoproducts, suggesting a role of sun exposure in N-*ras* mutation (van't Veer *et* al., 1989).

In several investigations, base-substitution mutations were found in Ha-, Ki- and N-*ras* genes in human skin melanomas (Table 27) and in squamous-cell and basal-cell carcinomas (Table 28) from xeroderma pigmentosum and normal patients. In single studies, Ha- and N-*ras* gene amplification was found in squamous-cell carcinomas of the skin (Ananthaswamy & Pierceall, 1990), and loss of the Ha-ras allele was seen in basal-cell and squamous-cell carcinomas (Ananthaswamy *et al.,* 1988). Whether exposure to the sun was involved in tumour induction in these studies is, however, less clear.

2.4.2 *p53 Gene mutations*

Brash *et al.* (1991) found p53 mutations at various codons in 14 out of 24 (58%) invasive squamous-cell carcinomas from sun-exposed skin (Table 29). The mutations found were predominantly C→T (5 of 14 total mutants, 36%) and CC→TT (3 of 14, 21%) transitions exclusively at tandem pyrimidine stretches. This finding is consistent with the hypothesis that these mutations are induced by UV irradiation. CC→TT double-base changes in the p53 gene have not yet been found in turnouts in any internal organ. These results strongly suggest that solar radiation plays a role in the induction of p53 gene mutations.

Pierceall *et al*. (1991) found p53 mutations in exon 7 in 2 out of 10 squamous-cell carcinomas from sun-exposed body sites; one was a C→T transition and the other a C→A transversion.

Table 27. ras Gene mutations detected in human naevi and primary and secondary melanomas that developed at sites subject to sun exposure

Oncogene codon	Base change	Base-substitution mutation	Site of original tumour	Reference
N-*ras*-61	*GG*A C*AA* GAA			
	AAA	C to A	Neck	van't Veer *et al*. (1989)
	AAA	C to A	Lower leg	van't Veer *et al*. (1989)
	AAA	C to A	Nose	van't Veer *et al*. (1989)
	AAA	C to A	Cheek	van't Veer *et al*. (1989)
	CGA	[T to C]	Lower leg	van't Veer *et al*. (1989)
	CAT	[T to A/G]	Xeroderma pigmentosum patient[a]	Keijzer *et al*. (1989)
	CAT	[T to A]	Site unspecified, probably metastasis	Sekiya *et al*. (1984)
N-*ras*-13	*GG*T *GG*T G*TT*			
	GAT	[C to T]	Finger	van't Veer *et al*. (1989)
	GTT	[C to A]	Finger	van't Veer *et al*. (1989)
	GTT	[C to A]	Lower leg	van't Veer *et al*. (1989)
N-*ras*-12	GAT	[C to T]	Leg	van't Veer *et al*. (1989)
N-*ras*-61	CAT/C	[T to A/G]	Back	Shukla *et al*. (1989)
Ki-*ras*-61	*GG*A C*AA* G*AA*			
	AAA	C to A	Lower leg	Shukla *et al*. (1989)
Ki-*ras*-12	G*CT GGT GG*C			
	TGT	[C to A]	Abdomen	Shukla *et al*. (1989)
	TGT	[C to A]	Knee	Shukla *et al*. (1989)
	TGT	[C to A]	Site unspecified, probably metastasis	Shukla *et al*. (1989)
	TGT	[C to A]	Site unspecified, probably metastasis	Shukla *et al*. (1989)
	TGT	[C to A]	Site unspecified, probably metastasis	Shukla *et al*. (1989)
	TGT	[C to A]	Site unspecified, probably metastasis	Shukla *et al*. (1989)
		[C to T]	Buttock	Shukla *et al*. (1989)
		[C to T]	Site unspecified, probably metastasis	Shukla *et al*. (1989)
		[C to T]	Forearm (naevus)	Shukla *et al*. (1989)
		[C to T]	Abdomen (naevus)	Shukla *et al*. (1989)
Ha-*ras*-12	G*CC GG*C *GG*T			
	TGC	[C to A]	Abdomen	Shukla *et al*. (1989)

Italics indicate potential pyrimidine dimer site including neighbouring condon; [ ], base changes occurring in anti-sense strand

[a]Malignant melanoma probably resulting from metastasis of a primary skin tumour

Table 28. *ras* Gene mutations detected in human keratoacanthomas (KA), basal-cell carcinomas (BCC) and squamous-cell carcinomas (SCC) that developed at sites to sun exposure

Oncogene condon	Base change	Base-substitution mutation	Tumour	Site	Reference
Ki-*ras* 12	GCT *GG*T *GG*C				
	TGT	[C to A]	SCC	Lip	van der Schroeff *et al*. (1990)
			BCC	Shoulder	van der Schroeff *et al*. (1990)
			BCC	Neck	van der Schroeff *et al*. (1990)
	GAT	[C to T]	BCC	Face	van der Schroeff *et al*. (1990)
Ha-*ras* 61	*GG*C CA*G G*AG				
	CTG	[T to A]	SCC	Not specified	Corominas *et al*. (1989)
	CTG	[T to A]	KA	Not specified	Corominas *et al*. (1989)
	CAT	[C to A]	BCC	Face	van der Schroeff *et al*. (1990)
	AAG	C to A	KA	Not specified	Corominas *et al*. (1989)
Ha-*ras* 12	G*CC GG*C *GG*T				
	AGC	[C to T]	SCC	Not specified	Corominas *et al*. (1989)
	AGC	[C to T]	KA	Not specified	Corominas *et al*. (1989)
	AGC	[C to T]	KA	Not specified	Corominas *et al*. (1989)
	TGC	[C to A]	SCC	Not specified	Corominas *et al*. (1989)
	TGC	[C to A]	SCC	Not specified	Corominas *et al*. (1989)

Italics indicate potential pyrimidine dimer site including neighbouring codon; [ ], base changes occurring in anit-sense strand

Table 29. p53 Tumour suppressor gene mutations in human squamous-cell carcinomas that developed at sites subject to sun exposure

Codon	Nucleotide sequence	Base-substitution mutation	Incidence[a]	Site of tumour origin	Reference
7	TCT	TGT; C→G	1/14/24	Preauricular	Brash *et al*. (1991)
56	T TCA	TAA; C→A	1/14/24	Chest	Brash *et al*. (1991)
104/105	CG CCT	deletion of a C	2/14/24	Preauricular/temple	Brash *et al*. (1991)
151	CCC CC	CAC; C→A	1/14/24	Scalp	Brash *et al*. (1991)
152	CC CCC	CAC; C→T	1/14/24	Hand	Brash *et al*. (1991)
179	A CCA	CAA; C→A	1/14/24	Scalp	Brash *et al*. (1991)
244	CCG G	TCG; C→T	1/2/10	Face	Pierceall *et al*. (1991)
245	G CCG	CAG; C→A	1/14/24	Cheek	Brash *et al*. (1991)
245	G CCG	T T; CC→TT	1/14/24	Chest	Brash *et al*. (1991)
247/248	AC CG	T T; CC→TT	1/14/24	Nose	Brash *et al*. (1991)
248	GCC	GAC; C→A	1/2/10	Face	Pierceall *et al*. (1991)
258	T TCC	TTC; C→T	1/14/24	Face	Brash *et al*. (1991)
278	T CCT	TCT; C→T	1/14/24	Cheek	Brash *et al*. (1991)
285/286	TC CT	T T; CC→TT	1/14/24	Face	Brash *et al*. (1991)
286	TC CT	CTT; C→T	1/14/24	Forehead	Brash *et al*. (1991)
317	CC CCA	TCA; C→T	1/14/24	Postauricular	Brash *et al*. (1991)

Italics indicate potential pyrimidine dimer site

[a]No. of specific mutations/no. of total mutations found/Total number of samples tested only from sites continuously exposed to the sun

CONTINUED

3. Studies of Cancer in Animals

3.1 Experimental conventions

3.1.1 *Species studied*

The experimental induction of skin cancers in mice following exposure to a mercury-arc lamp was first reported by Findlay (1928). Initially, haired albino mice were used, but hairless and nude mice are now preferred.

An important development was the use of the hairless mouse as a model (Winkelmann *et al.,* 1960, 1963). In haired animals, the fur provides effective protection of the skin against UVR. This limits investigations to sparsely haired skin regions, mainly the ears, as, in long-term experiments with frequent exposures, the mechanical trauma caused by shaving might influence the process of tumorigenesis. The skin of hairless mice differs, however, from human skin in many respects. It is, for instance, much thinner and has abnormal hair follicles. The hairless mouse does, however, have a thymus and a functioning immune system, in contrast to the nude mouse (Eaton *et al.,* 1978; Hoover *et al.,* 1987). Many recent studies on carcinogenesis induced by UVR used the hairless mouse model (Forbes *et al.,* 1981; de Gruijl *et al.,* 1983; Gallagher *et al.,* 1984b). The changing designations of 'Skin' mice are listed in Table 30. Skin tumorigenicity has been evaluated experimentally in only a relatively small number of species other than the mouse.

Table 30. Alternative designations used for 'Skin' outbred stocks of hairless mice

Phenotype	1970-86	After 1986	Synonyms used in the literature	Inbred strains derived from Sk:hr stock[a]
Albino[b]	Skh: hairless-1	Skh:hr I	Sk-1; Skh-1; Skh/Hr-1; Skh:HR; HRA/Skh-1; Skh-hr1	HRA/Skh (Temple University, Philadelphia, PA, USA)
Pigmented[c] (any colour)	Skh: hairless-2	Skh:hr II	Sk-2; Skh-2; Skh/Hr-2	HRA/Skh-1 (University of Sydney, Sydney, Australia)

[a]From Forbes et al. (1990)
[b]Forbes et al. (1981); de Gruijl et al. (1983)
[c]Davies & Forbes (1988)

3.1.2 *Wavelength ranges*

As noted in section 1.1, for the purposes of this monograph, the UV wavelength range is subdivided according to the convention of the Commission Internationale de l'Eclairage (1987) into: UVA (315-400 nm), UVB (280-315 nm) and UVC (100-280 nm). The UVB

range is generally found to be most effective in inducing skin cancer, i.e., tumorigenesis may be achieved with smaller doses of radiant exposure than with UVA and UVC. A complete discussion of wavelength ranges is given in section 1.1.

3.1.3 *Measured doses*

Many investigators of the carcinogenicity of UVR have reported the type of lamps they used, which are frequently broad-spectrum lamps, sometimes in combination with filters. When estimates of the doses of UVR administered are given, the measuring instrument is usually mentioned and the result is given in terms of irradiance or dose, with no further detail. Such information is of some value, especially for comparing the results of experiments in which the same type of' ramps were used.

The action spectrum (see section 1) given in Figure 10 shows that the carcinogenic effectiveness of UVR in hairless mice changes steeply, even by orders of magnitude, over a wavelength range of 10 or 20 nm. This pattern indicates that irradiance must be spectrally specified in order to be meaningful, and not integrated into one value over a broad spectrum. One approach is to give irradiance weighted according to the action spectrum for UV carcinogenesis, but this is available only in provisional form (see Fig. 10 and discussion on pp. 46-47). Another approach is to provide data on erythemally weighted irradiance, since the action spectrum for erythema corresponds approximately to that for carcinogenesis (Forbes *et al*., 1978). A simple, direct way of calculating this is to relate the doses administered to the minimal elythema dose or to the minimal oedemic dose for the animal being investigated. When investigators supplied such measures of effect, they are mentioned in the summaries below.

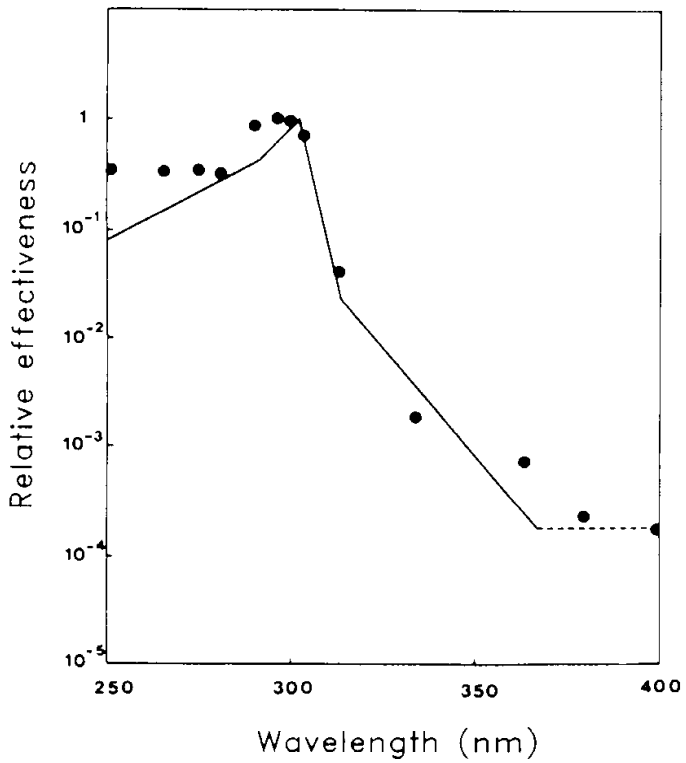
In experimental situations, there is never a perfectly sharp cut-off of wavelengths. The expression 'mainly UVA' is of questionable value, because even if UVB represents only 0.1% of the emission spectrum, it may still dominate the effect (see pp. 144-147, 151 and Fig. 10). Terms such as 'mainly UVB' are used below only when there are good reasons to assume that the effects considered are due mainly to UVB radiation.

3.1.4 *Protocols*

Experimental investigations on the carcinogenicity of UVR, conducted mostly on mice, have been reviewed (Blum, 1959; Urbach *et al.,* 1974; Kripke & Sass, 1978: WHO, 1979; van der Leun, 1984; Epstein, 1985).

Hundreds of studies have been reported. Most were not designed to test whether or not the radiation used was carcinogenic *per se* but to investigate the process of UV carcinogenesis. The methods used in these studies differ in many respects from those in standard lifetime studies to evaluate the carcinogenicity of chemicals. For example, many studies do not give complete details of the UVR emission spectrum used or exposure dose, do not enumerate all tumours, do not provide data on survival or do not provide histological details of tumours. Control groups are not always included; however, spontaneous skin tumours are rare in mice and rats. In many of the studies presented in detail below, appropriate statistical analyses have been done demonstrating clear dose-related trends in numbers of tumourbearing animals, number of tumours per animal and/or median time to first tumour.

Fig. 10. Sterenborg-Slaper action spectrum for ultraviolet-induced skin carcinogenesis (1.0-mm tumours) in albino hairless mice. Effectiveness is defined as the reciprocal of the daily dose at each wavelength that leads to tumours of 1-mm diameter in 50% of animals in 265 days, relative to the corresponding value at the wavelength of maximal effectiveness. The effectiveness between 340 and 400 nm represents an average value for that wavelength range.



From van der Leun (1987a)

3.2 Broad-spectrum radiation

3.2. 1 *Sunlight*

In one study by Roffo (1934), 600 rats [sex and strain unspecified] were exposed to solar radiation (sunlight) at a latitude of 35 °S in Buenos Aires, Argentina. The average exposure was for 5 h per day, with avoidance of the hours around solar noon in the summer. In the first days, 365 rats died from sunstroke. Of the 235 remaining animals, 165 (70%) developed tumours. There were 140 tumours of the ear (58% squamous-cell carcinomas; 36% spindlecell sarcomas; 6% carcinosarcomas): 58 eye tumours (tumours of the conjunctive, 100% spindle-cell sarcomas; tumours of the eyelid, 50% squamous-cell carcinomas and 50% spindle-cell sarcomas); and 15 other tumours, mainly squamous-cell carcinomas, at sites including the nose, tail, paw and neck. In complementary experiments reported in the same paper, groups of animals were exposed either to sunlight filtered through various colours of glass, to radiation from various types of lamp (quartz mercury, glass mercury, neon gas and filament lamps) or to short Hertzian wavelengths. Tumours [types and sites unspecified] were observed in all 150 animals exposed to quartz mercury

lamps; no tumour was induced in any other experimental group. On the basis of this evidence, the author concluded that the carcinogenicity of sunlight could be attributed to UVR.

In another report by Roffo (1939), 2000 white rats and mice [exact numbers unspecified] were exposed to sunlight for an average of 5 h per day. After three to six months, benign neoplasms and, after seven to nine months, malignant neoplasms of the skin of the ear (88% of all malignant tumours), the forepaw (7.25%), the tail (my) and nose (one tumour) developed in 600 animals; 25% of the tumours were seen on the eyes. The ear tumours were diagnosed as squamous-cell carcinomas (58%), spindle-cell sarcomas (36%) and carcinosarcomas (6%) by detailed histological examination. Similarly, the paw tumours were diagnosed as squamous-cell carcinomas (42%) and spindle-cell sarcomas (58%); the tumours of the tail were all squamous-cell carcinomas. The distribution of tumours of the eye was similar to that in the study of Roffo (1934). [The Working Group considered that these are exceptional studies which fully document the carcinogenicity of solar radiation in rats and mice, even though quantitative detail is lacking. The resulting neoplasms are described and photographically illustrated in exact detail. The Working Group accepted the weight of evidence contained in these studies as to the carcinogenicity of solar radiation to rats and mice.]

Domestic and other animals of many species (cows, goats, sheep (reviewed by Emmett, 1973), cats (Dorn *et al.,* 1971) and dogs (Madewell *et al.,* 1981; Nikula *et al.,* 1992)) develop skin tumours, and there are good indications that sunlight is involved. The tumours described generally developed in sparsely haired, light-coloured skin. Cancers of the eye occur in many species, including dogs, horses, cats, sheep and swine, but are particularly frequent in cattle (Russell *et al.,* 1956).

3.2.2 *Solar-simulated radiation*

In several investigations on carcinogenesis by UVR, 'solar-simulated radiation' was used (Forbes *et al.,* 1982; Staberg *et al.,* 1983a; Young *et al.,* 1990; Menzies *et al.,* 1991). In one large, particularly informative experiment (Forbes *et al.,* 1982), more than 1000 hairless albino Skh-hrl mice were exposed to solar-simulated radiation from a xenon arc lamp, with various Alters to make the spectral distribution in the UV region similar to that of sunlight under various thicknesses of the ozone layer. The exposures lasted for up to 80 weeks. More than 90% of the mice developed skin tumours, predominantly squamous-cell carcinomas. The time to development of 50% of first tumours was shorter after exposure to the spectra that included higher irradiance in the wavelength range 290-300 nm. The other experiments mentioned were more limited and dealt with more specialized aspects of UV carcinogenesis.

3.2.3 *Sources emitting UVC, UVB and UVA radiation*

Sources emitting radiation in the entire UV wavelength range were used in experiments on UV carcinogenesis mainly between 1930 and 1960.

(a) Mouse

Grady *et al.* (1943) exposed 605 strain A mice to broad-spectrum UVR at a wide range of doses and irradiances (weekly doses, 3.6-43 x 107 ergs/cm^2 [40-430 kJ/m^2]; Blum & Lippincott, 1942). The investigation dealt primarily with skin tumours (mainly spindle-cell

sarcomas). About 5% of the mice developed tumours of the eye. Histological examination by Lippincott and Blum (1943) showed that the eye tumours arose mostly in the cornea end were spindle-cell sarcomas or fibrosarcomas; haemangioendotheliomas were also found.

A particularly large, informative series of investigations was carried out with unfiltered medium-pressure mercury arc lamps which emitted UVC, UVB and UVA (Blum, 1959). More than 600 strain A mice were irradiated (daily dose, 0.32-8.6 x 107 ergs/cm^2 [3-86 kJ/m^2]) in a series of investigations dealing with various aspects of UV carcinogenesis; the dose-effect relationship was addressed particularly. In most of the experiments, more than 90% of mice developed skin tumours, mainly of the ears, the only site for which quantitative data were given.

(b) *Rat*

Findlay (1930) exposed six epilated albino rats to broad-spectrum UVR from a mercury-vapour lamp at a distance of 18 in [46 cm] for 1 min three times a week. Rapidly growing papillomas were reported in one rat. The time required was, however, much longer than in mice exposed similarly, namely, 21 months as compared to eight months for mice.

Putschar and Holtz (1930) exposed 35 rats [strain unspecified] with very low spontaneous turnout incidence to almost continuous irradiation with broad-spectrum UVR from a quartz mercury lamp for 11 months. They reported regular occurrence of skin tumours, including papillomas, squamous-cell carcinomas and, occasionally, basal-cell carcinomas. The tumours were first seen after 27 weeks of exposure.

Huldschinsky (1933) exposed seven white rats to UVR from a solar lamp for 2 h per day, six days per week for one year or more. Another group of five rats was exposed to a quartz lamp emitting a predominantly UVC waveband (< 270 nm). The doses given per session were about 10 times higher than those used in phototherapy. Spindle-cell sarcomas of the eye were found in 2/7 and 5/5 rats in each group, respectively.

Hueper (1942) reported squamous-cell carcinomas and, rarely, spindle-cell carcinomas and sarcomas. round-cell carcinomas and basal-cell carcinomas of the skin in 20 rats [strain unspecified] exposed for up to 10 months to broad-spectrum UVR from a mercury vapour burner (a Hanovia Super S Alpine lamp) at a distance of 75 cm.

In a study by Freeman and Knox (1964), a group of 78 rats (66 pigmented and 12 unpigmented) was exposed to broad-spectrum UVR from mercury lamps at 50 cm from the skin on five days a week for one year; the doses per session corresponded to approximately 1 MED for rat skin. A total of 98 eye tumours developed, with more tumours in pigmented rats. The tumours arose in the corneal stroma; two-thirds were diagnosed as fibrosarcomas and one-third as haemangioendotheliomas.

(c) *Hamster*

Hamsters exposed to an irradiation regimen similar to that described above also developed eye tumours (Freeman & Knox, 1964). In 19 animals (9 pigmented, 10 unpigmented) exposed for one year, haemangioendotheliomas and fibrosarcomas developed in 14 eyes.

(d) Guinea-pig

Guinea-pigs were exposed to the same regimen as described above. None of 17 animals developed a tumour of the eye (Freeman & Knox, 1964).

3.3 Sources emitting mainly UVB radiation

Many experiments have been carried out with sources emitting mainly UVB radiation, in which increases in the number of tumour-bearing animals and/or in the number of tumours per animal were seen (Blum, 1959; Winkelmann *et al.,* 1963; Freeman, 1975; Stenback, 1975a; Daynes *et al.,* 1977; Kripke, 1977; Spikes *et al.,* 1977; Forbes *et al.,* 1981; de Gruijl *et al.,* 1983; Gallagher *et al.,* 1984b). The most informative studies are described below.

3.3.1 *Mouse*

Freeman (1975) studied carcinogenesis induced by chronic exposure to narrow-band UVB produced by a high-intensity diffraction grating monochromator with a half-power band-width of 5 nm. Exposure was three times per week to one ear of each haired albino mouse. Four wavelengths were used, and the doses were determined as the MED. Of a group of 30 mice exposed to 300 nm (weekly dose, 60 mJ/cm2), 16 developed squamous-cell carcinomas of the ear. Of a group of 30 mice exposed to 310 nm (weekly dose, 750 mJ/cm^2), 16 survived to 450 days and eight developed five squamous-cell carcinomas, two fibrosarcomas and one angiosarcoma of the ear. No skin tumour was observed among 30 mice irradiated with UVR at 290 nm (weekly close, 42 mJ/cm^2); of five mice irradiated with 320 nm (weekly dose, 4950 mJ/cm^2), two developed squamous-cell carcinomas of the ear.

Two fibrosarcomas and one unspecified tumour of the eye were reported in 24 C3H/HeN mice bearing 25 skin tumours (mostly fibrosarcomas) after exposure to UVR (168 J/m^2 three times a week) from Westinghouse FS40T12 sunlamps (280-340 nm) (Kripke, 1977).

In the experiment of Forbes *et al.* (1981), groups of 24 male and female hairless albino Skh:HR mice (the changing designations of sources of 'Skin' mice are listed in Table 30), six to eight weeks old, were irradiated on five days per week with Westinghouse FS40T12 sunlamps (see Fig. 9c, p. 64), emitting mainly UVB (with < 1% below 280 nm; two-thirds at 280-320 nm and one-third at > 320 nm). All animals had developed tumours by the end of the experiment (up to 45 weeks), and a dose-response effect was demonstrated, as assessed by time to tumours in 50% of animals (Table 31). Histological examination showed tumours of 4 mm or more in diameter to be squamous-cell carcinomas; those of about 1-4 mm formed a continuum from carcinoma in *situ* to squamous-cell carcinoma, and those less than 1 mm comprised epidermal hyperplasia and squamous metaplasia tending toward carcinoma in *situ.* Less than 1% of tumours were fibrosarcomas.

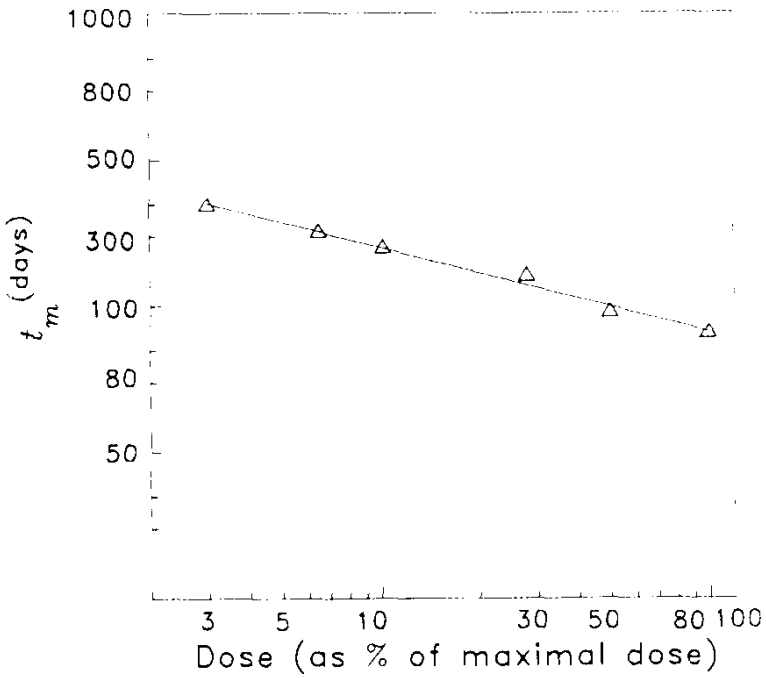
Six groups of 22-44 male and female Skh-hr 1 hairless albino mice (total, 199), six to eight weeks of age, were exposed to daily doses ranging from 57 to 1900 J/m^2 of mainly UVB radiation from Westinghouse FS40TL12 sunlamps; this dose range encompassed a factor of 33. Most of the animals developed skin tumours, although even the highest daily dose was sub-erythemic. A clear-cut relationship was shown between daily dose and time required for 50% of animals to develop skin tumours, which were predominantly squamous-cell carcinomas (Fig. 11). Squamous-cell carcinomas developed in 71 % of the

Table 31. Dose-response to ultraviolet radiation of hairless Skh:HR mice

Daily dose (J/m^2)	Time to 50% tumour incidence (weeks)	Terminated at week
420	38.6	45
587	33.3	45
822	29.2	45
1152	20.0	36
1613	17.6	36
2259	12.9	25

From Forbes *et a/.* (1981)

Fig. 11. Dose-effect relationship for the induction of < 1-mm skin tumours in hairless mice by exposure to UVB radiation over a wide range of daily doses; tm, median induction time



From de Gruijl *et al.* (1983)

mice in the lowest dose group, and two skin tumours were reported in a total of 24 nonirradiated control mice (de Gruijl *et al.*, 1983).

In albino hairless Skh:Hr-1 mice irradiated with UVB or UVB plus UVA radiation three times a week for 16 weeks, with a 17-week recovery period, the spectrum for UV tumorigenesis was sharp and had a maximum near 300 nm (Bissett *et al.*, 1989).

3.3.2 *Rat*

Skin tumour induction was studied in a group of 40 shaven female NMR rats,8-l0weeks old at the start of the experiment. The animals were irradiated chronically at a distance of 37.5 cm for 60 weeks with Westinghouse FS40T12 sunlamps (Fig. 9c), emitting mainly UVB (weekly dose, 5.4-10.8 x 104 J/m^2). A total of 25 skin tumours, most of which were papillomas of the ears, developed in 16/40 animals (Stenback, 1975a).

3.3.3 *Hamster*

Stenback (1975a) irradiated 40 shaven female Syrian golden hamsters, 8-10 weeks of age, using the same protocol as described above. A total of 30 skin tumours developed in 14/40 animals; 22 were papillomas (14 animals), four were keratoacanthomas (three animals), one was a squamous-cell carcinoma of the skin and three were papillomas of the ear (one animal).

3.3.4 *Guinea-pig*

Stenbäck (1975a) exposed guinea-pigs using the same protocol as above and found skin tumours in 2/25 animals (a fibroma and a trichofolliculoma).

3.3.5 *Fish*

Two hybrid fish strains susceptible to melanocytic neoplasms by UVR were developed by Setlow *et al*. (1989) by crossing platyfish and swordtails. A group of 460 fish were exposed to mainly UVB radiation from Westinghouse FS40 sunlamps, filtered with acetate sheets transmitting > 290 nm or > 304 nm at various doses (150 and 300 J/m^2 per day for > 290 nm; 850 and 1700 J/m^2 per day for > 304 nm) for 1-20 consecutive days. There were 103 controls. Depending on the wavelength, the level, the number of days of exposure and the strain, 19-40% of the irradiated fish developed melanocytic tumours; 13 and 2% of the controls in the two strains, respectively, developed such tumours.

3.3.6 *Opossum*

Monodelphis domestics, a South American opossum, is unusual in showing the phenomenon of photoreactivation (see Glossary) of pyrimidine dimers and erythema (Ley, 1985); it also developed actinic keratoses and skin tumours (mainly fibrosarcomas and squamous-cell carcinomas) on exposure to UVR from an FS-40 sunlamp (280-400 nm) (toy *et al.*, 1987). Animals were shaved regularly and exposed to mainly UVB radiation from Westinghouse FS40 sunlamps, with relative emissions of 0.04, 0.27, 0.69, 1.0 and 0.09 at a dose of 250 J/m^2 (which is approximately half of an average MED; see Fig. 9c) at 280, 290, 300, 313 and 360 nm, respectively. Eight of 13 animals developed localized melanocytic hyperplasia; 100 weeks after the start of the experiment, melanomas were found in 5/13 surviving animals. M. *domestica* do not develop spontaneous melanomas, as was apparent in a much larger colony not exposed to UVR. Exposure of another group to photoreactivating light after UV irradiation reduced the incidence of melanocytic hyperplasia (3/17); this was considered to be a precursor lesion of the melanomas, although photoreactivation could not be demonstrated in the melanoma (Ley *et al.*, 1989).

[The Working Group noted that the melanocytic lesions induced in fish and the South American opossum differ histologically from human melanoma: they grow to a larger size and do not metastasize readily.]

Ley *et al.* (1991) exposed groups of M. *domestica* to UVR from fluorescent sunlamps (Westinghouse FS40; 280-400 nm with a peak at 313 nm) three times a week for 70 weeks at a dose of 250 J/m^2. Besides skin tumours, tumours of the anterior eye were observed beginning 30 weeks after the start of exposure. At 69 weeks, 50% of the animals had eye tumours, which were classified as fibrosarcomas of the corneal stroma. In animals exposed to UVR followed immediately by photoreactivating light, tumours appeared later and in reduced numbers.

'Cancer eye' in cattle, which includes squamous-cell carcinoma of the eye and the circumocular skin, is thought to be caused by solar UVR. In an attempt to confirm this relationship experimentally (Kopecky *et al.,* 1979), four Hereford cattle (which lack pigment around the eyes) were exposed to UVB radiation from Westinghouse FS40 lamps. Three cows developed grossly observable tumours of the eye, one of which was histopathologically confirmed as a preneoplastic growth.

3.4 Sources emitting mainly UVC radiation

3.4.1 *Mouse*

Carcinogenicity studies have been performed mainly in mice, but no study is available in which animals were exposed solely to UVC radiation. Several studies have been reported in which the source of UVC radiation was low-pressure mercury discharge germicidal lamps, which emit 90-95% of their radiation at wavelength 254 nm and weaker spectral lines in the UVB, UVA and visible light regions (Rusch *et al*., 1941; Blum & Lippincott, 1942; Forbes & Urbach, 1975; Lill, 1983; Joshi *et al*., 1984; Sterenborg *et al*., 1988). In all of these investigations, the exposures induced tumours. Two of the most informative studies are described in more detail below.

A group of 40 female C3H/HeNCr1Br mice were irradiated with these lamps at a weekly dose of 3 x 10^4 J/m^2. Three animals died without tumours after 9, 43 and 63 weeks of irradiation; all of the other animals had tumours. By 52 weeks, 97% of the animals had developed skin tumours, with a median time to appearance of 43 weeks. The mean number of tumours per tumour-bearing mouse was 2.9. Tumour histology was carried out in 29/37 mice. Of a total of 83 suspected tumours, 66 were squamous-cell carcinomas, 10 were proliferative squamous lesions and 6 were invasive fibrosarcomas; one had the appearance of a cystic dilatation (Lill, 1983). [The Working Group that resulted in *IARC Monographs* volume 40 (IARC, 1986a) noted that the 4% UVB content of the source, representing a weekly dose of 1170 J/m^2, could not be excluded as contributing to the induction of skin tumours.]

Sterenborg *et al.* (1988) presented evidence that the tumours they induced in albino hairless mice were indeed due to UVC radiation. Groups of 24 male and female hairless albino mice (Skh-hr1), 6-10 weeks of age, were exposed to UVC radiation from Philips germicidal TUV 40W low-pressure mercury discharge lamps (mainly 254 nm) on seven days a week for 75 min per day at 230, 1460 or 7000 J/m^2 (30 times the MED); this dose was 60% less during the first seven days of the experiment. A total of 65 squamous-cell

carcinomas of the skin were found [number of animals with tumours not specified]. Both the percentage of tumour-bearing animals and the number of tumours per mouse were strongly dose-related. By comparing their results with those of experiments with UVB, the investigators concluded that (i) the UVB emitted by the low-pressure mercury discharge lamps was insufficient to account for the induction of tumours at the rate found, as at least 850 days of exposure to the UVB radiation present would be required to induce skin tumours at the rate observed, as compared to 161 days with the low-pressure mercury discharge lamp used; (ii) there is a qualitative difference between the effects of low-pressure mercury discharge and UVB lamps, in that the tumours induced by the mercury discharge lamps were scattered more widely over the skin of the mice than in the experiments with UVB; and (iii) the dose-effect relationship for tumorigenesis was less steep with the mercury discharge lamps than with UVB sources. [The Working Group noted that the evidence given to exclude UVB as contributing to the induction of skin tumours does not obviate the possibility that some interaction between UVC and UVB radiation led to turnout induction.]

3.4.2 *Rat*

Nine groups of 6 or 12 male CD-1 rats, 28 days of age, were shaved and exposed to varying doses of UVC from Westinghouse G36T6L sterilamps emitting predominantly 254 rim (dose range, 0.08-26.0 x 104 J/m^2). Survival ranged from 75 to 92% for the nine experimental groups. Keratoacanthoma-like skin tumours developed at a yield that was approximately proportional to dose throughout the dose range 0.65-26.0 x 104 J/m^2, although no tumor was observed at 0.32 x 104 J/m^2 or below (Strickland *et al.,* 1979).

3.5 Sources emitting mainly UVA radiation

The carcinogenic properties of UVA radiation received little attention before the introduction of UVA equipment for tanning, which led to the development of powerful sources of UVA. Many experiments have now been performed, using mainly hairless mice, to examine the possible carcinogenicity of UVA radiation (Zigman *et al.,* 1976; Forbes *et al.,* 1982; Berger & Kaase, 1983; Staberg *et al.,* 1983a,b; Kaase *et al.,* 1984; Santamaria *et al.,* 1985; Strickland, 1986; van Weelden *et al.,* 1986; Slaper, 1987; Kligman, 1988 [abstract]; van Weelden *et al.,* 1988; Kligman *et al.,* 1990 [abstract]; Sterenborg & van der Leun, 1990; van Weelden *et al.,* 1990a; Kelikens *et al.,* 1991a; Kligman *et al.,* 1992). Some have shown no induction of tumours (Staberg *et al.,* 1983a,b; Kaase *et al.*. 1984; Kligman, 1988 [abstract]). The Working Group noted that the doses may have been too small (daily doses in the range of 160 kJ/m^2) (Staberg *et al.,* 1983b) or the exposure period too short (Berger & Kaase, 1983; Kaase *et al.,* 1984; Kligman, 1988 [abstract]), as noted by the authors in a subsequent report (Kligman *et al.,* 1992).] In the other experiments, tumours were induced. [The Working Group noted that in some of the latter experiments either it is unclear whether UVB radiation was sufficiently excluded from the spectrum (Zigman *et al.,* 1976; Berger & Kause, 1983; Staberg *et al.,* 1983a; Santamaria *et al.,* 1985) or the exclusion of UVB radiation was not fully convincing (Strickland, 1986).]

Studies in which the exclusion of UVB radiation was documented to be sufficient and which led to the induction of tumours by UVA in hairless mice were reported by van Weelden *et al.* (1986, 1988, 1990a), Slaper (1987), Kligman *et al.* (1990 [abstract], 1992),

Sterenborg and van der Leun (1990) and Kelttens *et al.* (1991a). A few of the most informative studies are described below.

Groups of 24 male and female albino hairless Skh-hr 1 mice were exposed to UVA radiation from a bank of Philips TL40W/09 fluorescent tubes, filtered through a 10-mm glass plate selected for strong absorption of UVB radiation, for 12 h a day on seven days a week for about one year, at which time the experiment was terminated. The daily dose was 220 kJ/m^2. Most animals developed scratching lesions before they contracted skin tumours, which occurred in all animals; the median time to tumour appearance was 265 days. At the end of the experiment, the larger lesions were examined histologically: 60% were classified as squamous-cell carcinomas, 20% as benign tumours, including papillomas and keratoacanthoma-like lesions, and 20% as mild cellular and nuclear atypia. The histological findings were similar to those observed in a parallel experiment with UVB, but the tumours in the UVA-exposed group appeared over a longer time span. Residual UVB radiation was excluded as the cause of tumours in UVA-exposed mice on quantitative considerations: the authors concluded that more than 100 000 times the UVB present would have been required in order to induce tumorigenesis at the rate observed (van Weelden *et al.*, 1986, 1988).

Groups of 48 male and female hairless albino Skh-hr 1 mice were exposed to 220 kJ/m^2 UVA radiation (> 340 nm) from four high-pressure mercury metal-iodine lamps (Philips HPA 400 W), passed through liquid filters, for 2 h per day on seven days per week for up to 400 days. The spectrum matched that of a damp used for tanning (the UVASUN 5000); UVB was effectively excluded by the filters. Skin tumours developed in most of the animals, and 31 developed tumours before any scratching was observed. The largest tumours were examined histologically at the end of the experiment: 15/20 tumours examined were squamous-cell carcinomas (Sterenborg & van der Leun, 1990).

The desire to tan safely has raised interest in the possible carcinogenicity of long-wavelength UVA (340-400 nm). In some experiments, UVB was excluded so rigorously that there was also very little UVA in the range 315-340 nm; exposure was therefore mainly to wavelengths in the region of 340-400 nm (van Weelden *et al.*, 1988; Sterenborg & van der Leun, 1990; van Weelden *et al.*, 1990a). These experiments yielded squamous-cell carcinomas in most animals. [The Working Group noted that if these were to be ascribed to the small proportion of shorter-wavelength UVA present in the spectra, a sharp peak in the action spectrum for UV carcinogenesis would have to occur between 330 and 340 nm, which does not appear likely.] In experiments by Kligman *et al.* (1990 Abstract], 1992), wavelengths shorter than 340 nm were filtered out rigorously. Female hairless albino Skh-hr 1 mice were exposed several times per week for 60 weeks to UVA at wavelengths of 340-400 nm at daily doses of 360 and 600 kJ/m^2, as used in artificial suntanning. Eighteen weeks later, 44 surviving mice had 19 skin tumours, mostly papillomas. At week 100, 22 surviving mice had 40 tumours. many of which were considered clinically to be squamous-cell carcinomas.

The carcinogenicity of short-wavelength UVA (315-340 nm) was investigated in one experiment. Groups of 24 male and female albino hairless Skh:hr 1 mice were exposed to average daily doses of 20 or 56 kJ/m^2 radiation from specially developed fluorescent tubes with peak emission near 330 nm (UVB radiation was filtered out efficiently using a glass

filter) on seven days a week for 650 days. All mice in the high-dose group developed multiple tumours, first mainly papillomas and later predominantly squamous-cell carcinomas. In the lower-dose group, three mice developed skin tumours, all of which were papillomas. The lamps also emitted long-wavelength UVA (340-400 nm), but in a proportion considered by the authors to be too small to account for the rate of tumorigenesis observed (Kelfkens *et al.,* 1991a). The investigators estimated the carcinogenic effectiveness of short-wavelength UVA (315-340 nm) to be approximately five times greater than that of long-wavelength UVA (340-400 nm)

3.6 Interaction of wavelengths

In daily life, the skin is exposed frequently to several wavelength ranges (UVA, UVB, UVC) simultaneously, or to different combinations at different times. The simplest explanation of an effect of such combined exposures is 'photoaddition', i.e., each exposure contributes to the effective dose in an additive way. The validity of this hypothesis is one of the assumptions underlying widely used concepts such as 'erythemal effective energy' and the derivation of the action spectrum shown in Figure 10 (p. 141). It implies that any additional exposure to an effective dose, in any wavelength region, increases the carcinogenic effect.

Several studies provide indications, however, that the situation is more complicated. Interactions are seen between the effects of different wavebands that result in deviations from photoaddition (for reviews, see van der Leun, 1987b, 1992). The literature on this topic is controversial and cannot be summarized in detail here. The following two sections form an attempt to give an overview and interpretation.

3 .6.1 *Interaction of exposures given on the same day*

Several types of interactions have been reported between different wavelength ranges administered simultaneously or in close temporal proximity. These have led to concepts of processes such as:

- photorecovery: the effect of UVB or UVC is reduced by simultaneous or immediately subsequent exposure to UVA or visible light [The Working Group noted that photoreactivation is a special case of photorecovery but applies only to species that have the 'photoreactivating enzyme', photolyase (see Glossary).];
- photoprotection: the effect of UVB or UVC is reduced by prior administration of UVA or visible light;
- photoaugmentation: the effect of UVB or UVC is enhanced by prior, simultaneous or subsequent administration of UVA or visible light.

Photoaugmentation of UVB carcinogenesis by UVA was suggested by several investigators (Urbach *et al.,* 1974; Willis *et al.,* 1981, 1986; Kligman, 1988 [abstract]; Talve *et al.,* 1990) but could not be confirmed by others (Forbes *et al.*, 1978; van Weelden & van der Leun, 1986). The latter investigators found evidence of photorecovery: the effect of UVB plus UVA was smaller than that of the same UVB exposure given alone. The reduction was small; however, UVA reduced the carcinogenic effective dose of UVB by 16%.

Interactions of different wavelength ranges when given simultaneously, prior to or immediately after each other appear to be either nonexistent or unproven, as in the case of photoaugmentation, or small, as in the case of photorecovery. Such interactions currently

play a small role in the evaluation of risks (see, for example, Health Council of the Netherlands, 1986). Other uncertainties in the estimates, such as the dose received, are likely to have a greater influence than interactions. Photoreactivation, is, however, a well-defined process in those species which possess photolyase and may result in reduction of effects.

3.6.2 *Long-term interactions*

A different type of interaction occurs when exposures to one wavelength band are separated temporally from exposures to another. For example, a prolonged course of UVB exposures, by itself sufficient to induce tumours, is compared with an identical UVB course that is preceded or followed by a course of UVA exposures, usually over several weeks.

Forbes *et al.* (1978) exposed hairless mice to tumorigenic UVB or to UVB followed by UVA and visible light for 30 weeks. The longer-wavelength exposures reduced the tumorigenic effect of the UVB. Staberg *et al*. (1983b) gave mice a tumorigenic combination of UVB and UVA and found that subsequent exposures to UVA increased the tumorigenic effect. The UVA was derived from Philips TL40W/09 lamps filtered through 2-mm plain glass to remove the UVB. [The Working Group noted that since the glass transmitted some UVB the increased carcinogenic effect may have been due to added UVB radiation.] Bech-Thomsen *et al.* (1988a) pretreated lightly pigmented hairless female hr/hr C3H/Tif mice with UVA for four weeks before exposure to broad-spectrum UVR. The UVA reduced the carcinogenic effect of the broad-spectrum UVR. This result was not corroborated in a subsequent, similar experiment by the same investigators (Bech-Thomsen *et al.,* 1988b), in which mice were pretreated with radiation from various UVA sources. The purest UVA radiation neither increased nor decreased the carcinogenic effect of UVB.

Slaper (1987) exposed one group of mice daily to UVB and a second group daily to UVA at doses matched for approximately equal carcinogenic effect. In a third group of mice that received the two regimens alternately every week, the carcinogenic effect was less than that in the UVA- or the UVB-exposed group. The effective dose in the alternating regimen was estimated to be 80% that in the UVB regimen. The investigator concluded that both UVA and UVB contributed to the carcinogenic effect of the alternating regimen.

[The Working Group noted that the effect of long-term interactions appears to be similar to that of interactions of exposures given on the same day. Photoaddition gives a reasonable prediction, but the combined effects tend to be slightly less than would be predicted.]

3.7 Additional experimental observations

3.7.1 *Tumour types*

Skin tumours in UV-exposed animals are commonly epidermal, benign papillomas and malignant squamous-cell carcinomas; adnexal neoplasms, mainly basal-cell carcinomas, are less common. Attempts have been made to induce naevi and malignant melanomas. Many tumours are found, since the animals are followed for long periods of time; however, tumours coalesce and regress, and all tumours are not examined histologically.

Squamous-cell carcinoma is the commonest type of tumour found after exposure to UVR. These tumours have been reported in mice exposed to predominantly UVB radiation (Winkelmann *et al*., 1960, 1963; Epstein & Epstein, 1963; Freeman, 1975; Forbes *et al*.,

1981; de Gruijl *et al.,* 1983), to predominantly UVA radiation (van Weelden *et al.,* 1988; Sterenborg & van der Leun, 1990) and to predominantly UVC radiation (Lill, 1983; Sterenborg *et al.,* 1988). They have also been found in rats (Putschar & Holtz, 1930; Roffo, 1934, 1939; Hueper, 1942), hamsters (Stenbäck, 1975a) and opossums (Ley *et al.,* 1989) following exposure to broad-spectrum UVR.

Papillomas were reported to be the commonest tumour after exposure of hairless mice to UVR consisting of UVB and UVA (Gallagher *et al.,* 1984b). Papillomas were also reported to precede or accompany squamous-cell carcinomas induced in hairless mice by UVA (van Weelden *et al.,* 1988), UVB (Stenbäck, 1978) or UVC radiation (Sterenborg *et al.,* 1988). Papillomas were also common in rats (Findlay, 1930; Putschar & Holtz, 1930; Stenback, 1975a) and hamsters (Stenbäck, 1975a) exposed to broad-spectrum UVR.

The main type of tumour diagnosed after exposure of haired mice to broad-spectrum UVR was *fibrosarcomas* (Grady *et al.,* 1941, 1943). Squamous-cell carcinomas were less common, but the ratio of carcinomas to sarcomas increased with the number of exposures per week (Grady *et al.,* 1943). Spikes *et al.* (1977) reported many squamous-cell carcinomas in clipped C3Hf mice irradiated with UVB, especially at low doses; the high-dose group had a much higher proportion of fibrosarcomas. The investigators suggested that the type of tumour induced might be dose-dependent. Norbury and Kripke (1978) found that the type of tumour might depend on immunological factors. They compared UVB tumorigenesis in normal C3H/HeN (MTV^-) mice, in T cell-depleted mice and in T cell-depleted mice reconstituted with thymus grafts. In the normal mice, fibrosarcomas predominated: in the T-cell depleted, reconstituted mice, squamous-cell carcinomas predominated. Spindle-cell sarcomas were reported in rats irradiated with sunlight (Roffo, 1934), and fibrosarcomas were seen in opossums irradiated with UVB (Ley *et al.,* 1989).

The diagnosis of fibrosarcoma was questioned by Morison *et al.* (1986). After C3H/HeNCr (mammary tumour virus-free) haired pigmented mice were exposed to mainly UVB radiation, the tumours induced were almost all squamous-cell carcinomas. The investigators noted that the same type of tumour had been diagnosed in many previous reports as fibrosarcoma: they diagnosed squamous-cell carcinomas by studying specific markers for cell differentiation in the tumours. In a study by Phelps *et al.* (1989) in which hairless albino Skh/hr-1 mice were exposed to UVA and UVB at 0.3 J/cm^2 [30 kJ/m^2], all mice developed epidermal neoplasia and 25% of animals developed spindle-cell tumours that resembled human atypical fibroxanthoma. [The Working Group noted that earlier studies did not use presently available cellular markers.]

Keratoacanthomas and similar benign epidermal neoplasms have been reported in mice exposed to UVB (Stenbäck, 1978), rats exposed to UVB and UVC (Strickland *et al.,* 1979) and hamsters exposed to UVB (Stenbäck, 1975a).

Actinic keratosis, or solar keratosis, a precursor lesion of squamous-cell carcinomas, has been reported in hairless mice exposed to UVA and UVB (Kligman & Kligman, 1981) and in haired mice exposed to UVB (Stenbäck, 1978).

Basal-cell carcinomas have not been reported in studies in mice. A few studies on UV carcinogenesis in nude mice, which have a deficient immune system, have been reported

(Eaton *et al.,* 1978; Anderson & Rice, 1987; Hoover *et al.,* 1987). The skin tumours induced by mainly UVB radiation in these studies were mostly squamous-cell carcinomas, but in the experiments reported by Anderson and Rice (1987) in nude mice of BALB/c background there were several basal-cell carcinomas. Basal-cell carcinomas were found occasionally in rats exposed to broad-spectrum UVR (Putschar & Holtz, 1930; Hueper, 1942). [The Working Group noted that the classification of these neoplasms and their relation to the corresponding neoplasms in humans is not clear.]

There is no report in which cutaneous *malignant melanoma* was induced in mice by UVR alone (Epstein, 1990; van Weelden *et al.,* 1990b; Husain *et al.,* 1991), in spite of concerted attempts to achieve this.

No study was found in which the primary objective was to examine the susceptibility of the eye to UVR; rather, eye tumours were found incidentally in studies designed to investigate skin carcinogenesis. All of the tumours of the eye identified in these reports involved superficial parts of the eye (cornea and conjunctive); no turnout of the interior eye was reported.

Studies of the effect of UVR on turnout induction in other organs (lymphoma in mice) are few and were not designed to determine this effect (Ebbesen, 1981; Joshi *et al.*, 1986). [The Working Group considered that the data were inadequate for evaluation and that data on survival among treated and control groups, sample selection and analysis of data were limited.]

3.7.2 *Dose and effect*

Quantitative information is available mainly on the induction of squamous-cell carcinoma in mice. In most of the experiments, exposure was regular, several times per week or every day, until tumours developed. The daily doses of UVR required for skin tumorigenesis are usually well below those present outdoors in the environment, and most experiments have been conducted with UVB doses lower than those required to elicit acute reactions in mouse skin (erythema or oedema). In one experiment in hairless mice, with a UVB dose 33 times lower than that required for acute reactions, 71 by of the skin tumours were squamous cell carcinomas (de Gruijl *et al.,* 1983). The effectiveness of UVB radiation is increased at lower dose rates (Kelfkens *et al.,* 1991b).

The higher the dose given, the less time it takes for tumours to appear. In most experiments. the time required for 50% of mice to develop tumours ranged between a few months and one year. By maximizing the exposure regimen in hairless mice (escalating doses of UVB radiation), the time could be reduced to 18 days (Willis *et al.,* 1981). In a few experiments, in both mice and rats, skin tumours resulted from a single exposure to UVB radiation (Hsu *et al.,* 1975; Strickland *et al.,* 1979); in mice, this required a dose that first caused skin ulceration: hairless mice, 60 kJ/m^2 (Hsu *et al.,* 1975); Sencar mice, 29 kJ/m^2 (Strickland, 1982).

Quantitative dose-effect relationships have been derived for mice exposed regularly (usually daily) to UVR. The median time to first tumour, t_m, has been used as a measure of the effect and is related to dose level. Dose-effect relationships of the form

$$t_m = c\, D^{-r},$$

where *c* is a constant incorporating the susceptibility of the strain of mice as well as the effectiveness of the radiation spectrum, *D* is the daily dose of radiation and *r* is a numerical exponent giving the steepness of the relationship, have been proposed by several authors. Estimates of *r* vary from 0.2 (Sterenborg *et al.,* 1988) for small tumours of the skin induced by UVC radiation in hairless mice, to 0.5 (Blum *et al.,* 1959) for large tumours on the ears of haired mice induced by broad-spectrum UVR and to 0.6 (de Gruijl *et al.,* 1983) for small tumours induced by broad-band UVB in hairless mice. Figure 11 (p. 145) illustrates the shape of this dose-response relationship for $r = 0.6$; other forms of the relationship have been proposed (Forbes *et al.,* 1982). All of them provide adequate descriptions of the dose-response within the range of the available data, although extrapolations outside this range differ substantially.

3.7.3 *Dose delivery*

The tumorigenic effect of UVR depends not only on the dose but also on the temporal pattern of exposure. In general, the effectiveness of treatment increases with the number of fractions of the dose per week (Forbes *et al.,* 1981), for both daily and accumulated doses. A daily dose administered over 12 h is more effective than the same daily dose administered in 1 h (Kelfkens *et al,* 199lb). The same weekly dose is more effective when given over three to five days than if given in one day (Forbes *et al.,* 1981).

3.7.4 *Action spectra*

Ideally, the carcinogenic effectiveness of UVR can be expressed as a continuous function of wavelength. That function, called the action spectrum for UV carcinogenesis, is not yet completely delineated. Freeman (1978) made an early attempt to determine this spectrum and found that it was limited to a few narrow bands around the wavelengths 290, 300, 310 and 320 nm. Narrow-band monochromatic sources are difficult to achieve.

Since that time, various action spectra have been proposed to weight the spectral irradiance of a source. Forbes *et al.* (1982) and Cole *et al.* (1986) determined dose-effect relationships similar to that shown in Figure 11 for many different UV spectra. By weighting these lamp spectra with various existing action spectra for photobiological effects, effective doses were computed for each experiment. In this way, the investigators tried to align the results from the experiments with different UV spectra into one dose-effect relationship. One of the action spectra (MEE48), originally determined for the induction of oedema in mice 48 h after exposure to UVR and which is similar to the human erythema action spectrum, fitted well. The authors concluded that the mouse oedema spectrum was also appropriate for describing skin cancer induction (Cole *et al.,* 1986).

Sterenborg and van der Leun (1987) attempted to determine an action spectrum directly from observations on UV carcinogenesis. They exposed hairless albino mice to seven different lamp spectra under otherwise identical circumstances. The lamp spectra overlapped to some extent, and the action spectrum was derived by mathematical fitting. The analysis yielded an action spectrum for the wavelength range 250-360 nm. Slaper (1987) added observations in the UVA region and extended the action spectrum throughout the UVA range (see Fig. 10, p. 141).

The action spectrum shown in Figure 10 is for albino hairless Skh-hr 1 mice with an end-point of 1.0-mm tumours. Although different end-points may yield different action

spectra, this curve shows good agreement in the UVB range with the MEE48 spectrum and also with the observations of Freeman (1978) for wavelengths 300, 310 and 320 nm. [The Working Group noted that the action spectrum for UV carcinogenesis in the wavelength range 300-320 nm may be considered a good approximation.] The different shapes of Figure 10 and MEE48 in the UVC reflect a scarcity of data in this wavelength range. [The Working Group noted that the action spectrum for carcinogenesis by UVC is still highly uncertain.] The MEE48 left widely different options open for the action spectrum of long-wavelength UVA: the effectiveness in the wavelength range 330-400 nm could be either zero or as high as 0.0002 (Cole *et al.,* 1986). More recent data on the carcinogenesis of UVA, used to construct the curve in Figure 10, indicate a mean effectiveness of 0.00015 in this range (Slaper, 1987). [The Working Group noted that this value for the carcinogenic effectiveness for UVA may be regarded as an estimate of the order of magnitude.]

3.7.5 *Pigmentation*

Pigment was reported to be protective against tumours arising from the conjunctive in cattle (Anderson, 1963).

Freeman and Knox (1964) also examined the influence of pigmentation in a group of 78 rats composed of 66 pigmented rats of various strains (black, black and white, grey-brown, grey and white) and 12 albinos. Under the same irradiation regimen, the pigmented rats developed tumours in 73% of eyes and the albinos in only 8%. The tumour yield was consistently higher in the pigmented strains than in the albinos. In nine pigmented and 10 albino hamsters exposed for one year, 50% of pigmented animals and 25% of nonpigmented animals developed eye tumours.

Davies and Forbes (1988) exposed closely related albino hairless Skh-hr 1 mice and pigmented hairless Skh-hr 2 mice to broadband UVR from a filtered xenon arc lamp. Especially at high doses, the latent period until 50% of animals had first tumours was longer in Skh-hr 2 mice.

van Weelden *el al.* (1990a) derived mice of different degrees of pigmentation—'browns' end 'blacks'—by selective breeding from Skh-hr 2 stock and exposed 24 albinos (Skh-hr 1) (van Weelden *et al.,* 1988), 16 'browns' and eight 'blacks' to UVA radiation. The brown mice were less susceptible to skin tumours than the albinos, but the more heavily pigmented blacks were as susceptible as the albinos: the median times for tumour induction were 265 days for albinos, 267 days for blacks and 375 days for browns (van Weelden *et al.,* 1990a).

3.8 Administration with known chemical carcinogens

Since UVR alone produces tumours, it is a 'complete' carcinogen and may thus be involved in cocarcinogenicity. Several investigators have attempted to determine whether UVR has tumour 'initiating' and/or tumour 'promoting' activity when tested in a traditional two-stage protocol. For the purposes of this monograph, a 'tumour initiators' is defined as an agent that, at a stated amount and upon administration once, is incapable of causing tumours in the population of animals unless the skin is subsequently treated with a 'tumour promoter'. A 'tumour promoter' is defined as an agent that, under stated conditions is incapable of causing tumours unless the skin was previously treated with a 'tumour initiator'. The test systems used embody a number of variables, not all of which were necessarily

considered by the authors. For example, UVR has also been shown to influence the immune system, and polycyclic aromatic hydrocarbons are photochemically active.

3.8.1 *Administration with polycyclic aromatic hydrocarbons*

Most of the studies summarized below demonstrate that UVR has a cocarcinogenic action with other carcinogens. Other reports provide additional information on cocarcinogenesis, on photolysis ot polycyclic aromatic hydrocarbons and on other interference with chemical carcinogenesis (Clark, 1964; Ito, 1966; Santamaria *et al.*, 1966; Davies *et al.*, 1972 [abstract]; Shabad & Litvinova, 1972; Stenback & Shubik, 1973; Stenback, 1975b; Roberts & Daynes, 1980; Gensler & Welch, 1992).

(a) *3,4-Benzo[a]pyrene*

Groups of 18 female SPF (specific pathogen-free) BALB/c mice, six weeks of age, received 30-min exposures on the shaved dorsal skin to UVB from a Westinghouse FS40 sunlamp (280-320 nm) five times a week for 13 weeks (total close, 7.0 x 105 J/m^2) or no UVB exposure followed one week later by twice weekly applications of 0, 0.1 or 1.0 mg 3,4-benzo[a]pyrene in acetone on the shaved ventral skin for 20 (acetone only), 20 or 10 weeks, respectively. Pre-exposure to UVB enhanced tumour growth in the high-dose group: 29 tumours (of 20 examined histologically, 90% were squamous-cell carcinomas and 10% undifferentiated sarcomas) in the UVB-pretreated group compared to two (squamous-cell carcinomas) in the non-irradiated 3,4-benzo[a]pyrene-treated animals 18 weeks after the first treatment with 3,4-benzo[a]pyrene. No such effect was seen in the low-dose group (Gensler & Bowden, 1987; Gensler, 1988a).

(b) *7, 12-Dimethylbenz[a]anthracene*

In an attempt to assess the promoting effects of UVR, groups of 15-31 male and 16-22 female Swiss albino mice, 11-18 weeks of age, received a single application of two drops (0.1 ml) of 0 or 0.5% 7,12-dimethylbenz[a]anthracene (DMBA) in acetone on the posterior half of the dorsal skin, followed 14 days later by exposures to UVB (280-320 nm; high-pressure Hanovia hot quartz contact lamp) twice a week for 67 weeks (total dose, 13.33 x 107 ergs/cm^2 [133 kJ/m^2]) or no exposure. At the end of the UVB treatment, 16/31 mice treated with DMBA and UVB had developed 19 skin tumours, compared to 4/41 and 0/47, respectively, among mice treated with DMBA alone and UVB alone. Exposure to UVB also enhanced the multiplicity and degree of malignancy of DMBA-induced tumours (Epstein & Epstein, 1962).

Groups of 26-42 male and female outbred hairless mice, 7-12 weeks old, received a single application of two drops (0.1 ml) of 0 or 0.5% DMBA in acetone, followed six weeks later by exposures to UVB (280-320 nm; high-pressure Hanovia hot quartz contact lamp) three times a week for 29 weeks (total dose, 15.34 x 107 ergs/cm^2 [153 kJ/m^2]) or no exposure. All animals were observed for 63 weeks. UVB exposure produced skin tumours in 22/26 animals, and DMBA treatment alone in 3/41; acetone alone produce no skin tumour. Exposure to UVB following DMBA treatment enhanced carcinogenicity with regard to appearance time (first tumour observed at 14 weeks compared to 30 in the group treated with DMBA alone and 20 in that given UVB alone), multiplicity at 58 weeks after DMBA treatment (40 in 24 animals compared to 22 in 26 animals treated with UVB alone

and 3 in 41 animals treated with DMBA alone) and degree of malignancy. Two 'melanomas' appeared in the group receiving the combined treatment (Epstein, 1965).

Groups of 18-46 outbred hairless pigmented mice [sex unspecified], 8-11 weeks old, received a single application of 0.05 ml of 0.4% DMBA (0.2 ma) in acetone or no DMBA. After 13 months, mice treated with DMBA had developed pigmented lesions ('blue naevi') in the treated areas. For the following seven months, mice received UVB (280-320 nm; high-pressure Hanovia hot quartz contact lamp) three times a week or no UVB treatment. Exposure to UVB following DMBA treatment enhanced the growth of naevi into malignant-appearing pigmented tumours ('melanomas'): 5/18 *versus* 0/41 in the group treated with DMBA alone and 0/39 in the group treated with UVB alone (Epstein *et al.,* 1967). [The Working Group noted the limited reporting on metastases.]

A group of 56 B6D2F_1/J mice [sex unspecified], six weeks of age, was irradiated with UVB (280-340 nm; Westinghouse FS40 sunlamp) dorsally for 30 min per day on five daysper week (Roberts & Daynes, 1980) for 11.5 weeks (total dose, 6.2 x 105 J/m^2). A control group of 41 mice received no irradiation. Both groups subsequently received a single application of 100 µg DMBA in 0.1 ml acetone on the shaved ventral skin, followed four days later by applications of 5 µg 12-*O*-tetradecanoylphorbol 13-acetate (TPA) three times a week for 32 weeks. Tumour yield was significantly decreased at 32 weeks (2.2 *versus* 4.8 tumours/mouse) in the pre-irradiated mice (Gensler, 1988b).

Groups of 20-24 female hairless Skh-hr 2 mice, six to eight weeks old, received a single application of 0 or 0.5 % DMBA in acetone on the dorsal skin. Two weeks later, the animals were irradiated with UVB (290-320 nm; Westinghouse FS40-T12 sunlamp), UVA (320-400 nm; GTE-Sylvania fluorescent black light tubes) or a combination of UVA plus UVB three times a week for 30 weeks or were not irradiated, and were observed for 12 months. All mice receiving DMBA treatment developed multiple 'blue naevi'; virtually none of the untreated mice or mice that received UVR treatment only showed this effect. Irradiation of DMBA-treated animals induced a higher incidence of papillomas (70-100%), squamous-cell carcinomas (30-80%), melanomas (25-33%) and lymphomas (21-50%), than exposure to UVA alone (0-32% papillomas, 0-47% squamous-cell carcinomas, no melanoma and no lymphoma) or to DMBA alone (90, 25, 0 and 5% of these tumours, respectively). The authors also examined selected lesions induced by DMBA alone or by DMBA with UVR for the presence of H- or N-*ras* mutations. Mutations at codon 61 in N-*ras* were present in three (two induced by DMBA plus UVR, one by DMBA alone) out of eight of the early pigmented lesions examined and in one out of three of the malignant melanomas examined (induced by DMBA plus UVR); no H-*ras* mutation was observed (Husain *et al.,* 1991). [The Working Group noted that lesions were not induced by UVR alone.]

3.8.2 *Administration with other agents with promoting activity*

These studies were designed to evaluate the action of UVR as a tumour initiator.

(a) *Croton oil*

Groups of 15-53 male and 9-30 female random-bred hairless mice, 9-12 weeks old, received a single exposure to UVB (280-320 nm; high-pressure Hanovia hot quartz contact lamp) for 30 s (1.3 x 107 ergs/cm3 [13 kJ/m^2]) or no exposure, followed two weeks later by

applications to the dorsal skin of 0 or 0.1 ml croton oil in acetone twice a week for 18 months. Neither UVB exposure nor croton oil alone produced any skin tumour over the course of the study. The group of 79 mice that received both UVB exposure and croton oil had eight persistent skin tumours (one per mouse) (Epstein & Roth, 1968).

Groups of 30 female Swiss mice, eight weeks old, received UVB once (5.5 x 107 ergs/cm^2 [55 kJ/m^2]) from Westinghouse FS40T12 lamps or croton oil (0.02 ml of a 2.5% solution, twice a week for 30 weeks); a group of 60 mice received UVB followed after 10 days by croton oil for life. UVB alone produced no tumour; croton oil alone produced regressing tumours, and the combination produced 11 tumours (four papillomas, four fibromas and three regressing tumours) in seven mice (Stenbäck, 1975c).

Groups of 40 male haired mice (random-bred 'Hall' strain), 18 weeks of age, were clipped and exposed once to UVC (medium-pressure mercury discharge lamp). One group received no further treatment; the other received one application of croton oil one day before irradiation and, beginning two weeks later, received applications of 0.25 ml croton oil (0.5% solution) once a week for 30 weeks. By 35 weeks, the groups had 20 and 23 survivors, with 0 and 12 skin tumours, respectively (Pound, 1970).

(b) *12-O-Tetradecanoylphor1bol 13-acetate*

Six groups of 25 eight-week-old female C3H/HeNCr(MTV$^-$) mice were irradiated with UVB (Westinghouse FS40 sunlamps) on the shaved dorsum for 30 min, five times a week for two weeks (total dose, 1.44 x 105 J/m^2), followed two weeks later by 'promotion' with applications of 0 or 5 μg TPA in acetone twice a week. Ventral irradiation for 30 min, three times a week for 12 weeks (total dose, 4.54 x 105 J/m^2) (to produce a 'systemic' effect) was begun two weeks after completion of dorsal initiation. At 70 weeks, UVB exposure of the dorsum alone had produced no tumour, and dorsal applications of TPA alone had produced a 5% incidence of tumours. The combination of these treatments produced a 41% tumour incidence. Ventral irradiation of animals that had received TPA only produced a 33% incidence, and ventral irradiation of mice that had received both UVB and TPA produced a 100% incidence. The authors suggested that these findings reflect a systemic effect—possibly suppression of immune surveillance or a biochemical influence on the epidermal growth regulatory system (Strickland *et al.,* 1985).

(c) *Benzoyl peroxide*

Benzoyl peroxide is considered to be a prototype promoter of two-stage chemical carcinogenesis in the skin (Slaga *et al.,* 1981). The studies summarized below were motivated, however, by concerns about the safety of using this compound for treating acne vulgaris.

Groups of Uscd (Hr) stock hairless albino mice (total, 148) [sex unspecified], three to four months old, were exposed on the posterior half of the back to UVR (Hanovia hot quartz contact lamp emitting primarily UVB; 270 mJ/cm^2 [2.7 kJ/m^2]) three times a week for eight weeks. Four weeks later, the mice were divided into four groups. The final skin tumour incidences at the irradiated sites were: 38% in the group that received applications of 0.1 ml of a 0.1% solution of croton oil in acetone on the back skin five times a week for the duration of the experiment (62 weeks); 5% in the group that received applications of acetone

alone; 8% in mice that received applications of the benzoyl peroxide base; and 8% in those that received applications of a 5% lotion of benzoyl peroxide in water five times a week for the duration of the study (Epstein, 1988).

Five groups of Oslo hairless mice (16 males and 16 females) were irradiated under Philips HP3114 sunlamps (mostly UVB) twice a week for 52 weeks (total dose, 26.5 J/cm^2 [265 kJ/m^2]). The mice were treated before or after each exposure with 5% benzoyl peroxide in gel, with the gel alone or with no chemical. Throughout the study, the groups were indistinguishable in terms of the proportion with one of more tumours (median latent period, approximately 40 weeks) and of the total number of turnouts per survivor (approximately 1.5 at 40 weeks and approximately 4 at 48 weeks). Thus, benzoyl peroxide did not enhance photocarcinogenesis. The study also included several groups of SENCAR mice treated topically with DMBA once (51.2 µg) or with vehicle followed by benzoyl peroxide twice a week. Benzoyl peroxide reduced the number of DMBA-induced tumours (Iversen, 1988). Two unresolved concerns were raised by the author: Firstly, the fact that benzoyl peroxide reduced the tumorigenicity of DMBA was contrary to the author's previous experience (Iversen, 1986) and to that of several others; secondly, the UVR dose used in this study was lower (total dose, 265 kJ/m^2) than that used in the 1986 study (total close, 480 kJ/m^2), but the tumour response was significantly greater.

(d) *Methyl ethyl ketone peroxide*

A postulated mechanism for tumour promotion involves the generation of free radicals, possibly with reactive oxygen species, leading to enhanced lipid peroxidation and DNA damage and/or cell phenotype. A study was therefore designed to test whether methyl ethyl ketone peroxide (MEKP), which is known to produce lipid-peroxidizing activity *in vivo*, acts as a tumour promotor in skin 'initiated' by UVR. Furthermore, since glutathione has been shown to be a major endogenous reducing agent which protects against lipid peroxidation, the study also tested diethyl maleate (DEM), which is known to deplete the intracellular level of glutathione in mouse skin.

Groups of 24 male and female hairless albino mice (14-16 weeks old) were irradiated with UVB (280-320 nm; Westinghouse FS40 fluorescent sunlamps; 2054 J/m^2 daily) for 18 weeks. Three weeks later, topical application of MEKP (20 µl containing 0 or 10 µg MEKP) was begun and continued twice a week for 25 weeks. Other groups received DEM (0 or 1 µg in dibutyl phthalate) 1 h before each MEKP application. Otherwise identical control groups received either the chemical treatments or UVB alone. At 46 weeks, the groups that did not receive UVB irradiation had at most two tumours on two mice (among 21 survivors in mice exposed to MEKP plus DEM). Exposure to UVB produced five turnouts in four mice exposed to the solvent, out of 19 survivors; 11 tumours in eight mice exposed to MEKP, out of 21 survivors; and 18 tumours in nine mice exposed to MEKP plus DEM, out of 16 survivors. Using tumour onset rate analysis (Peso *et al.,* 1980), the overall effect of MEKP was statistically significant. Tumour enhancement by MEKP was greater in the presence of DEM (Logani *et al.,* 1984).

3.9 Interaction with immunosuppressive agents

Investigations have been reported on agents known to influence immunological responses in humans and on agents chosen to test some aspect of immunological response in mice. [The Working Group noted that in most cases the effect on the immune system of the animas was not evaluated directly; these agents have effects other than immunosuppression, which may explain their interaction with photocarcinogenesis.]

Three groups of 12 male Skh-Hrl hairless mice, eight weeks of age, were irradiated with 280-320 nm UVB (Westinghouse FS40T12 sunlamps) on five days per week for 30 weeks at daily doses of 470 J/m^2. Two weeks after the first UVB exposure, one group received subcutaneous injections of 0.1 ml *anti-mouse lymphocytic serum* twice a week for 20 weeks; a second received intraperitoneal injections of 12 mg/kg *bw6-mercaptopurine* (Purinethol) five times a week for 20 weeks; and a third received intraperitoneal injections of 0.1 ml isotonic saline five times a week for 20 weeks. Treatment with anti-mouse lymphocytic serum resulted in an earlier appearance and a greater numbers of tumours than did treatment with saline; in contrast, 6-mercaptopurine appeared to delay the appearance of tumours (Nathanson *et al.,* 1976).

Groups of 24-28 female albino HRA/Skh-1 hairless mice, 21-35 weeks of age, were irradiated with UVR (UVB from an Oliphant FL40SE tube and UVA from six Sylvania 40BL tubes) to simulate the UVR portion of terrestrial sunlight on five days per week for 10 weeks to achieve a MED. At the same time, the animals received intraperitoneal injections of 15 mg/kg bw *azathioprine* in 0.1 ml glycine buffer, 10.6 mg/kg bw *cyclophosphamide* in 0.1 ml glycine buffer or 0.1 ml vehicle alone. At day 200, mice receiving UV irradiation alone had a tumour incidence of 77%; those also receiving azathioprine had an incidence of 96% (marginally significant enhancement of tumour growth); and those receiving cyclophosphamide had an incidence of 85% (nonsignificant increase) (Reeve *et al.,* 1985).

Groups of 15 female albino HRS/J hairless hr/hr mice, eight weeks old, were irradiated with UVB (280-320 nm; Westinghouse FS40 sunlamps) on five days a week for 24 weeks; further groups also received injections of 4 or 8 mg/kg bw *azathioprine* or 10 or 25 mg/kg bw *cyclosporine* three times a week. The mean latent period for tumour development was 16 weeks in the group receiving UV irradiation only and 12-13 weeks in the groups also receiving azathioprine or cyclosporine, indicating enhancement of photocarcinogenesis by both drugs (Nelson *et al.,* 1987).

Groups of female C3H/HeN(MTV$^-$) mice [initial numbers unspecified], four to six weeks of age, received grafts of fragments of an antigenic ('regressor') tumour (fibrosarcoma) previously induced in a host animal by UVB. Some animals received no further treatment; other groups received UVB irradiation (Westinghouse FS40; 5 kJ/m^2 per day on five days a week for four to six weeks), subcutaneous injections of 25 or 75 mg/kg bw *cyclosporine* once a day on eight consecutive days, or injections of 20 mg/kg bw *cyclophosphamide* 1, 3, 6, 9 and 13 days after tumour challenge. Tumours grew progressively in the groups treated with UVB or cyclosporine, but not in the groups receiving no further treatment or cyclophosphamide (Servilla *et al.,* 1987).

Groups of six female albino HRA/Skh-1 hairless mice, 10-12 weeks of age, were irradiated with UVA plus UVB (one Oliphant FL40SE tube and three Sylvania F4/350 BL tubes)

on five days a week until death (about 35 weeks). During that time, they were also injected intraperitoneally with 15 mg/kg bw *azathioprine*, 20 mg/kg bw *prednisolone* or 15 mg/kg bw *cyclophosphamide* in 0.1 ml saline or given 60 mg/kg bw *cyclosporine* in 0.1 ml peanut oil by gavage or 0.1 ml vehicle alone. Azathioprine, cyclophosphamide and cyclosporine all significantly enhanced photocarcinogenesis with regard to median latent periods and tumour multiplicity. Prednisolone did not enhance this effect, nor did it interfere with the enhancement by other drugs when given in combination with them (Kelly *et al.*, 1987).

Groups of 15-32 female albino Skh-hr 1 hairless mice, 10-12 weeks of age, were irradiated with UVA plus UVB (250-700 nm; one Oliphant FL40SE tube, three Sylvania F40/350 BL tubes and two True-Lite [Duro-Test Corp] tubes) on five days per week for 12 weeks. Two weeks after the first irradiation, mice received intraperitoneal injections on five days a week of 15 mg/kg bw *azathioprine* or *6-mercaptoptlrine* in 0.1 ml saline or 0.1 ml vehicle alone. Both compounds significantly enhanced skin photocarcinogenesis with regard to median latent period, proportion of malignant:benign growths and tumour multiplicity (Kelly *et al.*, 1989).

3.10 Molecular genetics of animal skin tumours induced by ultraviolet radiation

Three skin papillomas and three skin carcinomas produced in female SENCAR mice after a single exposure to UVB (280-315 nm; Westinghouse FS20; 70 kJ/m^2) were examined for ras gene alterations. A five- to 10-fold increase in cHa-*ras* RNA gene expression associated with the gene amplification was found in papillomas and carcinomas, while DNA from carcinomas, but not from papillomas, induced foci in the NIH-3T3 cell transfection assay (Husain *et al*., 1990).

CONTINUED

4. Other Relevant Data

4.1 Transmission and absorption in biological tissues

UVR may be transmitted, reflected, scattered or absorbed by chromophores in any layer of tissue, such as the skin and eye. Absorption is strongly related to wavelength, as it depends on the properties of the responsible chromophore(s). Accordingly, transmission is also wavelength-dependent. Transmission and other optical properties are affected by changes in the structure of the tissue and, especially in the case of the lens of the eye, by ageing.

Absorption of radiation by a tissue chromophore is a prerequisite for any photochemical or photobiological effect; however, absorption does not necessarily have a biological consequence.

4 .1.1 *Epidermis*

Since UVR-induced skin cancer is an epidermal phenomenon, this section focuses on epidermis and excludes the dermis.

The epidermis, a tissue with a high replication rate, can be divided functionally into two: an inner, living part (60-160-µm thick in humans) of cells at various stages of differentiation and the outermost, non-living, terminally differentiated stratum corneum (8-15-µm thick in humans). The dividing cell population is located in the innermost basal layer of the living epidermis. Optical properties have usually been studied using isolated strateum corneum or whole epidermis. Absorption and scattering of UVR by the stratum corneum afford some protection to the living part of the epidermis from UVR exposure.

Human and mouse epidermis have important structural differences. The living part and the stratum corneum of human epidermis have about 10 cell layers each. In mice, the living part has two to three cell layers and the stratum cornea one to two cell layers. The interphase of human epidermis and dermis is highly undulated (i.e., epidermal thickness varies), whereas in the mouse it is flat.

Skin contains sebaceous glands which secrete lipid-containing sebum, which forms a film on the stratum corneum.

(a) *Humans*

The optical properties of human skin have been reviewed (Anderson & Parrish, 1981, 1982).

Everett *et al.* (1966) used a variety of methods to obtain whole epidermal and stratum corneum preparations of human skin. Transmission characteristics (from 240 to 700 nm) were measured using a recording spectrophotometer *via* an integrating sphere which permits the measurement of forward scattered radiation. Transmission values of whole epidermis in

white skin ranged from 1% at 250 nm to 44% at 320 nm, while transmission at 400 nm was about 50%.

Kaidbey *et al.* (1979) compared the optical properties (250-400 nm) of whole epidermis and stratum corneum from black and white skins. In general, the absorption spectra from the stratum corneum were similar in shape and magnitude; however, the absorption spectra for whole epidermis were clearly different: At about 300 nm, the absorbance (accounting for scattering) of black epidermis was twice that of white epidermis.

Anderson and Parrish (1981, 1982) presented data which show that epidermal transmission between 260 and 290 nm will be overestimated if no correction is made for tissue fluorescence (330-360 nm). This is most evident at about 280 nm and is consistent with tryptophan or tyrosine fluorescence.

Bruls *et al.* (1984a) measured transmission in whole human epidermis and stratum corneum of UVR between 248 and 546 nm, using a solar blind detector which corrects for fluorescence, and found results different from those of Everett, in particular, that UVC transmission was one to two magnitudes lower. The transmission spectra of whole epidermis and stratum corneum showed a similar general shape but with differences in minima and magnitude. The minimum for epidermis was 265 nm and that for stratum corneum was 275 nm, presumably reflecting different chromophores in those tissues. At 254 nm, transmission in stratum corneum was about two orders of magnitude greater than that in whole epidermis. At about 300 nm, this difference was only one order of magnitude. The transmission in stratum corneum from previously sun-exposed skin was about one order of magnitude less than that in unexposed epidermis at 254 nm. The difference was less at wavelengths > 290 nm. The minimal transmission in stratum corneum from previously sun-exposed skin was shifted from 275 to 265 nm. The authors also showed that the relationship between tissue thickness and transmission of UVR and visible light (log scale) is linear.

Bruls *et al.* (1984b) studied the relationship between the MED of UVB (filtered mercury arc) and UVC (germicidal lamp) and epidermal transmission. A clear linear (log-log) relationship was demonstrated; the MED increased with decreased transmission. Repeated exposure to UVB resulted in higher MEDs of UVB and UVC and decreased transmission of UVB (only epidermis measured) and UVC (epidermis and stratum corneum measured).

Beadle and Burton (1981) extracted skin lipids from human scalps and measured their transmission spectra in hexane. They estimated that lipid concentrations normally present on the skin surface of the forehead would reduce transmission at 300 nm by about 10%.

(b) *Experimental systems*

No data are available on transmission in the stratum corneum of mice. Sterenborg and van der Leun (1988) measured transmission of 246-365 nm in Skh-hr 1 mouse epidermis *in vitro*. Minimal transmission (about 2%) was observed at 254 nm and 270 nm, 10% was transmitted at 290 nm, 50% at 313 mn and 70% at 365 nm. Agin *et al.* (1981a) studied changes in optical properties of the epidermis of six to eight Skh-1 albino and Skh-2 pigmented (ears and tails) hairless mice irradiated dorsally with a single, 125-h exposure to a UVA source (GE F8T5-BL) with and without a 3-mm glass filter. When unfiltered, 1.4% of the radiation was < 320 nm and when filtered, 0.12% was < 320 nm. The mid-back

(whole epidermis) was examined by forward scattering absorption spectroscopy (250-400 nm) at 48 h, 96 h, nine days and 23 days. With the filtered source, there was an increase in absorbance across the spectrum at 48 h, and the absorption spectrum was similar to that of control skin. Transmission returned to the control baseline by 23 days. With the unfiltered source, there was a smaller increase towards baseline absorbance at 48 h. With time, there was a general decrease in absorbance, except at 250-280 nm at which there was an increase at nine and 23 days. At 23 days, the spectrum had not returned to baseline level, despite a normal histological appearance.

de Gruijl and van der Leun (1982a) studied the effect of repeated exposure to UVR on epidermal transmission in Skh-hr 1 hairless albino mice. Groups of 11-40 mice were exposed to daily doses of UVR ranging from 0.11 to 1.9 kJ/m^2 from Westinghouse FS-40 sunlamps. Transmission measurements corrected for fluorescence of the epidermis were made at 313, 302 and 297 nm. After six weeks' exposure, the higher daily doses resulted in decreased transmission at all wavelengths. The optical density (the negative logarithm of transmission) ratios for the three wavelengths were fairly constant with each dose. There was a simple linear relationship between duration of treatment, increased optical density at 297 nm and epidermal thickness, measured microscopically from frozen sections, which indicates that increased optical density is a result of UVR-induced epidermal hyperplasia. These data show that UVR-induced changes in epidermal transmission may modify the UVR dose-response relationship for skin cancer.

(c) *Epidermal chromophores*

The influence of chromophores on the optical properties of the epidermis has been reviewed by Anderson and Parrish (1981). The main chromophores are urocanic acid (λ_{max}, 277 nm at pH 4.5), DNA (λ_{max}, 260 nm at pH 4.5), the aromatic amino acids tryptophan (λ_{max}, 280 nm at pH 7) and tyrosine (λ_{max}, 275 nm at pH 7), and melanins (Morrison, 1985).

Urocanic acid is the deamination product of histidine and is present in human and guinea-pig epidermis (mainly stratum corneum) at about 35 μg/cm^2 dry weight. It exists in two isomers, *trans* (E) and *cis* (Z); the trans-isomer is converted to the *cis*-isomer upon UV irradiation. The absorption spectra of the two isomers are virtually superimposable, but the extinction coefficient of the *cis* isomer at λ_{max} is 20% lower (Morrison, 1985). Norval *et al*. (1988) quantified urocanic acid isomers in mouse (C3Hf Bu/Kam) skin during development and after exposure to UVB radiation. Fetal dorsal mouse skin had a low total urocanic acid content, which increased in neonatal and older animals. Exposure to UVR increased the proportion of the *cis*-isomer within 16 h from 4.7% in nonirradiated mice to 31%, and this was maintained for days (16% after seven days). The photostationary state for in-vivo isomerization in guinea-pig skin is 45% *cis*-/55% trans-isomer (Baden & Pathak, 1967).

DNA is not present to any extent in the stratum corneum of guinea-pigs (Suzuki *et al*., 1977). Bruls *et al*. (1984a) attributed the differences in transmission minima between whole epidermis (265 nm) and stratum corneum (275 nm) in humans to the lack of DNA. Absorption by protein occurs throughout the epidermis.

Melanins are stable protein polymers packaged in melanosomes, produced by melanocytes and transferred to keratinocytes. Melanins absorb broadly over the UV and visible spectrum although they are not neutral density filters of the skin. For example, 3,4-dihydroxyphenylalanine (dopa)-melanin shows a steady decline in optical density

between 210 and 340 nm (Anderson & Parrish, 1981). There is no significant racial difference in the number of melanocytes/unit area of a given body site (Szabó *et al.,* 1972), so that differences in the transmission properties of black and white skin are believed to be due to differences in melanin content and in the packaging and distribution of melanosomes in the epidermis (Kaidbey *et al.,* 1979).

(b) *Enhancement of epidermal penetration of ultraviolet radiation*

Prolonged exposure of skin to water increases sensitivity to UVB. This effect is thought to be due to the removal of UVR-absorbing compounds, especially urocanic acid, from the stratum corneum (Anderson & Parrish, 1981).

Spectral remittance at 300-400 nm has been measured in normal and psoriatic white skin after the application of mineral oil. No effect was observed in normal skin, but remittance in psoriatic skin was reduced within seconds after application of oil, implying greater transmission (Anderson & Parrish, 1982). A similar enhancement of transmission was proposed to explain the observation that topically applied arachis oil enhances tumorigenesis by solar-simulated radiation in hairless albino mouse skin (Gibbs *et al.,* 1985).

4.1.2 *Eye*

(a) Humans

Boettner and Wolter (1962) measured transmission of direct and forward scattering UVR (220-400 nm) in the cornea, aqueous humour, lens and vitreous humour from nine freshly enucleated normal eyes. There was no corneal transmission of < 300 nm, beyond which the transmission spectrum showed a very steep increase to about 80% transmission at 380 nm (the curve was almost vertical between 300 and 320 nm). Aqueous humour transmitted > 220 nm, with a steep rise to 90% transmission at 400 nm and no evidence of scattering. In a young (4.5-year-old) lens, transmission started at 300 nm with a peak at 320 nm, declining sharply to no measurable transmission between 370 and 390 nm; thereafter, it showed a steep increase. A similar but slower pattern was reported for two older lenses (53 and 75 years old), with greater light scattering. Transmission in the vitreous humour began at 300 nm with a steep increase to 80% transmission at 350 nm. Lerman (1988) showed that transmission of UV at 300-400 nm in normal human lenses decreases with age between three days and 82 years. A review by Sliney (1986) stated that 1% of incident radiant energy in the 300-315 nm range reaches the human retina early in life.

(b) *Experimental systems*

Kinsey (1948) measured transmission of direct UVR [no mention of instrumentation to detect scattering] in the corneal epithelium, whole cornea, aqueous humour, lens and vitreous humour of young adult albino rabbits. The cornea, aqueous and vitreous humor absorbed virtually all radiation at < 300 nm; the lens absorbed > 90% radiation at wavelengths < 370 nm.

Bachem (1956) measured absorption of UVR at 293-435 nm by the lens and cornea from rabbit eyes. Few technical details were given, but the author indicated that scattering was taken into account. The cornea absorbed all radiation at 293 nm, and the lens absorbed

all radiation < 334 nm. Calculation of absorption by the lens *in situ* gave a maximum at 365 nm, with little or no absorption at > 400 and < 300 nm.

Ringvold (1980) studied the absorption of UVR at 200-330 nm by cornea from young adult albino rabbits, rats, guinea-pigs and domestic cats. In contrast to the results of other studies, the cornea did not completely absorb wavelengths < 300 nm; depending on the species, absorption at 300 nm ranged from about 30 to 80%. [The Working Group noted that this discrepancy cannot be explained by scattering, as presumed failure to take its effect into account would overestimate absorption.]

4.2 Adverse effects (other than cancer)

This section deals generally with adverse effects of UVR; however, beneficial effects also occur in humans. The vitamin D3 precursor, previtamin D3, is formed in the epidermis and dermis through the photochemical action of UVB (Holick *et al.,* 1980). The total daily requirement of vitamin D3 (cholecalciferol) is supplied in most people by the combination of synthesis in the skin and contribution from dietary sources of animal origin. Older people are at particular risk for developing vitamin D3 deficiency, partly because the capacity for its formation decreases with age (MacLaughlin & Holick, 1985). The sunscreen para-aminobenzoic acid efficiently blocks the photosynthesis of previtamin D3 in the skin (Matsuoka *et al*., 1987). It has been estimated that exposure of the cheeks for 10-15 min in the midday sun in Boston, USA, would be sufficient to provide the daily requirement of vitamin D.

4.2.1 *Epidermis*

(a) *Humans*

The most prominent acute effects of UVR on human skin are erythema ('sunburn') and pigmentation, with cellular and histological changes.

(i) *Erythema and pigmentation* (*sunbum and suntanning*)

Dose-response curves for erythema were constructed for four radiation wavelengths, 254, 280, 300 and 313 nm, by Farr and Diffey (1985); the erythemal response on the back was assessed quantitatively by a reflectance instrument. At 254 nm, erythema was maximal approximately 12 h after irradiation at doses up to about five times the MED. At higher doses, erythema was more persistent, with little change in intensity from about 12 h to at least 48 h after irradiation.

At 313 nm, with doses around the MED, the maximal response was seen 7 h after irradiation; with doses of two to three times the MED, the maximal response occurred at about 4 h. The MED at 254 and 280 nm was substantially lower than that at 300 and 313 nm; however, the slopes of the dose-response curves for erythema with 254 nm and 280 nm radiation were much flatter than those at 300 nm and 313 nm (Farr & Diffey, 1985).

The time-course of UVA erythema following irradiation with a high-intensity UVA source (predominantly 360-400 nm) was found to be biphasic. Erythema, which may be due to heat, was present immediately. It was minimal at about 4 h then increased between 6 and 24 h. The intensity of the early phase was dose-rate dependent, whereas the intensity in the latter phase depended on dose only. The slope of the log dose-erythema response to UVA at 24 h did not differ from that to UVB (Diffey *et al.,* 1987).

A number of variables affect the observation of erythema. including anatomical site, time of observation after irradiation, size of irradiated area, method of recording erythema and season (Diffey, 1982).

The pharmacological changes that may be responsible for erythema have been studied. Plummer *et al.* (1977) examined suction blisters raised on UVB-intlamed human abdominal skin. Bioassayable prostaglandin activity was elevated 6 and 24 h after irradiation, and levels of prostaglandin $F_{2\alpha}$, measured by radioimmunoassay, were elevated at 24 h: levels had returned to normal at 48 h, but erythema persisted. Greaves *et al.* (1978) extended these observations. Following UVC irradiation, arachidonic acid and prostaglandin E_2 and F_2 levels were elevated at 6 hi reached a maximum between 18 and 24 h, when erythema was most intense, but returned to control levels by 48 h, at which time the erythema had subsided. Indomethacin substantially reduced blood flow, with a good correlation between the reduction in visible erythema and prostaglandin E_2 and F^2 activity in irradiated skin. The results are compatible with the view that UVC-induced erythema is mediated by products of arachidonic acid metabolism. Changes in UVB-induced erythema were similar to those with UVC at 24 h, but by 48 h the levels of arachidonic acid and of metabolites had returned to normal, although erythema persisted. Further, although indomethacin suppressed prostaglandin formation, it altered blood flow only slightly, indicating that other factors must play an important role in inflammation following UVB irradiation. Elevated histamine levels have also been observed, but antihistamines have little effect in diminishing erythema (Gilchrest *et al.*, 1981).

Increased pigmentation of the skin by UVR occurs in two distinct phases: immediate pigmentation and delayed tanning (Hawk & Parrish, 1982; Gange, 1987), immediate pigmentation, thought to result from oxidation and redistribution of melanin in the skin, begins during irradiation and is maximal immediately afterwards: it occurs following exposure to UVA and visible light and may fade within minutes or, after greater doses to people with darker skin, may last up to several days. Delayed tanning is induced maximally by exposure to UVB and becomes visible about 72 h after irradiation. It is associated with an increase in the number of melanocytes as well as with increased melanocytic activity, elongated dendrites, increased tyrosinase activity and increased transfer of melanosomes to keratinocytes. Small freckles may be formed, particularly in fair-skinned individuals.

Not all pigmentary changes induced by UVR are localized at the site of irradiation. Experimental exposures to UVB three times a week for eight exposures at the MED increased the number of melanocytes and produced larger, more dendritic melanocytes in both exposed skin and, to a much lesser extent, areas of skin shielded from the radiation. The increase in melanocyte number in both exposed and covered areas was greater in individuals whose melanocyte density was lower prior to exposure than in individuals with a high initial density (Stierner *et al.*, 1989).

The erythemal and tanning responses of human skin are genetically determined. Responses to a first seasonal exposure of about 30 min to the midday sun have been used as part of the basis for a skin type classification for white-skinned people ranging from Celtic to Mediterranean (Morison, 1983a; Pathak *et al.*, 1987):

Skin type I	Always burn, never tan
Skin type II	Usually burn, tan less than average (with difficulty)

Skin type III	Sometimes mild burn, tan about average
Skin type IV	Rarely burn, tan more than average (with ease)

UVA radiation produces immediate changes in melanocytes in white-skinned people. In individuals with type-II skin, multiple pinocytotic vesicles, larger vacuoles, swelling and partial-to-total dissolution of the inner membranes of mitochondria and numerous small vesicles associated with an enlarged Golgi apparatus were seen with doses that did not produce immediate pigment darkening (Beitner & Wennersten, 1983). In those with type-III skin, similar changes occurred but only with doses that produced immediate pigment darkening (Beitner, 1986).

Three Japanese skin types have been described on the basis of personal reactions to the sun (Kawada, 1986). Experimental exposure to monochromatic UVR showed that the MED correlated well with skin type. Immediate tanning occurred but was not related to skin type. After irradiation with the minimal dose that would produce immediate tanning, the tan faded within 3-15 mini after greater exposures, the tan remained longer but never for more than 60 min. The action spectrum for immediate tanning had a maximum at 320 nm and decreased gradually towards 400 nm. New pigment formation (delayed tanning) after exposure to 290 nm and 305 nm radiation began about 65 h after irradiation and increased until it reached a maximum at 124 h (with a dose four times the MED) or 151 h (with a dose eight times the MED). Following a dose three times the MED, some delayed tanning was still evident after two months. The minimal melanogenic dose (producing delayed tanning) was greater than the MED for all Japanese skin types, in contrast to findings in white Caucasians.

Parrish *et al.* (1981) showed that repeated daily exposure to doses of broad-band UVB and UVA lower than the MED lowered the threshold for both erythema and true melanogenesis for several subsequent days; the threshold for melanogenesis was decreased to a greater extent than that for erythema, a separation that was more pronounced for UVA than for UVB radiation.

(ii) *Pigmented naevi*

Exposure to the sun appears to stimulate the occurrence and behaviour of acquired pigmented naevi. Kopf *et al*. (1985) showed, in 80 consecutive patients with dysplastic naevus syndrome, that the concentration of naevi on areas of the thorax protected relatively well from the sun was substantially lower than that on areas exposed to the sun. Augustsson *et al.* (1990) showed that, in melanoma cases as weld as in controls, the concentration of common naevi was higher on the sun-exposed skin of the back than on the protected skin of the buttocks. An Australian study compared naevi excised in summer to those excised in winter in Western Australia. Inflammation, regression, mitotic activity and lymphocytic infiltration were significantly more prevalent in naevi excised in summer than in winter (Holman *et al.,* 1983b; Armstrong *et al.,* 1984). [The Working Group noted that these observations may be confounded by the site of the naevi.]

In an Australian cross-sectional study of 511 people, the presence of palpable naevi on the forearm was associated with female sex, young age, not having southern European grandparents, being born in Australia and intermediate categories of variables indicating sun exposure (Armstrong *et al.,* 1986).

Gallagher *et al.* (1990a,b) studied risk factors for common naevi in school children in Vancouver, British Columbia, Canada. The number of naevi increased with age (from six to 18 years). Naevi occurred most commonly on intermittently than on constantly exposed parts of the body and less commonly in skin that was rarely exposed. Light and freckled skin, propensity to burn rather than tan upon exposure to the sun and a history of frequent or severe sunburn were associated with a large number of naevi.

Green *el al.* (1988b) compared the prevalence of melanocytic naevi (benign pigmented moles) in children aged 8-9 in Kiddermister, United Kingdom, and Brisbane, Australia. Regardless of skin colour, the mean number of naevi was at least five times larger in the Australian children than in the British children. In both populations, naevi were more prevalent in children with fair skin.

(iii) *Ultrastructural changes*

Jones, S.K. *et al.* (1987) and Roth *et al.* (1989) each described a patient who developed many freckle-like lesions on all exposed sites following repeated exposure to high-dose UVA from a home sunbed for tanning the skin. Biopsy showed increased numbers of large melanocytes in the basal layers.

Rosario *et al.* (1979) examined the sequential histological changes produced by single exposures to UVA, UVB and UVC radiation on untanned skin of the lower back. Exposures were designed to cause approximately equal degrees of erythema. Following UVB and UVC, dyskeratotic cells ('sunburn cells') were scattered throughout the malpighian layer of the epidermis at 24 and 48 h. By 72 h and seven days, they formed a continuous band in the upper malpighian layer or the stratum corneum. Epidermal hyperkeratosis, parakeratosis and acanthosis appeared concurrently at 72 h. The granular layer was focally absent at 24 and 48 h and had increased focally at 72 h and seven days. There was a minimal-to-moderate lymphocytic infiltrate in the dermis which was most pronounced after 48-72 h. Infrequent mitotic figures were observed in keratinocytes. UVA caused fewer dyskeratotic cells at all time intervals, and these never coalesced into a band. UVA, however, elicited the greatest degree of inflammation at 24, 48 and 72 h in terms of both quantity and depth of cellular infiltrate. Endothelial cell swelling, nuclear dust and extravasation of red blood cells were generally observed together. These dermal findings were more pronounced at 72 h. Neither epidermal hyperkeratosis, parakeratosis nor acanthosis was observed. Intracellular oedema of moderate degree was noted with all wavebands at all time intervals. The authors considered that the production of more prominent dermal changes by UVA than by UVB and UVC might be related to greater penetration of longer wavelengths. The histological changes returned to normal earliest after UVB and latest after UVA irradiation.

Pearse *et al.* (1987) examined the effects of repeated irradiation with UVB (0.5, 1 and 2 times the MED three times a week for six weeks) and UVA (6 J/cm^2 [60 kJ/m^2] three times a week for three weeks). UVB irradiation at twice the MED led to significant increases in epidermal thickness, stratum corneum thickness and keratinocyte height, as did UVA irradiation. Both UVA and UVB significantly increased glucose-6-phosphate dehydrogenase activity and decreased succinic dehydrogenase activity throughout the epidermis. The autoradiographic labelling index was significantly increased following the highest dose of UVB.

The benign skin changes attributed to sunlight and seen on physical examination include wrinkles, atrophy, cutis rhomboidalis nuchae (thick, yellow, furrowed skin, particularly on the back of the neck), yellow papules and plaques on the face, colloid milium (firm, small, yellow, translucent papules on the face, forearms and hands), telangiectasia, diffuse erythema, diffuse brown pigmentation, ecchymoses in sun-damaged areas, freckles, actinic lentigo (large, irregular, brown areas), Favre-Racouchot syndrome (yellow, thick comedones and follicular cysts of the periorbital, malar and nasal areas) and reticulated pigmented poikiloderma (reddish-brown reticulated pigmentation with telangiectasia and atrophy and prominent hair follicles on exposed chest and neck) (Goldberg & Altman, 1984). Although most commonly seen in fair-skinned Caucasians, these changes may also be seen in Chinese heavily exposed to the sun (Giam, 1987). A visual system using facial photographs has been developed to enable grading of the degree of elastosis (Cameron *et al.*, 1988).

Holman *et al.* (1984a,b) made silicone rubber moulds of the microtopography of the skin of the hands of 1216 subjects and developed a grading system to describe alterations in skin surface characteristics observed under a low-power microscope. Using multivariate analysis, independent risk factors for topographic evidence of actinic skin damage were: male sex, age, tendency to burn upon exposure to the sun and outdoor occupation. Similar results were reported by Green (1991).

Everett *et al.* (1970) reported ultrastructural changes in the epidermis of six elderly, fair-skinned, freckled, blue-eyed, Caucasian male farmers with a history of multiple actinic keratoses and skin cancers. Light microscopy showed effacement of epidermal rete ridges and an irregular decrease in epidermal thickness in areas of skin exposed to sunlight. Three groups of changes were apparent upon transmission electron microscopic examination: firstly, local areas of degeneration involving groups of adjacent cells, with degenerative changes resembling dyskeratosis in both the basal and the spinous layers of the epidermis; secondly, disturbed cellular cohesion, with variable numbers, distribution and degrees of maturity; and thirdly, changes in epidermal pigment—with the melanin concentration varying from none to excessive—and melanosome complexes that were often abnormally large.

Kligman (1969) described the changes in elastic tissue (elastic hyperplasia or actinic elastosis) seen in the dermis of sun-exposed Caucasian facial skin. Such changes were quite advanced before the extent of the damage became visible clinically. Some elastic hyperplasia was seen in elderly blacks over the age of 70, but the changes were markedly less extensive than those seen in whites.

Bouissou *et al.* (1988) studied elastic fibres in protected skin and skin highly exposed to the sun from normal Caucasians of different ages, using light and electron microscopy. In skin exposed to the sun, there was elastotic degeneration in the reticular dermis and progressive thickening and curling of the elastic fibres in the upper dermis. Altered fibres progressively formed thick, irregular masses, with clumps of amorphous, granular, elastotic material and large areas of uneven staining appearing frequently thereafter. Electron microscopy revealed that normal collagen and elastotic material were often contiguous but never continuous.

(iv) *Keratosis*

The occurrence of keratosis, a benign but probably premalignant squamous neoplasm of the skin (Marks *et al.*, 1988), has been studied in relation to exposure to sunlight in several cross-sectional studies.

Chronic solar damage (assessed by cutaneous microtopographs and paraocular photographs) was associated with keratosis, after adjustment for age, in a study of 1216 people in Busselton, Australia (Holman *et al.,* 1984a). A similar association between cutaneous microtopography and prevalence of keratosis was observed by Green (1991) in a study of 1539 people in Nambour, Australia.

Vitasa *et al.* (1990) conducted a study of 808 white watermen in Maryland, USA. The prevalence of keratosis was 25%. The risk factors for this condition were found in a multivariate analysis to be age, individually estimated cumulative exposure to sunlight, blue eyes, childhood freckling and a tendency to sunburn.

Marks *et al.* (1983) studied 2113 adults in Maryborough, Australia. The prevalence of keratosis was 56.9%. Adjusted for age, the prevalence of keratosis was significantly associated with being born in Australia, with a tendency to sunburn and not tan and with blue eye colour. In another survey by these authors, of 2000 adult in-patients from a hospital in Melbourne, Australia, the prevalence of keratosis on the light-exposed areas of the head and neck, forearms and back of hands was 37.7%. Prevalence of keratosis was significantly associated with age and with being born in Australia and, among men, with outdoor occupation (Goodman *et al.,* 1984). The Melbourne and Maryborough populations were compared further by Marks and Selwood (1985), who attributed the higher prevalence of keratosis in Maryborough to the fact that this population had a 14.2 higher erythemal UVR level.

Foley *et al.* (1986) studied 766 consecutive patients with keratosis. Lesions on the hands and forearms in men were seen more often on the right side than on the left, which the authors attributed to the higher exposure of the right side while driving an automobile. In women, more lesions of the head and neck were on the left side.

(v) *Photosensitivity disorders*

Abnormal reactions to solar radiation, termed photosensitivity disorders, occur in a relatively small number of exposed individuals; these have been reviewed comprehensively (Harber & Bickers, 1981; Bernhard *et al.,* 1987). Genetic and metabolic diseases that maybe associated with photosensitivity include xeroderma pigmentosum, phenylketonuria, Bloom's syndrome, Cockayne's syndrome, Rothmund-Thomson syndrome, certain porphyrins, Hartnup syndrome and pseudoporphyria cutanea tarda. The excision repair disorders are discussed on pp. 191-194. Defects in pigmentation due to an absence of melanocytes (vitiligo) and defective functioning of melanocytes (albinism) also confer susceptibility to UVR because of failure to develop photoprotection through tanning responses.

In idiopathic photodermatoses, the primary abnormality is an acquired alteration in reaction to sunlight. The commonest form is polymorphous light eruption, in which individuals who previously tolerated sun exposure develop itchy papules, vesicles or erythematous patches or plaques on exposed areas after moderate exposure to the sun (Bernhard *et al.,* 1987). Other photosensitivity conditions include solar urticaria (Armstrong, 1986),

hydroa vacciniforme (hydroa aestivale) (Halasz *et al.,* 1983) and actinic reticuloid (Bernhard *et al.,* 1987).

Photoaggravated dermatoses are conditions that may occur in the absence of exposure to sunlight but can be induced or exacerbated by such exposure. The commonest is recurrences of hel pes simplex viral eruptions, usually on the upper lip; this viral infection has been reproduced by exposure to artificial sources of UVR (Spruance, 1985).

Other skin diseases reported to be photoaggravated include lupus erythematosus, Darier's disease, acne vulgaris, atopic dermatitis, bullous pemphigoid, disseminated superficial actinic porokeratosis, erythema multiforme, lichen planus, pellagra, pemphigus, pityriasis alba, pityriasis rubra pilaris, psoriasis, acne rosacea, seborrheic dermatitis and transient acantholytic dermatitis (Grover's disease) (Bernhard *et al.,* 1987).

(b) *Experimental systems*

Agin *et al.* (1981b) found that single exposures to UVA plus UVB caused thickening of the whole epidermis and stratum corneum in pigmented and albino hairless mice. Sterenborg *et al.* (1986) found similar changes after repeated exposures to mainly UVB in hairless albino mice.

C57B1 mice irradiated with UVB daily for 10 days had a four-fold increase in the number of epidermal melanocytes, with increased pigmentation and local thickening of the epidermis (Rosdahl, 1979). A gradual, delayed, three-fold increase in the number of melanocytes also occurred in shielded contralateral ears, without increased pigmentation or epidermal thickening.

Generally consistent observations have been reported on chronic changes (photoageing) in hairless mice (Bissett *et al.,* 1987, 1989; Kligman, 1989). Bissett *et al.* (1987) described the progression of chronic UV damage to the skin in albino hairless Skh:Hr-1 mice irradiated with UVB or UVB plus UVA three times a week for 16 weeks, with a 17-week recovery period. UVB and a combination of UVA and UVB produced similar changes. An early increase in transepidermal water loss was seen, with a doubling of skin thickness and changes in the microtopography of the skin surface with visible skin wrinkling. Dose-dependent histological changes were seen, with thickening and hyperplasia of the epidermis. Dermal elastic fibres thickened and proliferated throughout the upper dermis, and there was a proliferation of fibroblasts, sebaceous cysts and dermal cysts in the upper dermis. By week 16, the skin was clearly elastotic, with thick, tangled masses of elastic fibres in the dermis. Use of a broad-spectrum sunscreen product with a claimed SPF (skin protector factor) of 15 retarded but did not completely prevent the effects of UVB and of UVB plus UVA radiation. Animals exposed to UVB and then allowed to recover for 12 weeks exhibited a zone of clearance of all abnormal elastin from the dermal-epidermal junction to mid-way down the dermis.

Animals exposed to UVA alone for 33 weeks with a recovery period of 18 weeks (Bissett *et al.,* 1987) exhibited a different pattern of changes. Epidermal thickening occurred at a slower rate, there was no increase in water loss; and sagging rather than wrinkling of the skin occurred. There was a very gradual increase in cellularity; focal areas of collagen damage and absence of elastic fibres were seen; the size and number of dermal cysts increased; and there was only slight evidence of recovery after 18 weeks. UVA

appeared to accelerate several changes similar to those that occur with chronological ageing in mice. Using a dual grating monochromator, Bissett *et al.* (1989) examined the action spectra for these changes. Most were similar and occurred in the UVB waveband: wrinkling, glycosaminoglycan increase, collagen darnage, elastosis, epidermal thickening, dermal cellularity and dermal inflammatory cell increase. In contrast, the spectrum for skin sagging was very broad, with a maximum near 340 nm. These results suggest that more than one chromophore is involved in UV-induced chronic skin changes.

High doses of UVA (cumulative dose, 3000 J/cm^2) were reported to produce severe elastic fibre hyperplasia, but no large aggregates of elastosis or destruction of collagen, in female Skh-hr 1 albino mice (Kligman *et al.,* 1985; Kligman, 1989). A dose of 13 000 J/cm^2 from a filtered (50% cutoff at about ≤ 345 nm) UVA source, however, produced only insignificant changes. Dose-response studies with another UVA source, filtered to remove all radiation below 340 nm, produced some elastin thickening at a total dose of 8000 J/cm^2 as well as increased epidermal proliferation and increased and enlarged dermal cysts (Kligman *et al.*, 1987).

Kligman and Sayre (1991) found that the action spectrum for elastosis in albino hairless mice was similar to that for erythema, except that longer UVA wavelengths (> 330 nm) were less effective for elastosis.

The chronic effect of repeated UV irradiation was also investigated in naked albino Ng/- mice using high total doses (> 20 000 J/cm^2) from a predominantly UVA source (but containing some UVB) administered for 16 h daily for 8.5 months (Berger *et al.,* 1980a). Dermal changes similar to those seen in human actinic elastosis were observed. There was endothelial swelling of dilated small capillary vessels and slight perivascular infiltration. Particularly in the upper dermis, collagen was replaced with an amorphous material that stained faintly with haematoxylin-eosin. Mast cells and a relatively increased number of spindleshaped fibroblasts were found in the middle and lower dermis. Large aggregates of numerous tangled, thickened fibres with the staining properties of elastic tissue were seen. Electron microscopy showed that elastic fibres were increased in number and size and there was splitting of collagen fibres. Most small blood vessels were dilated, with multiple basal lamina. The elastic tissue changes showed no signs of regression 2.5 months after irradiation had been discontinued, although the epitheliai changes regressed over this period.

Similar changes in elastic tissue (Berger *et al.,* 1980b) were found after exposure to a filtered UVA source which contained no UVB, but no alteration of collagen was observed and inflammatory changes were absent. Electron microscopy showed changes similar to those observed in actinic elastosis.

In female, lightly pigmented, hairless Oslo/Bom mice, UVB alone produced moderate elastosis, UVB and UVA together produced a slightly reduced degree of elastosis, but UVB followed by large doses of UVA produced severe elastosis; UVA alone was reported to have no effect (Poulsen *et a1*., 1984). In Skh:Hr 1 albino hairless mice, a combination of UVA and UVB had additive effects (Kligman *et al.,* 1985).

(c) *Comparison of humans and animals*

No direct comparison has been reported of the optical properties of whole human and mouse epidermis; however, the available data suggest that the absorption/transmission

spectra are of a similar general shape but have marked quantitative differences. For example, a comparison of data on a graph of effects on human epidermis not previously exposed to UVR (Bruls *et al.,* 1984a) with tabulated data on mouse epidermis not previously exposed (Sterenborg & van der Leun, 1988), generated in the same laboratory, showed that transmission in the mouse was two orders of magnitude greater in the UVC region and one order of magnitude greater in the UVB and UVA regions than in humans. In human and mouse epidermis, prior exposure to UVR resulted in marked decreases in UVR transmission. No study has been reported on mouse stratum corneum.

4.2.2 *Immune response*

Exposure to solar radiation and UVR can alter immune function in experimental animals and humans. This area of research is known as photoimmunology and has recently been reviewed (Daynes *et al.,* 1983*;* Parrish, 1983; Parrish *et al.,* 1983; Bergstresser, 1986; Roberts *et al.,* 1986; Krutmann & Elmets, 1988; Morison, 1989).

(a) *Humans*

(i) *Contact hypersensitivity* (*allergy*)

Exposure of normal subjects to radiation in a tanning solarium which emitted mainly UVA but also UVB radiation reduced allergic reactions to 2,4-dinitrochlorobenzene (Hersey *et al.,* 1983a). Ilalprin *et al.* (1981) and Nusbaum *et al.* (1983) found that UVB radiation partially suppressed the development of contact allergy to nitrogen mustard in patients with mycosis fungoides and psoriasis. Exposure to UVB was begun prior to treatment with mustard, and the field of exposure to the chemical was included in the area exposed to radiation, so that both a local and systemic effect may have been measured. In both studies, the proportion of patients sensitized to mustard gas was reduced by exposure to UVB radiation, and sensitization, when it did occur, was delayed. [The Working Group noted that the presence of diseases known to influence the immune system makes the findings difficult to interpret.]

Response to 2,4-dinitrochlorobenzene was diminished in sun-damaged skin in subjects previously sensitized to the allergen (Kocsard & Ofner, 1964; O'Dell *et al.,* 1980). UVB-induced suppression of contact allergy to nickel and other allergens (e.g., cobalt) has also been reported (Mørk & Austad, 1982; Sjövall & Christensen, 1986).

Studies on the possible mechanism of suppression have focused mainly on the effects on antigen presentation in the skin. At low doses of UVB (< 15 mJ/cm^2), Langerhans' cells are the only epidermal cells to be altered morphologically (Aberer *et al.,* 1981). Depletion of Langerhans' cells after a few exposures to UVB radiation is transient (Tjernlund & Juhlin, 1982; Scheibner *et al.,* 1986a); however, chronic exposure to sunlight appears to result in a sustained reduction, since fewer Langerhans' cells are found in exposed than in unexposed skin of older adults but not of young adults (Gilchrest *et al.,* 1982; Scheibner *et al.,* 1983; Thiers *et al.,* 1984; Czernielewski *et al.,* 1988). Pigmentation does not seem to protect Langerhans' cells, since exposure to UVB plus UVA radiation (simulating natural UVR) produced similar degrees of depletion of these cells in dark-skimled Australian aboriginals and in fair-skinned people of Celtic descent (Hollis & Scheibner, 1988); Langerhans' cells

were equally affected in fair-skinned and dark-skinned people after multiple exposures to sunlight (Scheibner *et al.,* 1986b).

The antigen-presenting function of Langerhans' cells is also diminished after irradiation *in vivo* with UVB (Cooper *et al.,* 1985; Rasanen *et al.,* 1989). The function returns to the epidermis within 24 h, owing to the appearance of two cell populations that are distinct and different from Langerhans' cells (Cooper *et al.,* 1986). Both populations have receptors for the monoclonal OKM5 antibody; one also has receptors for the OKM1 antibody and is possibly a dendritic cell from blood, while the other is $OKM1^-$ and is related to a subset of blood monocytes. These cells can activate T cells in the absence of exogenous antigen and lead to the generation of T-suppressor cells which can inhibit various immune responses. Baadsgaard *et al.* (1988) showed that epidermal cells from UVB-irradiated skin can stimulate suppressor/cytotoxic lymphocytes. This may occur *via* at least two pathways: activation of T-suppressor/inducer cells or induction of interleukin-2 production. These observations suggest that UV-induced immune suppression is more closely related to the appearance of $OKM5^+$ cells in the epidermis than to the disappearance of Langerhans' cells.

Systemic suppression of contact allergy may also result from exposure to UVR. Granstein and Sauder (1987) exposed subjects to a MED of mainly UVB radiation and measured levels of serum interleukin-1 activity that peaked 1-4 h after exposure and returned to baseline by 8 h. This activity may originate from the skin. in which increased levels have been detected after UVB irradiation (Kupper *et al.,* 1987; Oxholm *et al.,* 1988; Räsänen *et al*., 1989).

A recent study (Yoshikawa *et al*., 1990) showed that suppression of UVB-induced contact allergy may be a risk factor for nonmelanocytic skin cancer. Approximately 60% of normal subjects were sensitized by application of 2,4-dinitrochlorobenzene to UVB-irradiated skin compared to 8% of patients with a history of skin cancer. Many skin cancer patients were also immunologically tolerant to this allergen; this was not observed in normal subjects.

Pigmentation does not protect against UV-induced immunosuppression, since it occurs in the same proportion of black and white people (Vermeer *et al.,* 1991).

(ii) *Lymphocytes*

A single, whole-body exposure to UVB radiation which produced painful erythema produced a transient decrease in the proportion of circulating E rosette-forming cells and in the response of lymphocytes to a mitogen (Morison *et al.,* 1979a). McGrath *el al.* (1986) found a decrease in the proportion of circulating suppressor cells following exposure to half the MED of UVB, although the total number of T lymphocytes was not altered. Exposure of normal subjects to sunlight daily for two weeks, however, produced different effects: The total proportion of T lymphocytes was diminished owing to a pronounced drop in the proportion of helper/inducer cells associated with an increase in the proportion of suppressor cells in the peripheral blood (Hersey *et al*., 1983b). Similar changes occurred after exposure of normal subjects to UVAplus UVB radiation (Hersey *et al*., 1983a). When UVB radiation was removed by a Mylar filter (FIersey *et al*., 1988) or a sunscreen (Flersey *et al*., 1987), most of the effect was removed. The numbers of circulating T cells and helper-T cells were significantly reduced by exposure of normal subjects to solar lamps containing UVA (with

minimal UVB) and to fluorescent tubes emitting mainly visible light, which contained small quantities of UVB, but the number of T-suppressor cells was only slightly reduced. These effects were considered to be due to the UVB radiation (Rivers *et al.*, 1989).

(iii) *Infectious diseases*

Recurrent infections to herpes simplex virus types 1 and 2 can be induced by exposure to UVB radiation (Wheeler, 1975; Spruance, 1985; Klein & Linnemann, 1986; Perna *et al.*, 1987). Presumably, local alterations of immunity, associated with extensive UV-induced tissue damage, are responsible for this reactivation.

(iv) *Photosensitive disease*

An interaction between solar radiation and the immune system was first postulated on the basis of observations that the pathogenesis of several diseases is characterized by photosensitivity. Solar urticaria, photoallergy and lupus erythematosus are the main examples (for reviews, see Morison, 1983b,c; Morison & Kochevar, 1983).

(b) *Experimental systems*

(i) *Contact hypersensitivity*

The first report of UV-induced suppression of contact hypersensitivity was in guinea-pigs that received applications of a sensitizing chemical through UV-irradiated skin (Haniszko & Suskind, 1963). This effect has since been termed local suppression of contact hypersensitivity. Later, in studies of UV-induced tumour susceptibility in mice, it was found that UVR could also induce systemic suppression of contact hypersensitivity when the sensitizer is applied through unexposed skin only (Kripke *et al.*, 1977). This occurred during chronic treatment of mice, was transient and appeared to be due to failure of an ejector mechanism (efferent block) of the immune response (Jessup *et al.*, 1978). These two phenomena, local and systemic suppression of contact hypersensitivity, are probably mediated by different mechanisms.

Local suppression of contact hypersensitivity: Pretreatment of mice with low doses of UVB radiation (100-700 J/m^2 fluorescent sunlamp radiation daily for four days) suppressed the development of contact hypersensitivity to sensitizing chemicals (e.g., 2,4-dinitrotluorobenzene) applied subsequently to irradiated skin (Toews *et al.*, 1980; Elmets *et al.*, 1983). This effect was associated with generation of hapten-specific LyT-1$^+$ T cells which suppress the induction phase of the immune response (Elmets *et al.*, 1983). The most effective wavelengths are < 300 nm (Elmets *et al.*, 1985). Local suppression of contact hypersensitivity by UVB radiation also occurs in hamsters (Streilein & Bergstresser, 1981).

Several hypotheses have been explored to explain the mechanism of local suppression. Multiple exposures to sunlight result in a striking reduction in the number of Langerhans' cells in guinea-pigs, as detected by ultrastructural examination (Fan *et al.*, 1959). UV-induced alterations occur in Ia$^+$ Langerhans' cells (Streilein *et al.*, 1980; Perry & Greene, 1982; Gurish *et al.*, 1983; Stingl *et al.*, 1983), but alterations in other cells may be involved.

Thy-1 + dendritic epidermal cells (identified by antibodies to surface markers on lymphocytes), found in mouse but not reported in human skin, are bone marrow-derived lymphocytes which down-regulate contact hypersensitivity. They are not affected by low-

dose UVR, and hap/en-conjugated Thy- 1 $^{+}$ dendritic epidermal cells can induce tolerance on subcutaneous injection into the footpad or after intravenous injection (Welsh & Kripke, 1990). This finding is supported by the observations (Okamoto & Kripke, 1987) that (i) the draining lymph nodes of mice treated with low doses of UVR contained these hapten-conjugated cells after exposure to a contact sensitizer, (ii) injection of these cells into other syngeneic mice resulted in the generation of suppressor cells, and (iii) removal of these cells from the lymph node cells abolished the suppression.

I-J^{+}, Thy-1^{-}, Ia^{-} antigen-presenting cells, which are also resistant to low doses of UVB radiation and preferentially generate a suppressor cell pathway, may also be involved in local suppression (Granstein *et al*., 1984; Granstein, 1985; Granstein *et al*., 1987; Okamoto & Kripke, 1987).

Keratinocytes may also be involved through the production of epidermal cell-derived thymocyte-activating factor (ETAF), which is functionally and biochemically very similar to interleukin-1, a nonspecific helper factor necessary for activation of T cells by antigen. Interleukin-1 can reduce expression of contact hypersensitivity in mice (Robertson et *al.*, 1987). Studies by several workers have suggested that exposure to UVR inhibits the production of ETAF (Saucer *et al.*, 1983) or decreases its activity (Stingl *et al*., 1983). When antigen-presenting cells are exposed to UVR, their ability to activate T cells is markedly inhibited (Tominaga *et al*., 1983). UV irradiation of mice induces the release of a specific interleukin-1 inhibitor, keratinocyte-derived, EC-contra IL 1 (Schwarz *et al*., 1988). Other workers (Ansel *et al*., 1983; Gahring *et al*., 1984) have found increased production of ETAF. [The Working Group noted that differences in the radiation sources and model systems could explain the discrepancies between the results of these studies.]

Systemic suppression of contact hypersensitivity: Systemic suppression of contact hypersensitivity in mice requires a higher exposure dose (40-50 KJ/m^2) than local suppression (Kripke & Morison, 1986a). A dose of 8.2 kJ/m^2 at 320 nm produced nearly 50% systemic suppression, and 100 kJ/m^2 produced 80% suppression (Noonan *et al.,* 1984). Like local suppression, systemic suppression is associated with the generation of suppressor Lyt-1 $^{+}$ T lymphocytes (Noonan et *al.,* 1981a; Ullrich & Kripke, 1984). The pathways leading to the appearance of these lymphocytes are, however, probably different. Systemic suppression has also been induced in guinea-pigs (Morison & Kripke, 1984) and in the South American opossum, *Monodelphis domestica* (Applegate *et al.,* 1989). Artificial sources of UVB radiation and sunlight, but not UVA, induce systemic suppression of contact allergy in mice and guinea-pigs (Morison *et al.,* 1985).

Determination of an action spectrum for systemic suppression of contact hypersensitivity in mice revealed peak activity in the 260-270 nm region, which is consistent with a superficial location of the chromophore in the epidermis (De Fabo & Noonan, 1983; Noonan & De Fabo, 1985). Two candidate molecules, urocanic acid and DNA, have been suggested.

Several lines of evidence indicate that abnormalities in Langerhans' cells are not involved in systemic suppression, in contrast to local suppression (Lynch *et al*., 1983; Morison *et al.,* 1984; Noonan *et al*., 1984), and that a defect of antigen presentation is not an initial step (Kripke & McClendon, 1986). Soluble mediators are released from irradiated skin and may generate suppressor cells in a distant organ. Serum collected from

UV-exposed mice and epidermal cells exposed to UVR *in vitro* contain factors that can induce systemic suppression (Schwarz *et al*., 1986). The situation is far from straightforward, however, since a recent study indicated that multiple suppressive factors, with different immunosuppressive properties, may be released by different wavelengths of UVR (Kim *et al*., 1990). Indomethacin blocks the development of suppression (Chung *et al*., 1986; Jun *et al*., 1988), indicating that prostaglandins may also be involved in the pathway.

Several properties of the suppressor cells have been defined: (i) they suppress primary proliferative responses but not a secondary response *in vitro* (this is consistent with the idea that they suppress induction of sensitization but not with the proposal that they elicit a response in a previously sensitized animal) (Ullrich, 1985); (ii) their action is limited to T-dependent antigens (Ullrich, 1987); and (iii) they can modulate other immunological pathways, such as formation of anti-hapten antibodies and cytotoxic-T lymphocytes (Ullrich *et al*., 1986a).

(ii) *Delayed hypersensitivity injected antigens*

Systemic suppression of delayed hypersensitivity was induced by UVB irradiation of mice following injection of 2,4-dinitrochlorobenzene into the footpad (Jessup *et al*., 1978), of hapten-coupled spleen cells into the footpad (Greene *et al*., 1979) or the ear (Noonan *et al*., 1981b) or of erythrocytes and soluble protein antigens into the footpad (Ullrich *et al*., 1986b) and is associated with the generation of antigen-specific T lymphocytes. This suppression differs from the suppression of contact hypersensitivity to topically applied allergens because delayed hypersensitivity can be restored in UV-irradiated mice by injection of hapten coupled spleen cells from normal mice (Noonan *et al*., 1981b; Kripke & Morison, 1985, 1986b). Furthermore, systemic injection of methylprednisolone before immunization prevented suppression of delayed hypersensitivity but had no effect on the suppression of contact hypersensitivity (Kripke & Morison, 1986b).

Systemic depression of splenic antigen-presenting cell function was demonstrated in UVB-exposed mice (Letvin *et al*., 1980a,b; Gurish *et al*., 1982). Two explanations have been advanced: a transient redistribution of antigen-presenting cells to peripheral lymphoid tissues in response to UV-induced inflammation (Gurish *et al*., 1982; Spangrude *et al*., 1983) or direct damage to blood monocytes or other precursors of splenic antigen-presenting cells as they circulate through the skin (Spangrude *et al.,* 1983). The latter theory is supported by the observation that immunization with hapten-conjugated splenic antigen-presenting cells or epidermal cells exposed *in vitro* to UVR can induce hapten-specific T-suppressor cells (Fox *et al.,* 1981; Sauder *et al.,* 1981).

The role of one of the proposed chromophores, urocanic acid, has been explored. UV-irradiated urocanic acid (containing 74% cis-urocanic acid after 4 h) suppresses delayed hypersensitivity to HSV-1 when injected subcutaneously or applied to the skin of mice (Ross *et al*., 1986), and is thus similar to UVB radiation (Ross *et al*., 1987). In both instances, phenotypically similar suppressor cells were induced (Howie *et al*., 1986a; Ross *et al*., 1987). In addition, intravenous administration of cis-urocanic acid impairs antigen-presenting cell function in splenic dendritic cells. These observations suggest that trans-urocanic acid is the photoreceptor for UVB-induced systemic suppression of delayed

hypersensitivity and that cis-urocanic acid acts as an immunomodulator (Noonan *et al*., 1988).

(iii) *Immunology of ultraviolet-induced skin cancer*

Most UV-induced turnouts in mice are highly antigenic and are rejected upon transplantation into normal syngeneic recipients; however, they grow progressively in immunosuppressed recipients (Kripke, 1974). The specific immunological rejection of these transplanted tumours is mediated by cytolytic-T lymphocytes aided by natural killer and cytotoxic-T cells (Fortner & Kripke, 1977; Fortner & Lill, 1985; Streeter & Fortner, 1988a,b). Tumours grow in UV-irradiated recipients or primary hosts because T-suppressor lymphocytes induced by the exposure to UVR block the normal immunological surveillance system (Fisher & Kripke, 1977; Spellman *et al.,* 1977; Fisher & Kripke, 1978; Spellman & Daynes, 1978). The function of these suppressor cells is specific in that, whereas they prevent development of UVR-induced tumours, they do not alter the growth of chemically induced tumours or skin allografts (Kripke & Fisher, 1976; Fisher & Kripke, 1978).

The phenotype of the suppressor cells is LyT1 $^{+}$ 2^{-}, Ia^{-} (antibodies to surface markers on lymphocytes), similar to that of other UV-induced suppressor cells (Ullrich & Kripke, 1984). These suppressor cells are important in the development of primary neoplasms. de Gruijl and van der Leun (1982b, 1983) found accelerated development of UVR-induced tumours in hairless mice that had been exposed previously to UVR at a separate site. Fisher and Kripke (1982) observed that, if suppressor cells were present from the time of commencement of exposure to UVR, the latent period for development of turnouts was shortened and the tumour yield was increased. Thus, photocarcinogenesis in mice appears to involve at least two UVR-inducecd alterations: (i) an alteration in DNA leading to transformation of cells (see pp. 188-189) and (ii) a specific systemic immunological alteration that permits expression of the turnout (Fisher & Kripke, 1977).

Suppressor cells can be induced by doses of 40-50 kJ/m^2 of radiation from fluorescent sunlamps (see Fig. 9c, p. 64) (Kripke & Morison, 1986a), and susceptibility to transplanted tumours is evident long before the de-novo appearance of tumours (Fisher & Kripke, 1977). Suppressor cells can be induced by exposure to UVC (from low-pressure mercury discharge lamps) (Lill, 1983), UVB (De Fabo & Kripke, 1980), large doses of UVA (Morison, 1986) and sunlight (Morison & Kelley, 1985). Wiskemann *et al.*. (1986) described an effect of neutral white fluorescent bulbs. [The Working Group considered that this effect may have been due to low levels of UVB from this source.]

(iv) *Transplantation immunity*

The immune responses in graft rejection and graft-*versus*-host disease are complex and directed against class I antigens of the major histocompatibility complex which are expressed on all nucleated cells and class II Ia antigens which are expressed normally on lymphocytes and macrophages. Lindahl-Kiessling and Säfwenberg (1971) demonstrated that UV irradiation of stimulator cells could abrogate the proliferation of responder cells in a mixed lymphocyte reaction. Subsequent studies (Alter *et al.,* 1973; Bach *et al.,* 1977) indicated that this effect was due to alteration of class II Ia antigens on the cells bearing them. These initial observations have been extended to various systems.

Pre-transplant, donor-specific blood transfusions have been used to reduce the need for post-transplant immunosuppression, with varying success. The basis for this effect is

thought to be generation of donor-specific T-suppressor lymphocytes in the host. Lau *et al.* (1983) found that exposure of the blood to UVB radiation prior to transfusion greatly enhanced this effect and permitted long-term survival of allografts of islets of Langerhans across a major histocompatibility barrier in rats. The effect was shown to be due to inactivation of lymphocytes by radiation, resulting in cancellation of a signal from Ia antigen-positive cells and permitting the generation of donor-specific T-suppressor cells. A similar effect was demonstrated with rat heart allografts (Balshi *et al.,* 1985).

Deletion of Ia antigens or inactivation of cells bearing them may explain prolonged graft survival in other systems. Exposure of mouse tail skin to UVB radiation in vitro prolonged its survival as a graft when I-region differences only were present, but UVB had no effect in the case of complete H-2 differences (Claas *et al.,* 1985). Similarly, mouse corneal allograft survival was prolonged by exposure to UVB radiation *in vitro* (Ray-Keil & Chandler, 1986). Prolonged survival as grafts of r at islets of Langerhans exposed to UVB radiation *in vitro* was apparently due to inactivation of dendritic cells bearing Ia antigens (Lau *et al.,* 1984).

The model of UVR-induced systemic suppression of delayed hypersensitivity has been extended to transplantation studies, because of the considerable potential for manipulating the immune system in transplantation. Sensitization of mice with allogeneic spleen cells after a single exposure to UVB radiation suppressed the delayed hypersensitivity response to these cells and proliferation of lymphocytes from the irradiated mice in a mixed-lymphocyte reaction; these effects are due to generation of suppressor cells specific for donor antigens (Ullrich, 1986). Interestingly, exposure of the mice to radiation need not precede exposure to the antigen but can be delayed up to five days after first contact with the antigen, unlike other forms of suppression of delayed hypersensitivity (Magee *et al.,* 1989a). Similar observations have been made in rats, but suppressor cells were not demonstrated in the spleen (Magee *et al*., 1989b). Subcutaneous injection of epidermal cells that have been exposed to UVB radiation *in vitro* can similarly cancel a delayed hypersensitivity response in mice; this effect is associated with prolongation of skin allograft survival (Tamaki & lijima, 1989).

Graft-*versus*-host disease can also be reversed by UVR. Two rat models have been studied. Pretreatment of donor bone marrow with UVB radiation did not increase the failure of grafts, but it prevented graft-*versus*-host disease in most instances (Pepino *et al.,* 1989). Pre-irradiation of rat skin with UVB prevented subsequent development of cutaneous graft-versus-hcyst disease at the site of exposure (Glazier *et al.,* 1984). In both of these studies, an alteration of Ia-bearing cells was postulated as the mechanism.

(v) *Infectious diseases*

Classic delayed hypersensitivity to complex protein antigens (correlated with resistance to a number of infections) can be suppressed by exposure to UVB radiation (Ullrich et *al.,* 1986b).

Exposure of mice to low doses (1.3-3.4 kJ/m^2) of UVB (less than a human MED) at the site of intradermal infection with herpes simplex type 2 virus increased the severity of the disease. Unirradiated mice developed only a single vesicle at the site of inoculation, whereas irradiated mice developed zosteriform lesions which healed slowly and. at the highest dose of radiation, were lethal. At doses that increased the severity of the infections, systemic suppression of delayed hypersensitivity to the virus due to generation of

antigen-specific T-suppressor lymphocytes was observed (Yasumoto *et al*., 1987). In-vitro assays showed UVB-induced impairment of antigen presentation, which may have been due to the presence of suppressor factors in the supernatant (Hayashi & Aurelian, 1986). Similar results were found in a model of herpes simplex virus type 1 infections in mice (Howie *et al.,* 1986a,b,c; Otani & Mori, 1987). [The Working Group considered that these experiments have not demonstrated clearly that the effect of radiation on the induction of immunity is local, since the possibility of an indirect systemic effect has not been explored.]

Exposure to low doses of UVB radiation prevented the development of delayed hypersensitivity to the protozoan, leishmania, and reduced the number and severity of skin lesions when leishmania was inoculated at the site of exposure. Exposure to radiation did not, however, alter the viability of the organisms or the degree of their dissemination to distant sites—the spleen, lymph nodes and skin. Furthermore, the irradiated mice reacted to a second, distant inoculation as if it were a primary infection, presumably because they lacked the cell-mediated immunity that would be needed to control this second attack of the organism (Giannini, 1986).

Exposure of mice to UVB radiation also caused systemic suppression of delayed hypersensitivity to the yeast *Candida albicans* (Denkins *et al.,* 1989), through two possible mechanisms: one mediated by suppressor cells (detected in the spleen) triggered by exposure to radiation prior to contact with the antigen and another which did not involve splenic suppressor cells and was triggered by exposure to radiation following exposure to the antigen.

(vi) *Human lymphocytes* in vitro

Lymphocytes are highly sensitive to low doses of UVR. UVC was approximately 10 times more effective than UVB and 10^5 times more effective than UVA on mononuclear peripheral blood cells in *vitro* (Morison *et al.,* 1979b). Cripps *et al.* (1978) found that UVC was preferentially toxic to T lymphocytes, but that T and B lymphocytes were similarly susceptible to UVB. UVA did not appear to kill T or B cells. Exposure of mononuclear peripheral blood cells to UVB radiation inhibited both natural killer cell activity and the response of these cells to stimulation by a mitogen (phytohaemagglutinin) (Schacter- *et al.,* 1983), in the absence of any apparent change in viability. The effect on natural killer cell activity occurred selectively at the post-binding stage of lysis (Elmets *et al.,* 1987) and could be virtually reversed by the addition of interleukin-2 and superoxide dismutase (Toda *et al.,* 1986).

(c) *Comparison of humans and animals*

Firstly, most observations have been made in experimental systems and few studies have involved humans, and it can be only assumed that results of studies in mice can be extrapolated to humans. Furthermore, in no instance have parallel studies in an experimental system and in humans been performed to test this assurnption. Secondly, while most investigations of photoimmunology have focused on the effects of 'UVB' radiation, in most studies this term refers to the emission spectrum of a fluorescent sunlamp (see Fig. 9c, p. 64) which contains both UVC and UVA, as well as UVB radiation, besides having little in common with the spectrum of sunlight. Fortunately, in the few studies in which the effects of fluorescent sunlamps and sunlight have been compared in experimental

systems. similar alterations in immunity have been observed. Finally, with few exceptions, the effect of exposure to UVR is to suppress immunity highly selectively, at least in experimental animals. Thus, in mice, certain cell-mediated immune responses are suppressed by UVR, whereas humoral immunity is largely unaffected. The selective nature of UVR-induced immunosuppression has not been established in humans, but no evidence exists to suggest that it does not apply. The importance of such selectivity is that it differs from the forms of immunosuppression seen most commonly in humans, namely viral and drug-induced suppression, which affect most functions of the immune system. Exposure of humans to UVR is unlikely to cause paralysis of immune function but probably selectively negates a few immune responses.

4.2.3 *Eye*

(a) *Humans*

(i) *Anterior eye (cornea, conjunctiva)*

The cornea absorbs UVC and UVB radiation (Sliney & Wolbarsht, 1980). Sunlight has been implicated as causing nodular band keratinopathies (spheroidal degeneration and climatic droplet keratopathy), pinguecula, pterygium, photokeratitis and photokerato-conjunctivitis (Wittenberg, 1986). Artificial sources of UVR, including welding arcs and germicidal lamps, cause photokeratoconjunctivitis and photokeratitis (Sliney, 1986). A study by Taylor *et al.* (1989) of the association between exposure to broad-band UVR and corneal disease in 838 fishermen in Chesapeake Bay, Maryland, USA, reported a significant association with pterygium and climatic droplet keratopathy but a weak association with pinguecula.

(ii) *Lens*

The lens absorbs radiation between 305 and 400 nm (Wittenberg, 1986). UVR produces substantial photodamage to both the structural proteins and key enzymes of the lens (for review, see Andley, 1987).

Taylor *et al.* (1988) studied the two major types of senile cataract (nuclear and cortical cataracts) in 838 Maryland fishermen for each of whom mean annual and cumulative UVB exposure had been assessed. High cumulative exposure to UVB and high annual exposure to UVB were both associated with increased risk of cortical cataract, but no association was seen with nuclear cataracts. The association between exposure to solar radiation and cataract is also supported by studies of cataract in northern India and China and in aborigines in Australia and by an analysis of data from the US National Health and Nutritional Examination Survey. These studies were reviewed by Wittenberg (1986).

It has been claimed that the presence of low levels of photosensitizing compounds in lens tissue may contribute to cataractogenesis (Lerman, 1988).

(iii) *Posterior eye*

The posterior eye is composed of the vitreous humour and the retina (German, 1980). In the normal eye. solar radiation in the visible and near infrared regions (400-1400 nm) reaches these structures. Refraction of this waveband by the cornea and lens greatly increases the irradiance between the surface of the cornea and the retina (Sliney & Wolbarsht, 1980).

Permanent retinal damage was observed after direct viewing of the sun and viewing of solar eclipses and in aircraft spotters during the Second World War, but no epidemiological study has associated retinal pathology with routine environmental exposure to sunlight (Wittenberg, 1986). The suggestion that senile macular degeneration is related to solar exposure was not supported by a large study of fishermen in Maryland (West *et al.,* 1989).

(b) *Experimental systems*

(i) *Anterior eye*

Pitts *et al.* (1977) and Cullen (1980) studied the effects of exposure to UVR at 295 nm on the corneas of pigmented rabbit eyes. The threshold dose for corneal damage was 0.05 J/cm^2. Changes observed with a slit lamp biomicroscope included discharge, corneal debris, haziness, granular change, epithelial exfoliation, stromal opacities and stromal haze.

Applegate and Ley (1991) showed that UVR-induced corneal opacification and neovascularization of the cornea of the South American opossum *M. domestica* was due to DNA damage, as these effects could be delayed by subsequent illumination with photoreactivation light, which specifically monomerizes pyrimidine dimers.

(ii) *Lens*

Cataracts have been produced in pigmented rabbit eyes by exposure to UVB radiation (Pitts *et al.,* 1977). Cataracts were produced in young albino mice 60 weeks after irradiation with a black light (predominantly UVA) (Zigman & Vaughan, 1974; Zigman *et al.,* 1974). Albino mice developed anterior lens opacities after daily exposure for one to two months to a UVB plus UVA source (290-400 nm), but not after the source was filtered to remove radiation < 320 nm (Jose & Pitts, 1985).

(iii) *Posterior eye*

The effects of solar radiation on the posterior eye have been reviewed (Wittenberg, 1986, Andley, 1987). Irradiation ol' cali: vitreous humour *in vitro* with visible radiation in the presence of photosensitizers resulted in partial liquefaction, suggesting that photogenerated active species of oxygen may damage the vitreous structure. In rabbits *in vivo,* however, little liquefaction was seen, suggesting a protective mechanism in the intact organ (Pitts *et al.,* 1977).

Damage to the retina by exposure to sunlight may also be due to thermal effects at high irradiances or to photochemical effects at lower irradiances. In various animals, continuous exposure to sunlight produces a photochemical lesion involving the entire retina and affecting both rods and cones (Young, 1988). The photopigment, rhodopsin, is the chromophore for damage to the rods, while the three cone pigments are the chromophores for cones. In monkeys, blue-light damage caused by exposure to the 400-500 nm waveband affected the macular or paramacular region of the retinal pigment epithelium. The chromophore involved has been postulated to be melanin; active species of oxygen appear to act as mediators of the photochemistry (Lerman, 1980; Andley, 1987).

(c) *Comparison of humans and animals*

The limited data available indicate that the optical properties of the components of human and animal eye are broadly similar.

4.3 Photoproduct formation

4.3.1 *DNA photoproducts*

A multitude of photoproducts are formed in cellular DNA by solar UVR, many of which were first recognized after their induction by non-solar radiation at a wavelength of 254 nm. The ratio of the different photoproducts changes markedly with wavelength. A brief description of the photoproducts is given below, together with a note on the wavelength dependence of formation and susceptibility to repair. Substantial information on biological consequences is available only for cyclobutane-type pyrimidine dimers and pyrimidine-pyrimidone (6-4) photoproducts.

(a) *Cyclobutane-type pyrimidine dimers*

Shortly after the observation that thymine compounds irradiated with UVC in the frozen state rapidly lose their absorption (Beukers *et al.,* 1958), a dimer of thymine was shown to be responsible for this effect, the two molecules being linked by a cyclobutane ring involving the 5 and 6 carbon atoms (Beukers & Berends, 1960, Wulff & Fraenkel, 1961). Continued irradiation leads to a wavelength-dependent equilibrium between dimer formation and dimer splitting to reform the monomer. Dimer formation is favoured when the ratio of dimer to monomer absorbance is relatively small (wavelengths > 260 nm), whereas monomerization is favoured at shorter wavelengths (around 240 nm), when the ratio is larger (Johns *et al.,* 1962). Although several isomers of the cyclobutane-type thymidine dimer have been isolated from irradiated thymine oligomers, only the *cis-syn* isomer appears to predominate in biological systems (Ben-Hur & Ben-lshai, 1968; Varghese & Patrick, 1969; Banerjee *et al.,* 1988).

Cytosine-thymine (cyt↔thy), thymine↔thymine (thy↔thy) and cytosine-cytosine (cyt↔cyt) cyclobutane-type dimers are also formed in irradiated *Escherichia coli* DNA but deaminate to uracil↔thymine (ura↔thy) and uracil-uracil dimers after the acid hydrolysis usually used in chromatographic analysis (Setlow & Carrier, 1966). Cytosine moieties in dimers are also deaminated at a slower rate under physiological conditions that produce uracil residues (Fix, 1986), and recent evidence obtained in bacteria suggests that the rate may be more significant than was previously thought (Tessman & Kennedy, 1991). After treatment at 254 nm, thy↔thy, cyt↔thy and cyt↔cyt appear in irradiated DNA at a ratio of 2:1:1 (Unrau *et al.,* 1973), but this ratio changes quite markedly at longer wavelengths, e.g., to 5:4:1 at 265 nm (Setlow & Carrier, 1966). At 254 nm, the relative proportion of cyclobutane dimers was: 5'-thy↔thy, 0.68; 5'-cyt↔thy, 0.17; 5'-cyt↔thy, 0.08; and 5'-cyt↔cyt, 0.07 (Kraemer *et al.,* 1988). Ellison and Childs (1981) showed in E. *coli* that the ratio of cyt↔thy:thy↔thy increases from 0.75 at 254 nm to 1.5 at 313 nm then decreases to 0.8 at 320 nm, the longest wavelength tested. At 365 nm, the longest wavelength at which dimers have been detected, the ratio of thy↔thy:ura↔thy was 5-6:1 (Tyrrell, 1973). The proportion of cyt↔cyt:thy↔thy increased up to 300 nm, but cyt↔cyt was undetectable at longer wavelengths (Ellison & Childs, 1981). On the basis of these data, the latter authors argued that the predominant dimer species formed in *E. coli* by exposure to sunlight are likely to be mixed dimers of cyt↔thy rather than thy↔thy (cyt↔thy:thy↔thy, 1.2:1). The ratio of formation of thy↔thy:ura↔thy dimers in bacterial DNA at 254 and 365 nm is approximately 7 x 10^5 nm (Tyrrell, 1973). A similar ratio of

total dimer product formation was found in cultured human skin fibroblasts irradiated at 254-265 nm (Enninga *et al.,* 1986)

Fisher and Johns (1976) described the photochemistry and mechanism of formation of cyclobutane-type pyrimidine dimers in considerable detail. The mechanism of dimer formation in the UVB region almost certainly involves direct absorption, since the action spectrum for induction closely resembles that for the appropriate monomer for wavelengths as long as 313 nm (Ellison & Childs, 1981). The mechanism of formation by longer wavelengths (e.g., 365 nm) has not been clarified.

Cyclobutane-type dimers can be removed from the DNA of both prokaryotic and eukaryotic cells by the powerful excision repair mechanism that is deficient in cells from most sun-sensitive, skin cancer-prone patients with the hereditary disease, xeroderma pigmentosum (see Friedburg, 1984; Cleaver & Kraemer, 1989). Photoreactivation is specific for pyr↔pyr (pyrimidine dimers) and monomerizes them *in situ via* a photolyase. Many microorganisms and higher eukaryotes contain a photolyase, but the proteins and light-activation spectra differ from species to species. The specificity of this process has proved a powerful tool in analysing the role of pyr↔pyr in biological effects. For example, the potential photoreactivation of pyr↔pyr has been studied in a set of experiments to demonstrate that the presence of UVC-induced pyr↔pyr in fish can be a precarcinogenic lesion (Setlow, 1975). More recently, the small opossum, *M. domestica,* has been used by Ley and coworkers as an animal model in studies on the effects of UVR, predominantly UVB, mainly because cells of the skin of this animal, unlike that of the mouse, contain a photoreactivating enzyme(s). They showed that several biological effects, including decreased hair growth, erythema and tumour formation, were suppressed by exposure to longer wavelengths (photoreactivating light) (Ley & Applegate, 1989; Ley *et al.,* 1991).

Considerable evidence, including the fact that photoreactivation prevents formation of the majority of mutations induced in bacteria by UVC, shows that the argument that pyr↔pyr is a major premutagenic lesion is overwhelming (Doudney, 1976). Recognition that UV induced mutagenesis in bacteria is an inducible process (see Witkin, 1976), however, complicates this argument, since, assuming that a structure involving pyr↔pyr constitutes the inducing event, its elimination by photoreactivation would preclude error-prone repair at the site of any premutagenic lesion. When all inducible functions relevant to mutagenesis are turned on, the photoreversibility of UVC mutagenesis at several pyr↔pyr sites disappears (Bridges & Brownn, 1992); e.g., UV-induced mutagenesis to *his*$^+$ in certain *rec*A441 *lex*A51 bacteria was not photoreversible, indicating that pyrimidine dimers are not target lesions (Ruiz-Rubio *et al.*, 1986). This suggests that non-photoreversible photoproducts (such as the pyrimidine-pyrimidone 6-4 photoproduct) are the principal premutagenic lesions at dithymine sequences and that cyclobutane-type thymine dimers are weakly mutagenic. This conclusion is consistent with the results of other studies with single-stranded vector DNA containing cyclobutane-type (6-4) thy↔thy photoproducts at specific sites (Banerjee *et al.,* 1988, 1990; LeClerc *et al.,* 1991).

(b) *Pyrimidine-pyrimidone (6-4) photoproducts*

The most extensively studied non-dimer photoproduct is that formed from thymine and cytosine. Indirect evidence (Varghese & Patrick, 1969) suggests that this structure is the

in-vivo precursor of the compound 6-4'-[pyrimidin-2'-one]thymine (thy(6-4)pyo), originally found in acid hydrolysates of UV-irradiated DNA (Varghese & Wang, 1967; Wang & Varghese, 1967). Some years later, a type of UV-induced photoproduct, the pyrimidine nucleoside-cytidine lesion, was recognized in highly reiterated sequences of human DNA (Lippke *et al.,* 1981); this is also probably a precursor of the thy(6-4)pyo product (Brash & Haseltine, 1982; Franklin *et al.,* 1982). Using DNA sequencing analysis, UV photoproducts were more frequent at the 3' end of pyrimidine runs. Although the overall ratio of 6-4 photoproducts to dimers was 15% at certain 5'-thy↔cyt sequences, 6-4 photoproducts occurred at approximately the same frequency as that of the cyclobutane dimer (Kraemer *et al.,* 1988).

Patrick (1977) originally reported that the action spectrum for (6-4) photoproduct formation resembles that for cyclobutane dimer formation, although the quantum yields are two and ten times lower than that of cyt↔thy and thy↔thy formation, respectively. Using irradiation at wavelengths as long as 334 nm, Chan *et al.* (1986) found that the action spectrum for induction of hot alkali sites (presumably the thy(6-4)pyo hydrolysis product) was also similar to that for pyr↔pyr formation. The action spectra for the induction of thymine dimers and (6-4) photoproducts were similar from 180 to 300 nm, whereas the action spectrum values for thymine dimer induction were about nine and 1.4 times higher or more than the values for (6-4) photoproduct induction below 160 nm and above 313 nm, respectively (Matsunaga *et al.,* 1991).

Most xeroderma pigmentosum patients are defective in the excision of (6-4) photo-products (Mitchell *et al.,* 1985) and cyclobutane pyrimidine dimers (Cleaver & Kraemer, 1989). ln addition, a group of patients with trichothiodystrophy (type 3) showed a marked reduction in the repair of (6-4) photoproducts (Broughton *et al.,* 1990).

Glickman *et al.* (1986) demonstrated in E. *coli* that the cytosine-cytosine pyrimidine-pyrimidone (6-4) photoproduct is highly mutagenic; however, in other studies (e.g., Flutchinson *et al., 1988),* cyclobutane dimers were shown to be responsible for the majority of observed mutations. Assessment of the relative contributions to mutagenesis of all dipyrimidine photoproducts will require comprehensive studies in different biological systems with specifically designed sequences containing the appropriate photoproducts. Both pyrimidine dimers and pyrimidine-pyrimidone (6-4) photoproducts appear to be important in inducing cytotoxic and mutagenic lesions in human cells, although the relative contributions of each type remain controversial (Mitchell, 1988).

(c) *Thymine glycols*

A group of monomeric ring-saturated lesions of the 5,6-dihydroxydihydrothymine type (thymine glycols) have been detected by alkaline-acid degradation in the DNA of UV-irradiated human cells (Hariharan & Cerutti, 1976, 1977). Alkaline-acid degradation (see Cerutti, 1981) can be used to detect a class of structurally related lesions rather than a single lesion, with a yield that has been estimated to be approximately 20% of the total of ring-saturated thymine products (t_{sat}).

Two aspects of this class of UV photoproduct are of particular interest: firstly, they are closely related to a class of ionizing radiation products and are believed to arise through a similar mechanism, i.e., indirectly *via* the action of hydroxyl radicals; secondly, their yield (relative to that of other UV-induced base damage) increases with exposures in the UVB

region. Measurements in HeLa cells showed that at 265 nm the ratio of thy↔thy to t_{sat} was 21, whereas at 313 nm the ratio decreased to 1.3 (Cerutti & Netrawali.]979). The saturated thymine damage induced by UVA and UVB radiation may thus be due to the effects of active oxygen species generated *via* endogenous cell components. There is little evidence pertaining to the lethal or other biological consequences of such lesions in mammalian cells, although a glycosylase capable of repairing these lesions has been isolated from human cells (Higgins *et al.* 1987).

(d) *Cytosine damage*

The photochemical induction of pyrimidine hydrates has been reviewed (Fisher & Johns, 1976). Significant levels of hydrates are probably formed initially by UVR; however, their instability hampers measurement of their induction and removal in cells, and it has not been possible to establish a cause-and-effect relationship between photohydrate induction and biological effects *in viva.* Using sequencing techniques, Gallagher *et al.* (1989) observed incision by human endonucleases of unidentified cytosine photoproducts that were neither cyclobutane-type nor (6-4) pyrimidine dimers. The frequency of these two photoproducts was two orders of magnitude lower than that of pyrimidine dimers, and the optimal wavelengths for induction were between 270 and 295 nm.

(e) *Purine damage*

Purine damage has been studied less frequently than pyrimidine damage, since the quantum yields are at least one order of magnitude lower; however, the development of sequencing techniques has made their detection easier (Kumar *et al.,* 1991). Incisions (endonuclease V) are detected at unidentified purine or purine-pyrimidine moieties after broad-spectrum UV irradiation (Gallagher & Duker, 1986). Such damage appears to be induced maximally in the wavelength region of 260-300 nm (Gallagher & Duker, 1989). Although the overall yield is much lower than that of pyr↔pyr, similar yields occur at certain loci.

(f) *DNA strand breaks*

UVC radiation induces a lower proportion of single-strand breaks than of other photoproducts. In contrast, strand breaks are the commonest initial lesion induced by ionizing radiation. Although strand breaks form only a minority of lesions after irradiation at wavelengths up to 365 nm, they become increasingly important at longer wavelengths in the solar UV region (290-400 nm). At 313 nm, the ratio of DNA strand breakage to pyr↔pyr induction in intact *E. coli* was 1:44 (Miguel & Tyrrell, 1983), whereas at 365 nm one strand break was formed for approximately every two pyrimidine dimers (Tyrrell *et al.,* 1974). An action spectrum for break induction in *Bacillus subtilis* DNA *in vivo* is available (Peak & Peak, 1982). More recently, an action spectrum for single-strand breaks in human skin cells has been determined which shows that irradiation in the presence of deuterium (which enhances singlet oxygen lifetime) increases the number of strand breaks observed at 365 and 405 nm. At wavelengths of 405 nm and longer, strand breaks and DNA-protein cross-links are the only forms of photochemical damage that have been determined (Peak *et al.,* 1987). Between 10 and 20% of the breaks induced at 365 nm are not frank breaks but rather alkali-labile bonds which presumably include apurinic and apyrimidinic sites (Ley *et al.*,

1978; Peak & Peak, 1982). The formation of breaks is strongly dependent upon oxygen at both 313 (Miguel & Tyrrell, 1983) and 365 nm (Tyrrell *et al.,* 1974; Peak & Peak, 1982). Their formation *in vitro* at 365 nm is also quenched by free-radical scavengers. Strand breaks are repaired rapidly by a variety of cellular mechanisms in both prokaryotes and eukaryotes. The role of these lesions in the biological action of solar radiation is not well understood (Tyrrell *et al.,* 1974).

(g) *DNA-protein cross-links*

The photochemical addition of nucleic acids to amino acids and proteins both *in vitro* and *in vivo* has been the subject of several reviews (Smith, 1976; Shetlar, 1980). Of the 22 common amino acids, 11 undergo photochemical addition to labelled uracil, the most reactive of which is cysteine, and several heterophotoproducts involving cysteine have been isolated and characterized.

Several prokaryotic and eukaryotic proteins have been cross-linked photochemically to DNA *in vitro,* including DNA polymerase, RNA polymerase, helix destabilizing protein and mixtures of proteins (Shetlar, 1980).

There is evidence that DNA-protein cross-links are formed in mammalian cells in significant yields by wavelengths longer than 345 nm (Bradley *et al.,* 1979; Peak & Peak, 1991). Action spectra for the formation of DNA-protein cross-links in human cells have now been obtained. Two peaks of induction are observed: one at 254-290 nm, corresponding to the peak of DNA absorption, and a second at 405 nm, presumably resulting from a photosensitization reaction (Peak *et al.,* 1985). [The Working Group noted that DNA-protein cross-links are likely to have important consequences for cells, but no data are available to allow evaluation of their effects in eukaryotic cells.]

4.3.2 *Other chromophores and targets*

In addition to DNA, many other cellular components absorb and/or are damaged by solar UVR and may influence the biological outcome of exposure. Both informational and transfer RNA molecules are susceptible to photomodification. Studies in insects indicate that damage to messenger RNA may be relevant to embryonic development, but the relevance of these results to mammalian systems is unclear (Kalthoff & Jäckle, 1982). Detailed results of bacterial studies on the photolability of certain components of transfer RNA (Jagger, 1981) are almost certainly not relevant to mammalian cells. Damage to proteins could lead to modification of the level of persistent primary damage in DNA, such that cellular DNA repair and antioxidant pathways are compromised (Tyrrell, 1991). There is also evidence that components of electron transport and oxidative phosphorylation, as well as membranes and membrane transport systems, can be damaged by solar wavelengths (Jagger, 1985). Non-DNA chromophores and targets become particularly relevant at longer wavelengths.

(a) *Chromophores*

Both nucleic acids and proteins weakly absorb UVA, and, although direct photochemical events may occur, it appears likely that the initial event in the biological effects of UVA radiation is absorption by a non-DNA chromophore which results in generation of active oxygen species or energy transfer to the critical target molecules. As a consequence, at long

UV wavelengths, the range of targets is extended to all critical molecules that are susceptible to active intermediates generated by chromophores.

Most of the knowledge on relevant chromophores has been obtained from in-vitro experiments or from studies in bacteria (Eisenstark, 1987). Indirect evidence indicates that porphyrins play a role in the inactivation of *Propionibacterium acnes* by UVA (Kjeldstad & Johnsson, 1986). It has also been shown that E. *coli* mutants defective in the synthesis of δ-aminolaevulinic acid are resistant to inactivation by UVA (Tuveson & Sammartano, 1986), which strongly suggests that porphyrin components of the respiratory chain act as endogenous photosensitizers. This conclusion is supported by the finding that strains that overproduce cytochrome were sensitive to broad-band UVA radiation (Sammartano & Tuveson, 1987). Porphyrins are also essential to human cellular metabolism, and overproduction of iron-free porphyrins in erythropoietic or hepatic tissues is the underlying cause of the photodestruction of the skin seen in the group of diseases known as porphyrias. Although direct evidence is lacking, free porphyrins and proteins containing haem (such as catalase, peroxidases and cytochromes) are also potentially important chromophores in skin cells from normal individuals. Many other cellular compounds which contain unsaturated bonds, such as flavins, steroids and quinones, should also be considered potential chromophores. Although normal levels of catalase (which contains haem) and alkyl hydroperoxide reductase (which contains FAD) would be expected to exert a protective role in bacteria (see below), overproduction of these enzymes is correlated with an increase in sensitivity to UVA radiation in bacteria (Kramer & Ames, 1987).

Porphyrins are an important class of photodynamic sensitizers which are believed to exert their biological action *via* the generation of singlet oxygen. Recent experiments have shown that deuterium oxide (which prolongs the lifetime of singlet oxygen) sensitizes human fibroblast cell populations to the lethal action of UVA radiation, while sodium azide (which destroys singlet oxygen) protects them (Tyrrell & Pidoux, 1989). Although this finding is consistent with the involvement of porphyrins in the lethality of UVA, other cellular compounds may also generate singlet oxygen. It is also important to consider active oxygen species that may be generated intracellularly. Not only can hydrogen peroxide be generated by UVA irradiation of tryptophan (McCormick *et al.,* 1976), but both superoxide anion and hydrogen peroxide can be generated by photo-oxidation of NADH and NADPH (Czochralska *et al.,* 1984; Cunningham *et al.,* 1985).

The presence of chromophores (such as psoralens) in the diet may also influence susceptibility to damage, but this reaction is clearly subject to enormous individual variability. Accidental and deliberate application of chemical agents (such as sunscreens and drugs) to the skin may also introduce potentially damaging chromophores.

(b) *Membranes*

The lipid membrane is readily susceptible to attack by active oxygen intermediates. Many reports (e.g., Desai *et al.,* 1964; Roshchupkin *et al.,* 1975; Putvinsky *et al.,* 1979; Azizova *et al.,* 1980) have shown that UVR can induce peroxidation of membrane lipids. In-vitro studies with lecithin microvesicles have shown UVR-induced changes in the microviscosity of membrane bilayers (Dearden *et al.,* 1981) which are correlated with the degree of unsaturation of fatty acid chains (Dearden *et al.,* 1985). UVC and UVA radiation

and sunlight have been shown to cause lipid peroxidation in the liposomal membrane (Mandal & Chatterjee, 1980). Haem proteins such as cytochrome *c* and catalase are known to catalyse lipid peroxidation and peroxidative breakdown of membranes (e.g., Brown & Wüthrich, 1977; Goñi *et al.,* 1985; Szebeni & Tollin, 1988). A dose-dependent, linear increase in lipid peroxidation of liposomal membranes was induced by UVA radiation, which was inhibited to a large extent by butylated hydroxytoluene, a nonspecific scavenger of lipid-free radicals. Since both sodium azide and L-histidine (quenchers of singlet oxygen) led to 40-50% inhibition of peroxidation, the authors suggested that singlet oxygen is involved in initiation of the reaction (Bose *et al.,* 1989).

UVA irradiation of liposomes leads to lipid peroxidation in the absence of photosensitizer molecules, so that singlet oxygen may arise through direct stimulation of molecular oxygen (Bose *et al.,* 1989). Biological membranes are, however, rich in endogenous photosensitizer molecules, such as those involved in electron transport, and these may contribute to the peroxidation of lipids observed in biological systems (see Jagger, 1985). Membrane damage has long been implicated in the lethality of UVA in bacteria (Hollaender, 1943) and almost certainly contributes to the sensitivity of UVA-treated populations plated on minimal medium—a phenomenon which is highly dependent on oxygen (Moss & Smith, 1981). Sensitivity to UVA has been related to levels of unsaturated fat in membranes (Klamen & Tuveson, 1982; Chamberlain & Moss, 1987). Furthermore, the presence of deuterium oxide enhances the levels of membrane damage, sensitivity to UVA and lipid peroxidation (Chamberlain & Moss, 1987), suggesting that singlet oxygen plays a role in all three processes. Leakage experiments have also been used to assess UVA-induced membrane damage in yeast: again, changes in permeability correlated well with lethality and were highly oxygen dependent (Ito & Ito, 1983). UVA irradiation of cultured human and mouse fibroblasts led to the release of arachidonate metabolites from the membrane in a dose-dependent fashion. The release was also dependent on the presence of both oxygen and calcium ion and may be related to the induction of cutaneous erythema, which is also oxygen dependent (Hanson & DeLeo, 1989). Studies of the effects of UVR on membrane transport have been undertaken in prokaryotes (Jagger, 1985), but no information was available on the effects of UVR on eukaryotic membrane transport.

4.4 Human excision repair disorders

4.4.1 *Xeroderma pigmentosum*

The commonest, most characteristic photoproducts produced in DNA by UVB and UVC radiation involve adjacent pyrimidines. Evidence summarized above argues strongly that these products give rise to a wide variety of alterations in DNA sequence and gene expression. Like many other types of DNA damage, these photoproducts may be excised, and the resulting gap in one strand can be resynthesized accurately using the undamaged strand as a template. How this is accomplished is best understood in the bacterium *E. coli,* in which a multiprotein complex including the products of the *uvr* A, B and C genes excises an oligonucleotide 12 or 13 bases in length containing the photoproduct. The resulting gap is filled by a DNA polymerase (usually III), and the final ligase link to the adjacent DNA is effected by polynucleotide ligase (Bridges *et al*., 1987; Bridges, 1988; Bridges & Bates,

1990). Other gene products are involved in the process, and a more comprehensive discussion is given by Sancar and Rupp (1983). Bacteria that have defects in the *uvr* A or B genes cannot excise UV photoproducts and are 10-20 times more sensitive to killing and the induction of mutations by UVC. They are also more sensitive to UVB and (under certain conditions) UVA (Webb, 1977). It can be concluded that the function of excision repair is to minimize the deleterious consequences of DNA damage, such as the persistence of UV photoproducts.

A similar process takes place in humans. Although much less is known about the mechanism, many genes have been shown to be involved, and these are being cloned and the role of their products is being elucidated (Hoeijmakers & Bootsma, 1990; Bootsma & Hoeijmakers, 1991). Like bacteria, humans can also be deficient in aspects of excision repair. The prototypic example is the genetic disorder xeroderma pigmentosum, which is actually a complex of disorders comprising at least 10 different forms of DNA repair defect (nine excision defective complementation groups and one excision repair proficient variant group) (Kraemer *et al*., 1987; Cleaver & Kraemer, 1989). The sensitivity of fibroblasts and lymphocytes from excision-defective individuals with xeroderma pigmentosum to mutation and lethality by UVC is up to 10 times greater than that of cells from normal individuals (Arlett *et al.,* 1992) and for UVR from a solar simulator (Patton *et al.,* 1984). The pigmentary abnormalities are confined to sun-exposed portions of the skin.

The incidences of turnouts of the skin, anterior eye and tip of the tongue in these individuals are much higher than those in unaffected populations (Kraemer et *al.,* 1987), and the median age of patients at onset of skin cancers appears to be much younger than that of the general population. Multiple primary skin cancers are common which arise predominantly on sunlight-exposed areas of the body (Kraemer et *al.,* 1987); there is anecdotal information that they are largely prevented if protection against exposure to sunlight is afforded early in life (Kraemer & Slor, 1984). Studies of patients with excision-defective xeroderma pigmentosum provide the strongest evidence that sunlight-induced photoproducts can result (in the absence of repair) in the genesis of basal-cell carcinomas, squamous-cell carcinomas and melanomas and strongly support the contention that they can also do so in normal individuals in whom repair is more efficient (although probably never complete). The photoproducts that fail to be excised in xeroderma patients are known to be produced in human skin, not only by UVC (used in most laboratory experiments with cells) but also by UVB, particularly by wavelengths around 300 nm (Bridges, 1990; Athas *et al*., 1991). Action spectra show that the difference in the cytotoxic action of UVB on cultured cells from normal and xeroderma pigmentosum patients is similar to that of UVC, whereas the differences in the response to UVA are only slight (Keyse *et al*., 1983). The studies on xeroderma pigmentosum illustrate that DNA repair is a major defence of the human skin against the carcinogenic action of sunlight.

4.4.2 *Trichothiodystrophy*

The conclusions derived from studies of xeroderma pigmentosum have become more complex with the availability of information on two related excision disorders. Trichothiodystrophy is a rare disease in which patients generally have skin judged to be sun-sensitive by erythemal response but no indication of the pronounced freckling or elevated incidence of early skin tumours associated with xeroderma pigmentosum (Bridges, 1990). In the

majority of cases studied, trichothiodystrophy is associated with a deficiency in the ability to repair UV-induced damage in cellular DNA.

Three categories of response to UVR have been identified. In type 1, the response is completely normal, whereas type-2 cells are deficient in excision repair, with properties indistinguishable from those of xeroderma pigmentosum complementation group D. Type-3 cells survive normally after UV irradiation, and the rates of removal of cyclobutane pyrimidine dimer sites are also normal (Broughton *et al.,* 1990). In xeroderma pigmentosum diploid fibroblast lines, catalase activity was decreased on average by a factor of five as compared to controls, while heterozygotic lines exhibited intermediary responses. All trichothiodystrophy lines tested were deficient in UV-induced lesion repair and exhibited a high level of catalase activity; however, molecular analysis of catalase transcription showed no difference between normal, xeroderma and trichothiodystrophy cell lines. UV irradiation induces five times more hydrogen peroxide production in xeroderma lines than in trichothiodystrophy lines and three times more than in controls. These striking differences indicate that UVR, directly or indirectly, together with defective oxidative metabolism may increase the initiation and/or the progression steps in patients with xeroderma pigmentosum to a greater degree than in people with trichothiodystrophy, which may partly explain the different tumoral phenotypes in the two diseases (Vuillaume *et al.,* 1992).

Five patients with trichothiodystrophy type 2 appeared to be in one of the xeroderma pigmentosum complementation groups: Fibroblasts from these individuals were indistinguishable from xeroderma fibroblasts in the same complementation group and were equally sensitive to the lethal and mutagenic effects of UVC (Stefanini *et al.,* 1986; Lehmann *et al.,* 1988). Two other trichothiodystrophy patients (type 3) had cells markedly defective in the removal of (6-4) pyrimidine photoproducts but not cyclobutane-type dimers (Broughton *et al*., 1990).

4.4.3 *Cockayne's syndrome*

A third sun-sensitive excision repair disorder is Cockayne's syndrome. Patients with this condition have fibroblasts which undergo normal excision repair in the overall genome but which are defective in the excision of dimers from DNA strands undergoing active transcription (Mayne *et al.,* 1988). Cockayne's syndrome cells are sensitive to both killing and mutation induction by UVC (Arlett & Harcourt, 1983) and have reduced repair of cyclobutane dimers; they show, however, normal repair of non-dimer photoproducts in a UV treated shuttle vector plasmid. Like patients with trichothiodystrophy, those with Cockayne's syndrome do not have pronounced freckling or enhanced early incidence of skin cancers (Barrett *et al.,* 1991).

4.4.4 *Role of immunosuppression*

If it is assumed that UV-induced DNA damage sustained by patients with trichothiodystrophy type 2 results in the same photo-induced mutations in their skin cells (including mutations associated with the initiation of cancer) as is seen in xeroderma pigmentosum patients of the same complementation group (D) (Bridges, 1990; Broughton *et al.,* 1990), something other than unrepaired DNA damage and an elevated frequency of mutations must be needed to trigger initiated cells into clonal expansion and early tumours, as is seen in xeroderma pigmentosum. The assumed latency of initiated cells in such trichothiodystrophy

patients may be related to the latency seen in epidemiological studies of skin cancer in the normal population (see section 2).

The nature of the circumstances that allow initiated skin cells to develop into tumours in xeroderma pigmentosum patients, and perhaps later in life in other individuals, is unclear. Burnet (1971) first suggested that individuals with this disorder might be deficient in some immunosurveillance step. Bridges (1990) proposed that theywere also hypersensitive to both the immunosuppressive and the mutagenic action of UVR, so that the elevated skin cancer rate in individuals with xeroderma pigmentosum would not accurately reflect the actual increase in mutation frequency in exposed skin but would exaggerate it greatly.

4.5 Genetic and related effects

Any cell that is UV-irradiated can be expected to sustain DNA damage. The nature of this damage is wavelength-dependent, and the major photoproducts of short-wavelength UV irradiation are various types of dipyrimidine photoproducts, while DNA strand breakage and DNA-protein cross-linkage occur relatively more frequently after irradiation with long-wavelength UVR. As the wavelength is increased above 290 nm, the efficiency of formation of pyrimidine dimers and other DNA photoproducts decreases greatly. This wavelength dependency of response presents a fundamental problem for the quantitative interpretation of the genetic activities of different regions ofthe UV spectrum. In most experimental studies with UVA and UVB irradiation and, of course, simulated solar radiation, monochromatic radiation was not used. Also, the characteristics of the radiation emitted from the source are variable over time and from source to source. Because of these practical considerations, comparisons of the effects seen in different studies in terms of dose are commonly invalid: Photoproduct yield is dependent on the energy contributions from the different wavelengths within the spectrum used, but incident doses (fluences) are measured only as energy fluxes over the whole spectrum emitted from the source. The problem of dosimetry within experimental systems is compounded by the fact that absorbed dose is determined by the geometry of the system and the position of the target within it: absorption by one layer (e.g., the medium or a layer of cells) will affect the fluence incident upon the layer beneath. The fluence absorbed may thus differ substantially from the incident fluency of the system. For these reasons, it was considered inappropriate to compile quantitative genetic profiles as is customary in these monographs.

Given the generally significant responses in many different tests for the genetic activity of UVR in a wide range of organisms and cultured cells, the simple qualitative questions appear to have been answered in abundance. The main issues of outstanding interest are: identification of the types of damage induced by the valious portions of the UVspectrum; the mechanisms by which damage is translated into mutation or other genetic changes; and the dose characteristics of these responses.

4.5. 1 *Humans*

The portions of the body that receive most exposure to UVR are the skin, anterior eye and lip. Because dermal capillaries approach the skin surface, it can be anticipated that

Blood will be exposed to the portion of UVR (see Kraemer & Weinstein, 1977; Morison *et al.,* 1979a; Larcom *et al.,* 1991) that penetrates the dermis. The biological consequences of this exposure are unknown.

DNA damage in skin cells has been studied using three methods that are sensitive enough to detect DNA damage after exposure to doses of UVR too low to induce erythema:

(i) use of antibodies specific for UV-altered DNA, followed by immunofluorescence. This method can be used with immunoperoxidase staining and a secondary antibody (Eggset *et al.,* 1983, 1986) or without them (Tan & Stoughton, 1969);

(ii) autoradiography after tritiated thymidine incorporation (Epstein *et al*., 1969, 1970; Hönigsmann *et al*., 1987; Wolf *et al*., 1988); and

(iii) treatment of extracted DNA with Micrococcus luteus cyclobutyl pyrimidine dimer site-specific endonuclease, followed by alkaline agarose gel electrophoresis of the single-stranded DNA fragmented at the dimer sites (Sutherland *et al*., 1980; D'Ambrosio *et al*., 1981; Gange *et al*., 1985; Freeman *et al*., 1986, 1987, 1989; Alcalay *et al*., 1990). This method suffers the disadvantage that damage cannot be localized to particular layers of the skin, but dimer yield can be calculated. Methods for the study of resolved genetic damage have not been pursued.

(a) *Epidemis*

(i) *Broad-spectrum ultraviolet radiation, including solar simulation*

Effects on DNA synthesis were demonstrated in human skin *in vivo* which had been exposed to three times the MED of UVR (< 320 nm; mercury arc lamp [Fig. 9a, p. 64]) and then injected intradermally with tritiated thymidine (8-41 x 10^6 ergs/cm^2 [8-41 kJ/m^2]) in the irradiated area immediately and at 0.25, 3, 5 and 24 h subsequently. S Phase was suppressed in cells of the basal layer at 3-h and 5-h sampling times, but not at 24 h. Sparsely labelled cells (indicating DNA repair) occurred in greatly variable proportions from person to person in the basal, malpighian and granular layers at 0, 0.25. 3 and 5 h, but not at 24 h, indicating that repair was complete by 24 h (Epstein *et al.,* 1969). DNA repair was also reduced in the skin cells of three patients with xeroderma pigmentosum in comparison to eight normal controls (Epstein *et al.,* 1970).

Sutherland *et al.* (1980) demonstrated a dose-related response for the induction of pyrimidine dimers after exposure to a Westinghouse sun lamp (Fig. 9c, p. 64), with 50%, energy < 320 nm, at 0, 970, 1940 and 3880 J/m^2. In one subject. 0.5 of the MED of sun-lamp exposure resulted in about 6 ± 0.6 dimers per 10^8 Da.

D'Ambrosio *et al.* (1981) reported that approximately 12.8 and 23.6 dimers per $l0^8$ Da were induced in skin DNA *in vivo* following irradiation with a mercury arc lamp (200-450 nm) at 150 and 300 J/m^2, respectively. Repair or removal of dimers was measured 0-24 h following exposure. About 50% of the dimers were lost 58 min after irradiation, and less than 10% remained at 24 h. ln an experiment with patients with lupus erythematosus, D'Ambrosio *et al.* (1983) obtained results similar to those found in the skin of normal individuals.

Strickland *et al.* (1988) measured the induction of cyclobutane dithymidine photoproducts in human skin samples after exposure to simulated solar radiation. Tissue samples from three non-pigmented (white) individuals were exposed to 18 or 36 kJ/m^2 UVR (0.5-1 MED), and those from three constitutively pigmented (black) individuals were exposed to

72 and 144 kJ/m^2. Constitutively pigmented skin required doses of UVR two to four times higher than non-pigmented skin to produce roughly equivalent levels of thymine dimers. [The Working Group noted the small number of people studied.]

(ii) *UVA radiation*

Freeman *et al.* (1987) showed in two subjects that similar pyrimidine dimer yields were produced in skin by a broad-band UVA source (UVASUN 2000), by broadband UVA filtered to remove all light of wavelengths < 340 nm and by narrow-band radiation centred at 365 nm (xenon-mercury compact arc), indicating that UVA radiation and not stray shorter wavelength radiation was responsible. Dimer production was observed following exposures to 5 x 10^5 J/m^2. Since exposure to a UVA-emitting tanning lamp results in a dose of about 5 x 10^5 J/m^2, UVA exposure for cosmetic purposes could result in measurable levels of DNA damage.

(iii) *UVB radiation*

The efficiency of UVA- and UVB-induced tans in protecting against erythema and the formation of dimers induced by UVB was studied in five subjects by Gange *et al.* (1985). The radiation sources were a UVASUN 2000 lamp (UVA; Fig. 8d, p. 61) and an FS36 Elder fluorescent sunlamp (UVB). UVB-induced tanning protected against erythema produced by subsequent UVB exposure two to three times better than UVA-induced taming; however, tanning with either UVA or UVB was associated with a similar reduction in yield of endonuclease-sensitive sites in epidermal DNA (about 50%).

Eggset *et al.* (1983) observed DNA damage in both epidermis and dermis following exposure to a Westinghouse FS-20 sunlamp(Fig. 9c, p. 64) at 0.5-2 MED (2 MED , 900 J/m^2). The outer layers were more heavily damaged after small doses than the basal layer, which may be better protected by its deeper location and shielding by melanin. The authors claimed that DNA repair was well under way after 4-5 h and was apparently nearly complete at 24 h, as judged by immunofluorescence and immunoperoxidase staining. Repair was faster in the presence of visible light than when irradiated skin was shielded with thick black plastic. [The Working Group noted the absence of quantitative data.]

In a study of two volunteers (Eggset *et al.,* 1986), tanning was shown to protect against DNA damage in skin (induced in a UVB solarium), but the conclusions were based solely on observations of immunofluorescence. [The Working Group noted the absence of quantitative data.]

Freeman *et al.* (1986) measured UVB-induced DNA damage in the skin of seven individuals with different sensitivities to UVB irradiation, as measured by the MED, with irradiation from an FS36 Elder fluorescent sunlamp (280-320 nm). The production of dimers was correlated inversely with the MED. The slopes of the dose-response curves for the most UVB-sensitive individual (MED, 240 J/m^2) and for the least sensitive individual (MED, 1460 J/m^2) were 11.5 x 10^{-4} and 2.6 x 10^{-4} dimer sites per 1000 bases per mJ/cm^2 [10 J/m^2], respectively.

Hönigsmann *et al.* (1987) studied unscheduled DNA synthesis in epidermal cells in the skin of 25 male volunteers (four with skin type II and 21 with skin type III; see pp. 168-169) after exposure to doses of UVB of 0.06-6 MED, from a 6-k W xenon arc lamp (292-304 nm). The MED values ranged from 140 to 550 J/m^2. The dose-response curve showed a

significant increase in unscheduled DNA synthesis between 0.06 and 1 MED but no difference between 1 and 6 MED, suggesting a saturation of excision repair *in vivo.*

Freeman (1988) studied interindividual variability in 17 healthy volunteers in the repair of pyrirnidine dimers induced following exposure to 0.25-1.5 MED from a Westinghouse FS-40 sunlamp (see Fig. 9c, p. 64). Removal of dimers was detected within 6 h of irradiation. The average half-time for removal of dimers was 11.0 ± 4.3 (SD) h (range, 5.5-21.1 h). [The Working Group noted that the spectra and doses used in this study were different from those used by D'Ambrosio *et al.* (1981). It is not clear if the interindividual variability is greater than the experimental error.]

Interindividual variability in the repair of UVB-induced pyrimidine dimers was also studied by Alcalay *et al.* (1990) in 22 patients aged 31-84 with at least one basal-cell carcinoma. The control group consisted of 19 cancer-free volunteers aged 25-61. Both groups were given one MED of radiation from a 150-W xenon arc solar UV-simulated lamp equipped with a 50-cm liquid light guide and a filter eliminating wavelengths below 295 nm. Dimers were measured immediately and after 6 h. The two groups were similar at time 0, but after 6 h, 22 ± 4% (range about 8-64) of the dimers were removed in the cancer group compared to 33 ± 4% (range about 4-64) in the control group. Of the cancer patients, 23% had repaired more than 30%, of the DNA damage, compared to 53% of the control group. [The Working Group noted that it is not clear if the interindividual variability is greater than the experimental error.]

Wolf *et al.* (1988) observed measurable amounts of unscheduled DNA synthesis in the skin of 23 volunteers exposed to 0.5 MED UVB irradiation from a high-pressure mercury lamp [spectral emission not given]. Administration of carotenoids (to reduce light sensitivity in patients with erythropoietic protoporphyria) at a dose of 150 mg per day for 30 days did not significantly alter the amount of unscheduled DNA synthesis (6 ± 1.2 grains/cell before and 8 ± 2 grains/cell after carotenoid treatment; seven subjects). The same investigation showed no significant protection by carotenoids against UVA-, UVB- or PUVA-induced erythema, on the basis of pre- and post-carotenoid MED or minimal phototoxic dose.

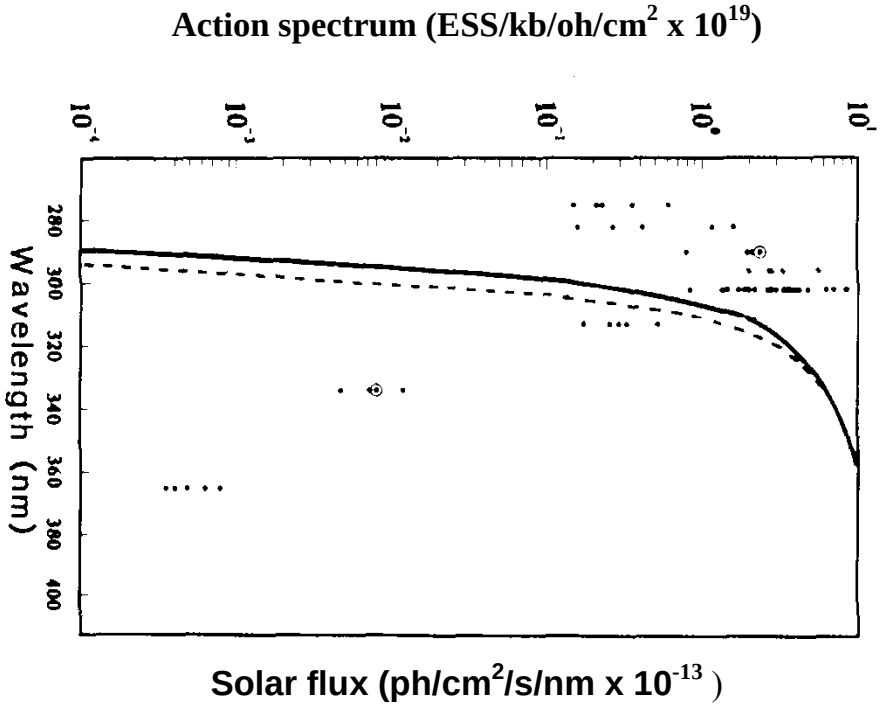
In 30 volunteers, it was demonstrated that the action spectrum for the frequency of pyrimidine dimer formation in human skin DNA for a given fluence (incident dose) has its maximum near 300 nm and decreases sharply on either side of this wavelength (Fig.12). The decrease at < 300 nm is probably due to absorption in the upper layers of skin. These data were used to estimate that, at a solar angle of 40 °, a reduction in the thickness of the stratospheric ozone layer from 0.32 cm down to 0.16 cm would be expected to result in a 2.5-fold increase in dimer formation (Freeman *et al.,* 1989).

A dose-response for the formation of thymine dimers in epidermal cells isolated from human skin irradiated with UVB *in vitro* was determined by Roza *et al.* (1988) using a monoclonal antibody.

(iv) *UVC radiation*

Exposure of human skin, from which the stratum corneum had been removed, to either a germicidal (UVC) or a Hanovia hot quartz lamp *in vivo* resulted in DNA damage demonstrable by immunofluorescence (Tan & Stoughton, 1969). When the stratum corneum was intact, DNA damage was detected only after exposure to the germicidal lamp.

Fig. 12. Action spectrum for pyrimidine dimer formation in human skin (•) and solar spectra at the surface of the Earth for stratospheric ozone levels of 0.32 cm (dotted line) and 0.16 cm (solid line). Each point in the action spectrum represents the slope of the dose-response line (dimer yields at three exposures) for one volunteer at one wavelength, obtained from triplicate independent determinations. Thirty points occur at 302 nm, although some points overlie other values; five points occur at each other wavelength: points at 290 and 334 nm are circled to indicate that identical dimer yields were recorded for two volunteers. ph, photon; ESS, endonuclease-sensitive site



From Freeman *et al*. (1989)

[The Working Group noted that more sensitive analytical techniques for DNA damage are now available.]

(b) *Lymphocytes*

(i) *Broad-spectrum ultraviolet radiation*

In addition to cells of the skin, white blood cells are also subject to exposure to UVB and UVA, partly because some are temporarily resident in the skin and partly because it has been estimated that the equivalent of the total blood volume circulates through the dermal capillaries approximately every 11 min (Kraemer & Weinstein, 1977). Detecting effects, e.g., on lymphocytes, is likely to be extremely difficult owing to the fact that they are continually moving between the blood and other tissues; indeed, 90% of the lymphocyte population at any given time is resident outside the blood. Thus, the concentration in the

blood of any lymphocytes irradiated while passing through the skin may fall substantially over time after irradiation ends as they are diluted in the whole body lymphocyte pool. Extravascular lymphocytes resident in the skin may also receive higher doses of UVR. Nevertheless, studies have been reported of genetic or related effects on lymphocytes sampled from peripheral blood.

Larcom *et al*. (1991) examined the capacity for DNA synthesis of lymphocytes from eight subjects exposed in two commercial tanning salons. Blood was taken immediately before tanning and again 24 h after tanning. System I used a sunlamp with a UVB:UVR ratio of 0.02% for 280-300 nm and 1.4% for 300-315 nm; the output of system II (Solana Voltarc lamp) was not indicated. There was a 24-84% (average, 53%) decrease in phytohaernagglutinin-induced DNA synthesis with system I and a 8-58% (average, 30%) decrease with system II.

(ii) *UVA radiation*

Seven of 13 psoriasis patients receiving oral 8-methoxypsoralen and high-intensity, long-wave UVA radiation had reduced leukocyte DNA synthesis; this did not occur in any of 10 controls (Kraemer & Weinstein, 1977). These results indicate that UVA reduces the incorporation of tritiated thymidine in lymphocytes circulating through the skin.

(iii) *UVP radiation*

In normal, fair-skinned subjects given whole-body exposure to 1.5-3 x MED doses of UVB from a sunlamp (280-380 nm), a dose-dependent decrease was seen in the incorporation of tritiated thymidine into DNA following stimulation by photohaemagglutinin; the proportion of circulating lymphocytes was decreased and the proportion of null cells was increased (Morison *et al.*, 1979a).

These studies indicate that leukocytes should be included in any inventory of human cells potentially exposed to solar radiation or artificial UVR.

4.5.2 *Experimental systems* [see Tables 32-35, in which exposures are separated according to type of UVR]

(a) *DNA damage*

Inhibition of DNA synthesis has been induced in hairless albino mouse epidermis at wavelengths of 260-320 nm, with a maximal effect at 290 nm. Inhibition was not detected at 335 nm (Kaidbey, 1988). The action spectrum was similar to that for formation of cyclobutane-type pyrimidine dimers (Cooke & Johnson, 1978; Ley *et al*., 1983) and pyrimidine-pyrimidone (6-4) photoproducts in mouse skin (Olsen *et al*., 1989). Pyrimidine dimers (measured as endonuclease-sensitive sites) have been measured in the corneal DNA of the marsupial, *M. domestica.* following exposure to a sunlamp (280-400 nm) (Ley *et al.* 1988).

While DNA is the main photochromophore for UVC, there is evidence that active oxygen intermediates are involved in the production of DNAdamage by UVA (Tyrrell, 1991). The production oi several types of photolesions is oxygen dependent (Tyrrell, 1484,1991). In addition, the irradiation lethality of both cultured bacterial (Webb, 1977) and mammalian (Danpure & Tyrrell, 1976) cells is dependent on the presence of oxygen; this observation was later linked with the production of singlet oxygen (Tyrrell & Pidoux,

1989). It has also been observed that irradiation of cultured human skin cells with UVB (302 nm, 313 nm), UVA (334 nm, 365 nm) and visible (405 nm) radiation is strongly enhanced in glutathione-depleted cells (Tyrrell & Pidoux, 1986, 1988). This apparent protection by glutathione appears to be due to its radical scavenging properties at the stated wavelength but may be due to induction of a more specific pathway (such as its essential role as a hydrogen donor for glutathione peroxidase) at longer wavelengths. Francis and Giannelli (1991) found that the abnormally high yield of single-stranded DNA breaks produced by UVA in six UVA-sensitive human fibroblasts (three from actinic reticuloid patients, two from sisters with familial actinic keratoses and internal malignancies and one from a patient with an abnormally high incidence of basal-cell carcinomas) could be reduced if sensitive cells were co-cultivated with normal fibroblasts or with radical scavengers. They suggested that the UVA-sensitive cells had deficits of small-molecular-weight scavengers of active oxygen species and that intercellular cooperation allows the transfer of these substances from resistant to sensitive cells. The presence of non-DNA chromophores that generate active oxygen species can also occur with UVC. Melanin, normally regarded as a solar screen, has also been associated with the formation of oxidative DNA damage, such as thymine glycols in mouse cells that vary in melanin content (Huselton & Hill, 1990). A slight increase in pyrimidine dimer yield was seen in human melanocytes as compared to keratinocytes following exposure to UVR at 254, 297, 302 and 312 nm but was significant only at 297 nm (Schothorst *et al.*, 1991).

(b) *Mutagenicity*

Numerous reports show that sunlight or solar-simulated radiation induces mutations in bacteria, plants, Chinese hamster ovary (CHO) and lung (V79) cells, mouse lymphoma cells and human skin fibroblasts.

Studies in bacteria exposed to radiation throughout the solar UV spectrum (reviewed by Webb, 1977) demonstrate mutagenic activity unambiguously. The effects of sunlight on mammalian cells have been reviewed (Kantor, 1985). UVA (320-400 nm) is mutagenic to yeast and cultured mammalian cells, UVB (290-320 nm) to bacteria and cultured mammalian cells and UVC (200-290 nm) to bacteria, fungi, plants, cultured mammalian cells, including CHO and V79 cells, and human lymphoblasts, lymphocytes and fibroblasts. Since wavelengths in the UVC range do not reach the surface of the Earth, they are of no significance as a source of damage in natural sunlight.

A characteristic of all of these studies is that UVA appears to be relatively inefficient as a mutagen in comparison with UVB and UVC when activity is expressed per unit of energy fluence, but not necessarily so when expressed per DNA photoproduct (see Tyrrell, 1984). Webb (1977) compiled action spectra for the introduction of mutations in bacteria, as did Coohill *et al.* (1987) for mutagenesis in human epithelial cells. In both *Salmonella* and human cells, wavelengths > 320 nm were at least 103 times less effective than those between 270 and 290 nm.

A comparison of the mutagenicity of various UV-containing light sources towards a set of S. *typhimurium* strains was reported by De Flora *et al*. (1990). The approach did not involve measurement of cytotoxicity, and mutagenicity was compared at roughly equitoxic doses rather than as a function of fluence. Halogen lamps were as mutagenic as 254-nm UVC and more mutagenic than fluorescent sunlamps or sunlight. The mutagenicity of

halogen lamps was attributed to their UVC component, in contrast to sunlight which produced mutagenic effects over a wide UV spectrum. The mutagenicity of halogen lamps, fluorescent lamps and sunlight was partially inhibited by catalase, suggesting that peroxides may be involved in this in-vitro system. It is also relevant that pretreatment of *E. coli* with hydrogen peroxide results in an increase in both UVA resistance and hydrogen peroxide scavenging ability (Moss, S.H., quoted by Tyrrell, 1985; Sammartano & Tuveson, 1985; Tyrrell, 1985).

Further evidence for the complexity of responses to the UVR region comes from Schothorst *et al. (* 1987b), who examined the mutational response of human skin fibroblasts to 12 lamps differing widely in their emission characteristics. Surprisingly, they found that, whatever the light source, mutation induction per MED was similar with UVC, UVB and solar radiation; with UVA (only one data point), mutation induction per MED was much greater. The authors emphasized that these conclusions hold only if it is valid to calculate the mutagenicity of a light source by adding the effects of the contributing wavelengths; however, the data of Coohill *et al.* (1987) argue against this assumption.

The inevitable consequence of the absorption spectrum maximum of DNA is that there is a considerable body of data on mutagenicity toward microorganisms of UVC, which is usually delivered by radiation from germicidal lamps with more than 90% of their output at 254 nm. The types of mutations that are induced by UVC and the mechanisms of their induction have been reviewed (Witkin, 1976; Hall & Mount, 1981; Walker, 1984; Hutchinson & Wood, 1986; Bridges *et al.,* 1987; Hutchinson, 1987). Specific cellular proteins, including the products of *rec*A and umuC genes, together with a cleaved derivative of the umuD gene product, must be present for mutations to result from most types of DNA damage. These proteins are themselves part of an inducible response to DNA damage, and their intracellular level increases dramatically when photoproducts or other lesions are detected in DNA. It is not yet clear to what extent inducible systems are involved in UV mutagenesis in higher eukaryotes.

Current evidence suggests that all photoproducts are likely to be potentially mutagenic, although with greatly different specificities and potencies. The major UV photoproducts, cyclobutane-type thymine-thymine dimers, are, for example, relatively weakly mutagenic (Banerjee *et al.,* 1988, 1990), owing in part to the propensity of polvmerases to insert adenine when the template instruction is unclear or missing (Sagher & Strauss, 1983; Schaaper *et al.,* 1983; Kunkel, 1984). The relatively minor (6-4) thymine-thymine photoproduct is, in contrast, highly mutagenic, the dominant mutation being a 3' T→C transition (LeClerc *et al.,* 1991). By far the most frequent UVC-induced change in human cells is the transition from G:C to A:T (Bredberg *et al.,* 1986; Seetharam *et al.,* 1987; Hsia *et al.,* 1989; Dorado *et al.,* 1991). A number of investigators have noted the production of tandem transitions from G:C,G:C to A:T,A:T. Although this is not the most frequent change, it seems to be particularly characteristic for UVC mutagenesis in human cells. The frequency of mutation per lethal event at the *hprt* locus (which detects a broad spectrum of mutations) is approximately the same at 254 nm and 313 nm in human lymphoblastoid cells: however, the mutation frequency per lethal event at the Na^+/K^+ ATPase locus (which detects point mutations) is considerably higher at 313 nm. This finding may indicate a difference in types of premutagenic lesions and/or rates of mutation between the two wavelength regions

(Tyrrell, 1984). Two bacterial studies provide positive evidence for the mutagenic activity of fluorescent lamps. De Flora *et al.* (1990) employed Sylvania 36 W cool white tubes with *E. coli* and *Salmonella* strains. [The Working Group had difficulty in evaluating these data because they are presented in a highly transformed format.] Hartman *et al.* (1991) used General Electric F15T8CW lamps; a lowest effective dose of 5500 J/m^2 can be estimated from the results with *Salmonella* tester strains. Filters that block wavelengths < 370 nm effectively eliminated mutagenesis, while radical scavengers such as superoxide dismutase or catalase stimulated mutagenesis.

Hsie *et al.* (1977) irradiated the *hprt* CHO system with Westinghouse white light F40CW lamps. The minimal effective dose was 3.96 x 106 J/m^2. Putting lids on the petri dishes reduced mutant frequency by 30%. [The Working Group noted that the results were based on a single dose point in a single experiment.] Jacobson *et al.* (1978) exposed mouse lymphoma L5178Y *tk*$^{+/-}$ cells to Sylvania F18T8 cool white lamps. The estimated lowest effective dose was 2 x l0^4 J/m^2. [The Working Group noted that the selective agent used, BUdR, is regarded as inefficient and has been superseded by trichlorothymidine, so these results require confirmation.]

(c) *Chromosomal effects*

Sunlamps have been shown to produce sister chromatic exchange in amphibian cells (Chao & Rosenstein, 1985) and in human fibroblasts (Bielfe1d *et al.,* 1989; Roser *et al.,* 1989). Fibroblasts from a panel of cutaneous malignant melanoma patients (Roser *et al.,* 1989) and heterozygotes of xeroderma pigmentosum (Bielfeld *et al.,* 1989) were more susceptible to the induction of both sister chromatic exchange and micronuclei than those from normal donors. Micronuclei were also induced in mouse splenocytes by exposure to sunlamps *in vitro* (Dreosti *et al.,* 1990).

A study with CHO cells provided evidence for a dose-related increase in the induction of sister chromatic exchange by UVA, but the increased induction of chromosomal aberrations showed no dose-response relationship (Lundgren & Wulf, 1988).

UVB induced sister chromatic exchange in CHO cells (Rasmussen *et al.,* 1989) and chromosomal aberrations in frog ICR 2A cells (Rosenstein & Rosenstein, 1985). In the latter study, photoreactivation reduced the number of chromosomal aberrations more effectively at 265, 289 and 302 than at 313 nm, suggesting that non-cyclobutane dimer photoproducts are more important primary lesions at the higher wavelength.

For UVC, more extensive data are available. Sister chromatic exchange was induced in Chinese hamster V79 (Nishi *et al.,* 1984) and CHO (Rasmussen *et al.,* 1989) cells. Chromatid exchange was also recorded in cultured fetal fibroblasts from New Zealand black mice, which proved to be more sensitive than BALB/c cells (Ready *et al.,* 1978). The induction of chromosomal aberrations in Chinese hamster cells has been reported on a number of occasions (Chu, 1965a,b; Trosko & Brewen, 1967; Bender *et al.,* 1973; Griggs & Bender, 1973; Ikushima & Wolff, 1974).

Exposure of frog ICR 2A cells to 254 or 265 nm radiation induced both sister chromatic exchange (Chao & Rosenstein, 1985) and chromosomal aberrations, while photoreactivating light significantly reduced the frequency of chromosomal aberrations, which implies a role for pyrimidine dimers in their genesis (Rosenstein & Rosenstein, 1985). Chromosomal

aberrations were also seen with *Xenopus* cell cultures (Griggs & Bender, 1973). The frequencies of sister chromatic exchange and chromosomal aberrations induced by UVC were reduced by photoreactivating light in chicken embryo fibroblasts (Natarajan *et al.*, 1980), lending further support to the concept that the cyclobutane pyrimidine dimer represents a primary lesion in these two end-points.

Parshad *et al.* (1980a) reported the induction of chromosomal damage in human IMR-90 fibroblasts following treatment with 4.6 W/m^2 over 20 h (331 kJ/m^2) from F15T8-CW tubes. Shielding and radical scavengers reduced the level of damage.

Extensive data are available on the induction of sister chromatic exchange in fibroblasts from patients with Bloom's syndrome (Krepinsky *et al.*, 1980), xeroderma pigmentosum (De Weerd-Kastelein *et al.*, 1977; Fujiwara *et al.*, 1981) or Cockayne's syndrome (Marshall *et al.*, 1980; Fujiwara *et al.*, 1981), as well as from normal individuals. In comparison with normal individuals, more sister chromatic exchanges were induced per lethal lesion in fibroblasts from excision-competent Bloom's syndrome (Kurihara *et al.*, 1987) and Cockayne's syndrome (Marshall *et al.*, 1980) patients. No such increase in sister chromatic exchange was seen in fibroblasts from excision-defective xeroderma pigmentosum patients or from an individual defective in the ligation step of repair (Henderson *et al.*, 1985).

The induction of sister chromatic exchange by UV irradiation has also been studied in human lymphocytes, with conflicting results. In one study, they were reported to be less responsive than either human fibroblasts or CHO cells (Perticone *et al.*, 1986), while another report, in which chromosomal aberrations were also studied, suggested that lymphocytes were more sensitive than fibroblasts in their response at both end-points (Murthy *et al.*, 1982). These results may have implications for the interpretation of the effect of UV on the immune system.

Fibroblasts from xeroderma pigmentosum patients are more sensitive to the induction of chromosomal aberrations than cells from normal donors (Parrington *et al.*, 1971; Parrington, 1972; Marshall & Scott, 1976). Seguin *et al.* (1988) showed that lymphoblastoid cells from five Cockayne's syndrome patients were similarly hypersensitive to UVC-induced chromosomal aberrations. The induction of micronuclei in two normal and three Bloom's syndrome-derived fibroblast cell cultures was reported by Krepinsky *et al.* (1980). One culture from a Bloom's syndrome patient, GM1492, proved to be exceptionally sensitive to the induction of micronuclei; the other two were indistinguishable from normal cells. This result emphasizes the potential importance of heterogeneity in response among patients with rare genetic syndromes.

(d) *Transformation*

Morphological transformation of mammalian cells has been induced by solar radiation, unshielded fluorescent tubes, solar simulators, UVA, UVB and, most extensively, UVC. There is weak evidence (Baturay *et al.*, 1985) for the induction of transformation by predominantly UVA radiation (20T12BLB bulbs) in BALB/c 3T3 cells. In the same report, UVA was shown to have promoting activity following initiation with ß-propiolactone. The most effective wavelength for Syrian hamster embryo cells (Doniger *et al.*, 1981) and human embryonic fibroblasts (Sutherland *et al.*, 1981) appears to be in the UVC range at about 265 nm. Transformation of human cells can be enhanced by delivering the dose on a number of

separate occasions (Sutherland *et al.,* 1988). It has also been reported that excision repair-defective xeroderma pigmentosum cells can be transformed to the anchorage-independent phenotype at lower doses than those required for cells from normal individuals (Maher *et al.,* 1982). Fisher and Cifone (1981) showed enhanced metastatic potential of mouse fibrosarcoma cells. Plasmids containing the human N-*ras* gene which were irradiated with UVR (254 nm) *in vitro* acquired the ability to transform cultured rat-2 cells after transfection; photoreactivation of irradiated plasmids eliminated their transforming ability (van der Lubbe *et al.,* 1988). In another study, UVB irradiation activated the human Ha-*ras* gene on a plasmid in a transformation assay with mouse NIH-3T3 cells (Pierceall & Ananthaswamy (1991).

An investigation of chromosomal breaks and malignant transformation in embryonic mouse cells (Sanford *et al.,* 1979; Parshad *et al.,* 1980b) revealed that exposure of cultured cells to fluorescent lamps induced malignant transformation, as measured by tumour formation following implantation into syngeneic hosts. The potential importance of active oxygen species was revealed by experiments in which the partial pressure of oxygen in cultures was increased, resulting in increased malignant transformation and correlated chromosomal breakage.

Kennedy *et al*. (1980) reported induction of transformation in C3H 10T1/2 mouse embryonic cell cultures by light from General Electric F18T8 lamps. The lowest effective dose was estimated at 2 x 10^5 J/m^2, and use of petri dish lids was effective in reducing transformation.

(e) *Effects on cellular and viral gene expression*

A number of cellular oncogenes and other genes involved in the regulation of growth are implicated in the process of carcinogenesis, as they are subject to both gene mutation and alteration in expression due to chromosomal rearrangement. Many of these genes also show transient alterations in expression following DNA damage, which has led to the suspicion that such transient changes are involved, either directly or indirectly, in the carcinogenic process.

UVC radiation was found to increase transiently the expression of various cellular genes, including those that code for collagenase (Stein *et al.,* 1989), the fos protein (Hollander & Fornace, 1989; Stein *et al*., 1989), the jun protein (Ronai *et al*., 1990), metallothioneins I and II (Fornace *et al*., 1988) and human plasminogen activator (Miskin & Ben-Ishai, 1981). UVA radiation enhanced expression of the genes that code for the fos protein (Hollander & Fornace, 1989), and UVB radiation increased the level of ornithine decarboxylase (Verma *et al*., 1979). Different levels of cytotoxicity were seen in these experiments. UVA radiation at doses that inactivate a small fraction of the fibroblast cell population induced expression of the haem oxygenase gene (Keyse & Tyrrell, 1989) by a transient enhancement in transcription rate (Keyse *et al*., 1990). *cis*-Acting enhancer elements have been shown to be involved in activation of the collagenase and *c-fos,* as well as human immunodeficiency promoter (Stein *et al.,* 1989). In both rat fibroblasts and human keratinocyte cell lines, exposure to UVR increased the levels of *c-fos* RNA within 10 min and of *c-myc* RNA after about 1 h. The levels peaked at 30 min and 7 h and returned to normal within 1 h and 24 h, respectively. The order of effectiveness was UVC > UVB > UVA (Ronai *et al.,* 1990).

Elevated levels of p53 protein were observed in mouse cells treated with UVR; the increase was due to post-translation activation or stabilization (Maltzman & Czyzyk, 1984). In human keratinocytes exposed to UVA, increased levels of human epidermal growth factor receptor RNA (HER-1) were found (Yang *et al.*, 1988).

The mechanisms that mediate these transient and immediate inducible responses are largely unknown. Some of them, however, overlap with those seen in response to tumour promoters, and it is significant that natural sunlight has been reported to enhance the expression of protein kinase C in cultured human epithelial P3 cells (Peak *et al.*, 1991a). For reviews of this general area, see Ananthaswamy and Pierceall (1990) and Ronai *et al.* (1990).

Other transient responses to UVR have been noted at somewhat later times (12-48 h). Methotrexate resistance due to gene amplification was reported in 3T6 mouse cells (Tlsty *et al.*, 1984). Another selective DNA amplification response is induction by UVR of viral DNA synthesis, e.g.. of polyoma virus in rat fibroblasts. UVC was more effective than UVB, and UVA was ineffective (Ronai *et al.*, 1987). In Chinese hamster embryo cells, UVC irradiation increased DNA binding to the early domain of the SV40 minimal origin, resulting in SV40 DNA amplification (Lucke-Huhle *et al.*, 1989). The induction of asynchronous viral replication is mediated by cellular proteins that bind to specific sequences in the DNA of polyoma (Ronai & Weinstein, 1988) and SV40 viruses (Lücke-Huhle *et al.*, 1989).

Exposure to UVR can activate viruses. This phenomenon has been known for herpes simplex virus for a long time (for a recent report, see Rooney *et al.*, 1991). It was reported recently that UVC can activate the gene promoters of the human immunodeficiency virus (HIV) (Valerie *et al.*, 1988) and Moloney murine sarcoma virus (Lin *et al.*, 1990). Furthermore, activation of complete HIV grown in cells pre-exposed to UVC radiation was observed (Valerie *et al.*, 1988). HIV activation may contribute to faster development of AIDS, which in turn may facilitate development of malignancies. Further studies showed that the HIV promoter and HIV are activated by UVC and UVB, but not UVA radiation even at very high exposures (Stanley *et al.*, 1989; Beer *et al.*, 1991 [abstract]; Lightfoote *et al.*, 1992). There are indications that pyrimidine dimers (Stein *et al.*, 1989) or chromatin damage (Valerie & Rosenberg, 1990) play a role in the initiation of HIV activation by UVR. The in-vitro observations have been verified for UVC, UVB and UVA in experiments with transgenic mice carrying the HIV promoter/reporter gene constructs (Cavard *et al.*, 1990; Frucht *et al.*, 1991; Vogel *et al.*, 1992). For reviews on the activation HIV by UVR, see Zmudzka and Beer (1990) and Beer and Zmudzka (1991).

Table 32. Genetic and related effects of solar, simulated solar and sunlamp (UVA and UVB) irradiation

Test system	Result[a]	Reference
BS?, *Bacillus subtilis*, mutation	+	Munakata (1989)
SSB, *Saccharomyces cerevisiae* D7, DNA damage	+	Hannan *et al*. (1984)
PLM, Wheat mutation	+	Morgan *et al*. (1988)
DIA, DNA damage, ICR 2A frog cells *in vitro*	+	Chao & Rosenstein (1986)
DIA, DNA damage, ICR 2A frog cells *in vitro*	+	Rosenstein *et al*. (1989)
DIA, DNA strand breaks, Chinese hamster V79 cells *in vitro*	+	Elkind & Han (1978)
DIA, DNA damage, Chinese hamster V79 cells *in vitro*	+	Suzuki *et al*. (1981)
DIA, DNA damage, C3H 10T1/2 mouse cells *in vitro*	+	Suzuki *et al*. (1981)
GCO, Gene mutation, Chinese hamster ovary cells *in vitro*	+	Hsie *et al*. (1977)
G9H, Gene mutation, Chinese hamster V79 lung cells *in vitro*, 6-TG^{r}	+	Zölzer *et al*. (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells *in vitro*	+	Jacobson *et al*. (1978)
G9H, Gene mutation, Chinese hamster V79 lung cells in vitro, 6-TG^{r}	+	Bradley & Sharkey (1977)
GCO, Gene mutation, Chinese hamster ovary cells *in vitro*	+	Burki & Lam (1978)
G9H, Gene mutation, Chinese hamster V79 lung cells in vitro, 6-TG^{r}	+	Suzuki *et al*. (1981)
SIA, Sister chromatid exchange, ICR 2A frog cells *in vitro*	+	Chao & Rosenstein (1985)
MIA, Micronucleus test, mouse splenocytes *in vitro*	+	Dreosti *et al*. (1990)
TBM, Cell transformation, BALB/c 3T3 mouse cells *in vitro*	+	Withrow *et al*. (1980)
TBM, Cell transformation, BALB/c mouse epidermal cells *in vitro*	+	Ananthaswamy & Kripke (1981)
TCM, Cell transformation, C3H 10T1/2 mouse embryo cells *in vitro*	+	Kennedy *et al*. (1980)
TCM, Cell transformation, C3H 10T1/2 mouse cells *in vitro*	+	Suzuki *et al*. (1981)
TCL, Cell transformation, mouse fibrosarcoma cells *in vitro*	+	Fisher & Cifone (1981)
TCL, Cell transformation, 10T1/2 mouse skin fibroblasts *in vitro*	+	Ananthaswamy (1984a)
DIA, DNA damage, fish *in vitro*	+	Applegate & Ley (1988)
DIH, DNA damage, human skin fibroblasts *in vitro*	+	Rosenstein *et al*. (1985)
DIH, DNA damage, human skin fibroblasts *in vitro*	+	Chao & Rosenstein (1986)
DIH, DNA damage, human skin fibroblasts *in vitro*	+	Rosenstein (1988)
DIH, DNA damage, human skin fibroblasts *in vitro*	+	Rosenstein & Mitchell (1991)
DIH, DNA damage, human HeLa cells *in vitro*	+	Elkind & Han (1978)
GIH, Gene mutation, human xeroderma pigmentosum fibroblasts *in vitro*	+	Patton *et al*. (1984)
SHF, Sister chromatid exchange, human[b] fibroblasts in vitro	+	Knees-Matzen *et al*. (1991)

Table 32 (contd)

Test system	Result[a]	Reference
SIH, Sister chromatid exchange, human xeroderma pigmentosum fibroblasts	+	Bielfeld *et al*. (1989)
SIH, Sister chromatid exchange, human malignant melanoma cells	+	Roser *et al*. (1989)
MIH, Micronucleus test, human xeroderma pigmentosum fibroblasts	+	Bielfeld *et al*. (1989)
MIH, Micronucleus test, human malignant melanoma cells	+	Roser *et al*. (1989)
DVA, DNA damage, BALB/c mouse skin cells *in vivo*	+	Ananthaswamy & Fisher (1981)
DVA, DNA damage, marsupial corneal cells *in vivo*	+	Freeman *et al*. (1988a)
DVA, DNA damage, marsupial corneal cells *in vivo*	+	Ley *et al*. (1988)
TVI, Cell transformation, 10T1/2 mouse skin fibroblasts treated in vivo scored *in vitro*	+	Ananthaswamy (1984b)
DVH, DNA damage, human skin cells *in vivo*	+	Eggset *et al*. (1983)
DVH, DNA damage, human skin cells *in vivo*	+	Freeman *et al*. (1988b)

[a] +, positive
[b]First-degree relatives of melanoma patients

Table 33. Genetic and related effects of predominantly UVA irradiation (near UV)

Test system	Result[a]	Reference
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	Calkins *et al*. (1987)
ECW, *Escherchia coli* WP2 *uvr*A, reverse mutation	+	Tyrrell (1982)
EC2, *Escherichia coli* WP2 hcr-, reverse mutation	+	Kubitschek (1967)
ECR, *Escherichia coli* B/r/l, *trp*, reverse mutation	+	Webb & Malina (1970)
ECR, *Escherichia coli* WP2 *rec*A, reverse mutation	+	Tyrell (1982)
ECR, *Escherichia coli* WP2 *uvr*A *rec*A, reverse mutation	+	Tyrell (1982)
ECR, *Escherichia coli* B/r *uvr*A *trp thy*, reverse mutation	+	Tyrell (1982)
ECR, *Escherichia coli* wild type, reverse mutation	+	Tyrell (1982)
ECR, *Escherichia coli*, mutation	+	Wood *et al*. (1984)
SSB, *Saccharomyces cerevisiae* wild type, DNA damage	+	Zölzer & Kiefer (1983)
SSB, *Saccharomyces cerevisiae* excision-deficient, DNA damage	+	Zölzer & Kiefer (1983)
SSB, *Saccharomyces cerevisiae* D7, DNA damage	+	Hannan *et al*. (1984)
DIA, DNA damage, Chinese hamster ovary cells *in vitro*	+	Zelle *et al*. (1980)
DIA, DNA strand breaks, Chinese hamster ovary cells *in vitro*	+	Churchill *et al*. (1991)
GCO, Gene mutation, Chinese hamster ovary cells *in vitro*	+	Zelle *et al*. (1980)
GCO, Gene mutation, Chinese hamster ovary cells *in vitro*	+	Singh & Gupta (1982)
GCO, Gene mutation, Chinese hamster ovary cells *in vitro*	+	Lundgren & Wulf (1988)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus	+	Wells & Han (1984)
G9O, Gene mutation, Chinese hamster lung V79 cells, 6-TG^r	+	Wells & Han (1984)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	+	Hitchins *et al*. (1987)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	Lundgren & Wulf (1988)
CIC, Chromosomal abberations, Chinese hamster ovary cells *in vitro*	(+)	Lundgren & Wulf (1988)
TCL, Cell transformation, Syrian hamster embryo cells *in vitro* (neoplastic transformation)	+	Barrett *et al*. (1978)
TCL, Cell transformation, Syrian hamster embryo cells *in vitro* (morphological transformation)	-	Barrett *et al*. (1978)
DIH, DNA strand breaks, human fibroblasts *in vitro*	+	Rosenstein & Ducore (1983)
DIH, DNA strand breaks, human teratoma cells *in vitro*	+	Peak *et al*. (1987)
DIH, DNA double strand breaks, human teratocarcinoma cells *in vitro*	+	Peak & Peak (1990)
DIH, DNA stand breaks, human fibroblasts *in vitro*	+	Francis & Giannelli (1991)
DIH, DNA-protein cross-links, human teratocarcinoma cells *in vitro*	+	Peak & Peak (1991)
DIH, DNA strand breaks, human epithelial P3 cells *in vitro*	+	Peak *et al*. (1991b)
DIH, Pyrimidine dimer formation, human skin fibroblasts *in vitro*	+	Enninga *et al*. (1986)

Table 33 (contd)

Test system	Result[a]	Reference
DIH, Pyrimidine dimer formation, human skin fibroblasts *in vitro*	+	Rosenstein & Mitchell (1987)
GIH, Gene mutation, human lymphoblastoid cell line *in vitro*	-	Tyrrell (1984)
GIH, Gene mutation, human skin fibroblasts *in vitro*	+	Enninga *et al*. (1986)
GIH, Gene mutation, human epithelial cells *in vitro*	+[b]	Jones *et al*. (1987)
DVH, Pyrimidine dimer formation, human skin *in vivo*	+	Freeman *et al*. (1989)

[a] +, positive; (+), weakly positive; -, negative
[b]Positive result with 365 nm but not with 334 nm at same fluence

Table 34. Genetic and related effects of predominantly UVB irradiation

Test system	Result[a]	Reference
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	Calkins *et al*. (1987)
EC2, *Escherichia coli* WP2, reverse mutation	+	Peak *et al*. (1984)
TSC, *Tradescantia*, chromosomal aberrations	+	Kirby-Smith & Craig (1957)
DIA, DNA damage, Chinese hamster ovary cells *in vitro*	+	Zelle *et al*. (1980)
DIA, DNA strand breaks, Chinese hamster V79 cells	+	Matsumoto *et al*. (1991)
DIA, DNA-protein cross-links, Chinese hamster V79 cells	+	Matsumoto *et al*. (1991)
GCO, Gene mutation, Chinese hamster ovary cells *in vitro*	+	Zelle *et al*. (1980)
GCO, Gene mutation, Chinese hamster ovary cells *in vitro*	+	Rasmussen *et al*. (1989)
G9H, Gene mutation, Chinese hamster V79 lung cells, *hprt* locus	+	Wells & Han (1984)
G9H, Gene mutation, Chinese hamster V79 lung cells, *hprt* locus	+	Zölzer & Kiefer (1984)
G9O, Gene mutation, Chinese hamster V79 lung cells, ouabainr	+	Wells & Han (1984)
G9H, Gene mutation, Chinese hamster V79 lung cells *in vitro*, 6TGr	+	Colella *et al*. (1986)
G51, Gene mutation, mouse lymphoma L5178Y cells *in vitro*	+	Jacobson *et al*. (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	Rasmussen *et al*. (1989)
CIA, Chromosomal aberrations, ICR 2A frog cells *in vitro*	+	Rosenstein & Rosenstein (1985)
TCS, Cell transformation, Syrian hamster embryo cells *in vitro*	+	Doniger *et al*. (1981)
DIH, DNA strand breaks, human skin fibroblasts *in vitro*	+	Rosenstein & Ducore (1983)
DIH, Pyrimidine dimer formation, human skin fibroblasts *in vitro*	+	Enninga *et al*. (1986)
DIH, Pyrimidine dimer formation, human skin fibroblasts *in vitro*	+	Rosenstein & Mitchell (1987)
DIH, DNA strand breaks, human teratoma *in vitro*	+	Peak *et al*. (1987)
DIH, DNA double strand breaks, human teratocarcinoma *in vitro*	+	Peak & Peak (1990)
DIH, DNA-protein cross-links, human teratocarcinoma *in vitro*	+	Peak & Peak (1991)
DIH, Pyrimidine dimer formation in human skin keratinocytes *in vitro*	+	Schothorst *et al*. (1991)
DIH, Thymine dimer formation, human fibroblasts *in vitro*	+	Roza *et al*. (1988)
GIH, Gene mutation, human lymphoblastoid cell line *in vitro*	-	Tyrrell (1984)
GIH, Gene mutation, human skin fibroblasts *in vitro*	+	Enninga *et al*. (1986)
GIH, Gene mutation, human epithelial cells *in vitro*	+	Jones, C.A. *et al*. (1987)
TIH, Cell transformation, human fibroblasts *in vitro*	+	Sutherland *et al*. (1981)
DVA, Cyclobutane dimers in SV40 plasmid DNA in human fibroblasts *in vivo*	+	Mitchell *et al*. (1991)
DVA, Cytosine photohydrates in SV40 plasmid DNA in human fibroblasts *in vivo*	+	Mitchell *et al*. (1991)

Table 34 (contd)

Test system	Result[a]	Reference
DVA, Pyrimidine dimer induction, mouse skin *in vivo*	+	Cooke & Johnson (1978)
DVA, Pyrimidine dimer formation, mouse skin *in vivo*	+	Ley *et al*. (1983)
DVA, (6-4) Photoproduct formation, mouse epidermis *in vivo*	+	Olsen *et al*. (1989)
DVH, Pyridime dimer formation, human skin *in vivo*	+	Freeman et al. (1989)
UVH, Unscheduled DNA synthesis, human cornea *in vivo*[b]	+	Grabner & Brenner (1981)

[a] +, positive; -, negative

[b]From people who had been dead for 15 min

Table 35. Genetic and related effects of UVC irradiation

Test system	Result[a]	Reference
ECB, *Escherichia coli*, thymine dimer formation	+	Setlow *et al*. (1963)
ECB, *Escherichia coli*, photoproduct formation	+	Setlow (1968)
ECB, *Escherichia coli*, thymine photoadduct formation	+	Smith (1964)
ECB, *Escherichia coli*, pyrimidine dimers	+	Brash & Haseltine (1982)
ECB, *Escherichia coli*, (6-4) photoproducts	+	Brash & Haseltine (1982)
ECF, *Escherichia coli*, miscellaneous strains, forward mutation	+	Miller (1985)
ECR, *Escherichia coli*, mutation	+	Witkin (1976
ECR, *Escherichia coli*, mutation	+	Walker (1984)
ECR, *Escherichia coli*, mutation	+	Franklin & Haseltine (1986)
ECR, *Escherichia coli*, mutation	+	Bridges *et al*. (1987)
ECR, *Escherichia coli*, mutation	+	Schaaper *et al*. (1987)
SSB, *Saccharomyces cerevisiae*, pyrimidine dimer formation	+	Wheatcroft *et al*. (1975)
SSB, *Saccharomyces cerevisiae*, pyrimidine dimer formation	+	Resnick *et al*. (1987)
SCN, *Saccharomyces cerevisiae*, aneuploidy	+	Parry *et al*. (1979)
SCF, *Saccharomyces cerevisiae*, forward mutation	+	Lee *et al*. (1988)
SCR, *Saccharomyces cerevisiae*, reverse mutation	+	Siede & Eckardt (1986)
PLU, Plants, DNA damage	+	McLennan (1987)
PLU, *Nicotiana tabacum*, unscheduled DNA synthesis	+	Cieminis *et al*. (1987)
PLU, *Chlamydomonas reinhardtii*, pyrimidine dimer formation	+	Vlček *et al*. (1987)
PLM, *Chlamydomonas reinhardtii*, mutation	+	Vlček *et al*. (1987)
TSC, *Tradescantia*, chromosomal aberrations	+	Kirby-Smith & Craig (1957)
DM?, *Drosophila melanogaster* embryo cells *in vitro*, DNA damage	+	Koval (1987)
DIA, DNA damage, ICR 2A frog cells *in vitro*	+	Chao & Rosenstein (1986)
DIA, DNA strand breaks, Chinese hamster V79 cells	+	Elkin & Han (1978)
DIA, DNA damage, Chinese hamster ovary cells *in vitro*	+	Zelle *et al*. (1980)
GCO, Gene mutation, Chinese hamster ovary cells *in vitro*	+	Zelle *et al*. (1980)
GCO, Gene mutation, Chinese hamster ovary cells *in vitro*	+	Rasmussen *et al*. (1989)
GCO, Gene mutation, Chinese hamster ovary cells *in vitro*	+	Drobetsky & Glickman (1990)
G9H, Gene mutation, Chinese hamster V79 lung cells *in vitro*	+	Colella *et al*. (1986)
G9H, Gene mutation, Chinese hamster V79 lung cells, *hprt* locus	+	Suzuki *et al*. (1981)
G9H, Gene mutation, Chinese hamster V79 lung cells, *hprt* locus	+	Zölzer & Kiefer (1984)
G9O, Gene mutation, Chinese hamster V79 lung cells, ouabain^{r}	+	Suzuki *et al*. (1981)

Table 35 (contd)

Test system	Result[a]	Reference
G51, Gene mutation, mouse lymphoma L5178Y cells *in vitro*	+	Jacobson *et al*. (1981)
SIC, Sister chromatid exchange, Chinese hamster V79 cells *in vitro*	+	Nishi *et al*. (1984)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	Rasmussen *et al*. (1989)
SIA, Sister chromatid exchange, ICR 2A frog cells *in vitro*	+	Chao & Rosenstein (1985)
SIA, Sister chromatid exchange, chick embryo fibroblasts *in vitro*	+	Natarajan *et al*. (1980)
CIC, Chromosomal aberrations, Chinese hamster fibroblasts *in vitro*	+	Chu (1965a)
CIC, Chromosomal aberrations, Chinese hamster fibroblasts *in vitro*	+	Chu (1965b)
CIC, Chromosomal aberrations, Chinese hamster V79 cells *in vitro*	+	Bender *et al*. (1973)
CIC, Chromosomal aberrations, Chinese hamster V79 cells *in vitro*	+	Griggs & Bender (1973)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	Ikushima & Wolff (1974)
CIC, Chromosomal aberrations, Chinese hamster CHEF-125 cells *in vitro*	+	Trosko & Brewen (1967)
CIA, Chromosomal aberration, chick embryo fibroblasts *in vitro*	+	Natarajan *et al*. (1980)
CIA, Chromosomal aberrations, A8W243 *Xenopus* cells *in vitro*	+	Griggs & Bender (1973)
CIA, Chromosomal aberrations, ICR 2A frog cells *in vitro*	+	Rosenstein & Rosenstein (1985)
CIA, Chromosomal aberrations, New Zealand black mouse fetal fibroblasts	+	Reddy *et al*. (1978)
TBM, Cell transformation, BALB/c 3T3 mouse cells	+	Withrow *et al*. (1980)
TCM, Cell transformation, C3H 10T1/2 mouse cells	+	Chan & Little (1976)
TCM, Cell transformation, C3H 10T1/2 mouse cells	+	Mondal & Heidelberger (1976)
TCM, Cell transformation, C3H 10T1/2 mouse cells	+	Chan & Little (1979)
TCM, Cell transformation, C3H 10T1/2 mouse cells	+	Suzuki *et al*. (1981)
TCM, Cell transformation, C3H 10T1/2 mouse cells	+	Borek *et al*. (1989)
TCS, Cell transformation, Syrian hamster embryo cells	+	DiPaolo & Donovan (1976)
TCS, Cell transformation, Syrian hamster embryo cells	+	Doniger *et al*. (1981)
TCS, Cell transformation, Syrian hamster embryo cells	+	Borek *et al*. (1989)
TEV, Cell transformation, SV-40/BALB/c 3T3 mouse cells	+	Withrow *et al*. (1980)
DIH, DNA strand breaks, human skin fibroblasts *in vitro*	+	Rosenstein & Ducore (1983)
DIH, DNA damage, human skin fibroblasts *in vitro*	+	Rosenstein *et al*. (1985)
DIH, Pyrimidine dimer formation, human skin fibroblasts *in vitro*	+	Enninga *et al*. (1986)
DIH, Pyrimidine dimer formation, human skin fibroblasts *in vitro*	+	Rosenstein & Mitchell (1987)
DIH, DNA strand breaks, human teratoma cells *in vitro*	+	Peak *et al*. (1987)
DIH, Thymine dimer formation, human skin fibroblasts *in vitro*	+	Roza *et a*l. (1988)
DIH, DNA damage, human skin fibroblasts *in vitro*	+	Chao & Rosenstein (1986)

Table 35 (contd)

Test system	Result[a]	Reference
DIH, DNA strand breaks, human fibroblasts *in vitro*	+	Lai & Rosenstein (1990)
DIH, DNA-protein cross-links, human fibroblasts *in vitro*	+	Lai & Rosenstein (1990)
DIH, DNA double strand breaks, human teratocarcinoma cells *in vitro*	+	Peak & Peak (1990)
DIH, DNA-protein cross-links, human teratocarcinoma cells *in vitro*	+	Peak & Peak (1991)
DIH, Pyrimidine dimer formation, human skin keratinocytes and melanocytes in vitro	+	Schothorst *et al*. (1991)
GIH, Gene mutation, human fibroblasts *in vitro*	+	Maher *et al*. (1979)
GIH, Gene mutation, human fibroblasts *in vitro*	+	Myhr *et al*. (1979)
GIH, Gene mutation, human lymphocytes *in vitro*	+	Sanderson *et al*. (1984)
GIH, Gene mutation, human lymphoblastoid cell line *in vitro*	+	Tyrrell (1984)
GIH, Gene mutation, human skin fibroblasts *in vitro*	+	Enninga *et al*.(1986)
GIH, Gene mutation, human epithelial cells *in vitro*	+	Jones, C.A. *et al*. (1987)
GIH, Gene mutation, human HeLa cells *in vitro*	+	Musk *et al*. (1989)
GIH, Gene mutation, human lymphocytes *in vitro*	+	Norimura *et al*. (1990)
GIH, Gene mutation, human fibroblasts *in vitro*	+	Dorado *et al*. (1991)
GIH, Gene mutation, human fibroblasts *in vitro*	+	McGregor *et al*. (1991)
GIH, Gene mutation, human melanoma cells *in vitro*	+	Musk *et al*. (1989)
SHF, Sister chromatid exchange, human fibroblasts *in vitro*	+	Fujiwara *et al*. (1981)
SHF, Sister chromatid exchange, human fibroblasts *in vitro*	+	Kurihara *et al*. (1987)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	Murthy *et al*. (1982)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	Perticone *et al*. (1986)
SHF, Sister chromatid exchange, human skin fibroblasts	+	De Weerd-Kastelein *et al*. (1977)
SHF, Sister chromatid exchange, human skin fibroblasts	+	Krepinsky *et al*. (1980)
SHF, Sister chromatid exchange, human skin fibroblasts	+	Marshall *et al*. (1980)
SHF, Sister chromatid exchange, human skin fibroblasts	+	Henderson *et al*. (1985)
MIH, Micronucleus test, human skin fibroblasts *in vitro*	+	Krepinsky *et al*. (1980)
CHF, Chromosomal aberrations, human fibroblasts *in vitro*	+	Parrington (1972)
CHF, Chromosomal aberrations, human skin fibroblasts	+	Parrington *et al*. (1971)
SHF, Sister chromatid exchange, human skin fibroblasts	+	Marshall & Scott (1976)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	Murthy *et al*. (1982)
CHL, Chromosome exchanges, human lymphocytes *in vitro*	+	Holmberg & Gamauskas (1990)
TIH, Cell transformation, human fibroblasts *in vitro*	+	Sutherland *et al*. (1981)
TIH, Cell transformation, human fibroblasts *in vitro*	+	Maher *et al*. (1982)

Table 35 (contd)

Test system	Result[a]	Reference
TIH, Cell transformation, human fibroblasts *in vitro*	+	Sutherland *et al*. (1988)
???, Cyclobutane dimers in SV40 plasmid DNA in human skin fibroblasts *in vitro* and *in vivo*	+	Mitchell *et al*. (1991)
???, Cytosine photohydrates in SV40 plasmid DNA in human skin fibroblasts *in vitro* and *in vivo*	+	Mitchell *et al*. (1991)
DVA, Pyrimidine dimer formation, mouse skin *in vivo*	+	Bowden *et al*. (1975)

[a] +, positive

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Terrestrial life is dependent on radiant energy from the sun. Approximately 5% of solar terrestrial radiation is ultraviolet radiation (UVR), and solar radiation is the major source of human exposure to UVR. Before the beginning of this century, the sun was essentially the only source of UVR, but with the advent of artificial sources the opportunity for additional exposure has increased.

UVR spans the wavelengths from 100 to 400 nm. The biological effects of UVR vary enormously with wavelength; by convention, the ultraviolet spectrum has been further subdivided into three regions: UVC (100-280 nm), UVB (280-315 nm) and UVA (315-400 nm).

Solar UVR that reaches the Earth's surface comprises approximately 95% UVAand 5% UVB: UVC is completely filtered out by the Earth' s atmosphere. The amount of solar UVR measured at the Earth' s surface depends upon a number of factors, which include solar zenith angle (time of day, season and geographical latitude), stratospheric ozone, atmospheric pollutants, weather, ground reflectance and altitude.

Exposed skin surface is irradiated differently depending on cultural and social behaviour, clothing, the position of the sun in the sky and the relative position of the body. Exposure to UVB of the most exposed skin surfaces, such as nose, tops of the ears and forehead, relative to that of the lesser exposed areas, such as underneath the chin, normally ranges over an order of magnitude. Ground reflectance plays a major role in exposure to UVB of the eye and shaded skin surfaces, particularly with highly reflective surfaces such as snow.

In cutaneous photobiology, radiant exposure is frequently expressed as 'exposure dose' in units of J/cm^2 (or J/m^2). 'Biologically effective dose', derived from radiant exposure weighted by an action spectrum, is expressed in units of J/cm^2 (effective) or as multiples of 'minimal erythema dose' (MED). In cellular photobiology, the term 'fluence' is often used incorrectly as equivalent to radiant exposure.

The cumulative annual exposure dose of solar UVR varies widely among individuals in a given population, depending to a large extent on occupation and extent of outdoor activities. For example, it has been estimated that indoor workers in mid-latitudes (40-60 °N) receive an annual exposure dose of solar UVR to the face of about 40-160 times the MED, depending upon propensity for outdoor activities, whereas the annual solar exposure dose for outdoor workers is typically around 250 times the MED. Because few actual measurements have been reported of personal exposures, these estimates should be considered to be very approximate and subject to differences in cultural and social behaviour, clothing, occupation and outdoor activities.

Cumulative annual outdoor exposures may be augmented by exposures to articial sources of UVR. For example, the use of cosmetic tanning appliances increased in popularity in the 1980s. The majority of users are young women, and the median annual exposure dose is probably 20-30 times the MED. Currently used appliances emit primarily UVA radiation; prior to the 1980s, tanning lamps emitted higher proportions of UVB and UVC.

UVR has been used for several decades to treat skin diseases, notably psoriasis. A variety of sources of UVR are employed, and nearly all emit a broad spectrum of radiation. A typical dose in a single course of UVB phototherapy might lie between 200 and 300 times the MED.

UVR is used in many different industries, yet there is a paucity of data concerning human exposure from these applications, probably because in normal practice sources are well contained and exposure doses are expected to be low. Acute reactions to overexposure are common among electric arc welders. Staff in hospitals who work with unenclosed phototherapy equipment are at potential risk of overexposure unless protective measures are taken. Individuals exposed to lighting from fluorescent lamps may typically receive annual exposure doses of UVR ranging from 0 to 30 times the MED, depending on illuminance levels and whether or not the lamps are housed behind plastic diffusers. There is increasing use of tungsten-halogen lamps, which also emit UVR, for general lighting.

5.2 Human carcinogenicity data

5.2.1 *Solar radiation*

Subjects with the inherited condition xeroderma pigmentosum appear to have frequencies of nonmelanocytic skin cancer and melanoma that are much higher than expected. Some evidence suggests that the greatest excess occurs on the head and neck.

(a) *Nonmelanocytic skin cancer*

The results of descriptive epidemiological studies suggest that exposure to sunlight increases the risk of nonmelanocytic skin cancer. These tumours occur predominantly on the skin of the face and neck, which is most commonly exposed to sunlight, although the distribution of basal-cell carcinomas is not as closely related to the distribution of exposure to the sun as is that of squamous-cell carcinomas. There is a strong inverse relationship between latitude and incidence of or mortality from skin cancer and, conversely, a positive relationship between incidence or mortality and measured or estimated ambient UVR. Migrants to Australia from the British Isles have lower incidence of and mortality from nonmelanocytic skin cancer than the Australian-born population. People who work primarily outdoors have higher mortality from these cancers, and there is some evidence that outdoor workers have higher incidence.

In several cross-sectional studies, positive associations have been seen between measures of solar skin damage and the prevalence of basal- and squamous-cell carcinomas. Measures of actual exposure to the sun have been less strongly associated with these cancers, possibly because of errors in measurement and inadequate control for potential confounding variables. In a study of US fishermen, estimates of individual annual and cumulative exposure to UVB were positively associated with the occurrence of

squamous-cell carcinoma but not with the occurrence of basal-cell carcinoma. Only two population-based case-control studies have been conducted. In one of these, from Canada, the response rate was low and the measures of exposure were crude. In the other study, from Australia, facial telangiectasia and solar elastosis of the neck were strongly associated with the risk for squamous-cell carcinoma, and cutaneous microtopography and solar elastosis of the neck were strongly associated with risk for basal-cell carcinoma. Migrants to Australia had a lower risk of squamous-cell carcinoma than did native-born Australians, and migrants who arrived after childhood had a lower risk for basal-cell carcinoma.

The hospital-based case-control studies that have been conducted suffer from methodological deficiencies, including choice of controls, measurement of exposure and confounding by reaction to sunlight, and are therefore difficult to interpret.

In a cohort study of nurses in the USA, those who spent more than 8 h per week outside without sunscreens had a similar incidence rate of basal-cell carcinoma to those who spent fewer than 8 h per week outdoors. In a cohort study from Victoria, Australia, the rates of both types of skin cancer were increased in outdoor workers, but the effect was not significant after adjustment for reaction to sunlight.

(b) *Cancer of the lip*

Cancer of the lip has been related to outdoor occupation in a number of descriptive studies. Migrants to Australia and Israel have lower risks than native-born residents.

Three case-control studies provide useful information about the association between outdoor work, taken as a proxy measure for exposure to UVR, and cancer of the lip. All of them showed a significantly increased risk, although potential confounding by tobacco use was not controlled adequately in any of the studies.

Assessment of the carcinogenicity of solar radiation for the lip is complicated by the fact that carcinoma of the lip as actually diagnosed is a mixture of cancers of the external lip and cancers of the buccal membranes. Use of alcohol and tobacco are known causes of the latter tumours.

(c) *Malignant melanoma of the skin*

Descriptive studies in whites in North America, Australia and several other countries show a positive association between incidence of and mortality from melanoma and residence at lower latitudes. Studies of migrants suggest that the risk of melanoma is related to solar radiant exposure at the place of residence in early life. The body site distribution of melanoma shows lower rates per unit area on sites usually unexposed to the sun than on usually or regularly exposed sites.

A large number of case-control studies are pertinent to the relationship between melanoma and exposure to the sun. These include large, carefully conducted population-based studies carried out in Western Australia, Queensland, western Canada and Denmark. Their results are generally consistent with positive associations with residence in sunny environments throughout life, in early life and even for short periods in early adult life. Positive associations are generally seen between measurements of cumulative sun damage expressed biologically as microtopographical changes or history of keratoses or nonmelanocytic skin cancer.

In contrast, the associations with total exposure to the sun over a lifetime or in recent years, as assessed by questionnaire, are inconsistent. This inconsistency may be due to differences in the effects of chronic and intermittent exposure. Chronic exposure, as assessed through occupational exposure, appeared to reduce melanoma risk in three of the large studies, particularly in men; this observation is consistent with the descriptive epidemiology of the condition, which shows lower risks in groups that work outdoors. Several other studies, which were generally smaller or had less detailed methods of exposure assessment, show either no effect or an increased risk associated with occupational exposures.

Assessment of intermittent exposure is complex; nonetheless, most studies show positive associations with measure of intermittent exposure, such as particular sun-intensive activities, outdoor recreation or vacations.

Most studies show positive associations with a history of sunburn; however, this association cannot be easily interpreted, because while it might accurately reflect sunburn it could just as well reflect either the tendency to sunburn, if exposed, or intermittent exposure more generally.

(d) *Melanoma of the eye*

There is no latitude gradient among white populations of the incidence of ocular neoplasms, some 80% of which are likely to be ocular melanomas. No effect of southern US birthplace was seen in the two descriptive studies in the USA that examined this aspect.

Four case-control studies, from western Canada and from Philadelphia, San Francisco and Boston, USA, provided information on the association between exposure to solar radiation and ocular melanoma. All of these studies demonstrate an increased risk of ocular melanoma in people with light skin, light eye colour or light hair colour. Two of the studies compared effect of southern US birthplace with birth elsewhere in the USA; a significant difference was seen in the Philadelphia study.

Past residence south of 40 °N latitude was positively associated with ocular melanoma in the Boston study but was not significant in the Philadelphia study after control for southern birthplace. Although several outdoor activities, such as gardening and sunbathing, were associated in the Philadelphia study with ocular melanoma, participation in outdoor activities did not increase risk significantly in Boston or San Francisco.

The lack of consistency of the results of these studies makes their interpretation difficult.

(e) *Other cancers*

No adequate study was available to evaluate the role of solar radiation in cancers at other body sites.

5.2.2 *Artificial sources of ultraviolet radiation*

No adequate study was available on nonmelanocytic skin cancer in relation to exposure to artificial sources of UVR.

Two case-control studies, one from Scotland and one from Ontario, with detailed information on use of sunbeds and sunlamps showed positive relationships between duration of use and risk of melanoma of the skin. Several other studies with limited information showed no association.

One case-control study from Sydney, Australia, showed a positive relationship between melanoma of the skin and exposure to fluorescent lights at work among women, but the measurement of exposure was crude and among exposed cases there was a relative excess of melanoma on the trunk, a site likely to be covered at work. A more detailed study from Australia showed no consistent association between cumulative exposure or rate of exposure to fluorescent lights and melanoma. Two other studies had detailed information on exposure. One, from Scotland, showed no such association, while the other, from England, had inconsistent effects depending on the method of ascertainment of information. Another study, from New York, with limited information also showed inconsistent effects depending on the source of information.

Two case-control studies, from Boston and Philadelphia, USA, showed significant positive associations between use of sunlamps and melanoma of the eye. Another case-control study, from San Francisco, showed an increased risk for exposure to 'UV or black light', although the nature of the exposure was not specified.

Two studies, from Philadelphia and Montreal, showed significant positive associations between welding and melanoma of the eye.

5.2.3 *Molecular genetics of human skin cancers*

Base substitutions in a tumour suppressor gene, p53, found in human squamous-cell skin carcinomas that had developed at sites exposed to the sun were similar to those found in experimental systems exposed to UVR, and especially to UVB.

5.3 Carcinogenicity in experimental animals

Solar radiation was tested for carcinogenicity in a series of exceptional studies in mice and rats. Large numbers of animals were studied, and well-characterized benign and malignant skin turnouts developed in most of the surviving animals. Although the reports are deficient in quantitative details, the results provide convincing evidence that sunlight is carcinogenic for the skin of animals.

Broad-spectrum UVR (solar-simulated radiation and ultraviolet lamps emitting mainly UVB) was tested for carcinogenicity in many studies in mice, to a lesser extent in rats and in a few experiments in hamsters, guinea-pigs, opossums and fish. Benign and malignant skin tumours were induced in all of these species except guinea-pigs, and tumours of the cornea and conjunctive were induced in rats, mice and hamsters.

The predominant type of tumours induced by UVR in mice is squamous-cell carcinoma. Basal-cell carcinomas have been observed occasionally in athymic nude mice and rats exposed to UVR. Melanocytic neoplasms of the skin were shown to develop following exposure of opossums and hybrid fish to broad-spectrum UVR.

Studies in hairless mice demonstrated the carcinogenicity of exposures to UVR in the wavelength ranges 315-400 nm (UVA), 280-315 nm (UVB) and $\leq$ 280 nm (UVC), UVB radiation being the most effective, followed by UVC and UVA. UVB radiation is three to four orders of magnitude more effective than UVA. Both short-wavelength UVA (315-340 nm) and long-wavelength UVA (340-400 nm) induced skin cancer in hairless mice. The carcinogenic effectiveness of the latter waveband is known only as an average value over

the entire range; the uncertainty of this average is about one order of magnitude. In none of the experiments involving UVC was it possible to exclude completely a contribution of UVB, but the size of the effects observed indicate that they cannot be due to UVB alone.

No experimental data were available on the carcinogenicity to animals of radiation from general lighting fixtures, including fluorescent and quartz halogen lamps.

UVR has been studied in protocols involving two-stage chemical carcinogenesis (substituting UVR for the chemical initiator or for the chemical promoter or giving it in addition to both). UVR has been reported to exert many effects on the carcinogenic process, including initiation, promotion, cocarcinogenicity and even tumour inhibition. Chemical immunosuppressive agents have been shown to enhance the probability of developing UVR-induced tumours m mice.

5.4 Other relevant data

5.4.1 *Transmission and absorption*

Studies of transmission in whole human and mouse epidermis and human stratum corneum *in vitro* show that these tissues attenuate radiation in the solar UVR range. This attenuation, which is more pronounced for the UVB than for the UVA wavebands, affords some protection from solar UVR to dividing cells in the basal layer.

The different components of the human eye act as optical filters for the UVR range. Consequently, little or no UVR reaches the retina in the normal eye.

5.4.2 *Effects on the skin*

UVR produces erythema, melanin pigmentation and acute and chronic cellular and histological changes in humans. Generally consistent changes are seen in experimental species, including the hairless mouse.

The action spectra for erythema and tanning in humans and for oedema in hairless mice are similar. UVB is three to four times more effective than UVA in producing erythema. In humans, pigmentation protects against erythema and histopathological changes. People with a poor ability to tan, who burn easily and have light eye and hair colour are at a higher risk of developing melanoma, basal-cell and squamous-cell carcinomas (see section 5.2).

In humans, acquired pigmented naevi and solar keratoses, indicators of melanomas and squamous-cell carcinomas, respectively are induced by exposure to the sun.

Xeroderma pigmentosum patients have a high frequency of pigmentary abnormalities and skin cancers on sun-exposed skin. These patients also have defective DNA repair.

5.4.3 *Effects on the immune response*

Relatively few investigations have been reported of the effects of UVR on immunity in humans, but changes do occur. There is evidence that contact allergy is suppressed by exposure to UVB and possibly to UVA radiation. The number of Langerhans' cells in the epidermis is decreased by exposure to UVR and sunlight, and the morphological loss of these cells is associated with changes in antigen-presenting cell function in the direction of suppression; this change may be due not only to simple loss of function but also to active

migration of other antigen-presenting cells into the skin. A reduction in natural killer cell activity also occurs, which can be produced by UVA radiation. These changes are short-lived, and their functional significance is unknown. Pigmentation of the skin may not protect against some UVR-induced alterations of immune function.

Several immune responses are suppressed by UVR in mice and other rodents. Suppression of contact hypersensitivity has received most attention, and this response may be impaired locally, at the site of exposure to radiation, or systemically, at a distant, unexposed site. The two forms of suppression have different dose dependencies—systemic suppression requiring much higher doses—and their mechanisms appear to differ, but the efferent limb of each involves generation of hap/en-specific T-suppressor cells that block induction but not elicitation of contact hypersensitivity. Systemic suppression of delayed hypersensitivity to injected antigens can also be produced by exposure to UVB radiation, and several observations suggest that the mechanism of this suppression differs from that of systemic suppression of contact hypersensitivity.

Alterations in immune function induced by exposure to UVR play a central role in photocarcinogenesis in mice. UVR-induced T-suppressor cells block a normal immunosurveillance system that prevents the growth of highly antigenic UVR-induced tumours. It is not known whether this mechanism operates in humans.

5.4.4 *DNA photoproducts*

Solar UVR induces a variety of photoproducts in DNA, including cyclobutane-type pyrimidine dimers. pyrimidine-pyrimidine (6-4) photoproducts, thymine glycols, cytosine damage, purine damage, DNA strand breaks and DNA-protein cross-links. Substantial information on biological consequences is available only for the first two classes. Both are potentially cytotoxic and can lead to mutations in cultured cells, and there is evidence that cyclobutane-type pyrimidine dimers may be precarcinogenic lesions. The relative and absolute levels of each type of lesion vary with wavelength. Substantial levels of thymidine glycols, strand breaks and DNA-protein cross-links are induced by solar UVA and UVB radiation, but not by UVC radiation. The ratio of strand breaks to cyclobutane-type dimer lesions increases as a function of increasing wavelength. In narrow band-width studies, the longest wavelength at which cyclobutane-type pyrimidine dimers have been observed is 365 nm, whereas the induction of strand breaks and DNA-protein cross-links has been observed at wavelengths in the UVB, UVA and visible ranges. Non-DNA chromophores such as porphyrins, which absorb solar UVR, appeared to be important in generating active intermediates that can lead to damage. Solar UVR also induces membrane damage.

5.4.5 *Genetic and related effects*

Measurable DNA damage is induced in human skin cells *in* vivo after exposures to UVA, UVB and UVC radiation, including doses in the range commonly experienced by humans. Most of the DNA damage after a single exposure is repaired within 24 h. The importance of these wavelength ranges depends on several factors. UVB is the most effective, UVC being somewhat less effective and UVA being much less effective, when compared on a per photon basis, probably owing to a combination of the biological effectiveness of the different wavebands and of their absorption in the outer layers of the skin.

Summary table of genetic and related effects of ultraviolet A radiation

Nonmammalian systems														Mammalian systems																												
Proka-ryotes		Lower eukaryotes				Plants			Insects					*In vitro*																				*In vivo*										
														Animal cell								Human cells												Animals						Humans				
D	G	D	R	G	A	D	G	C	R	G	C	A	D	G	S	M	C	A	T	I	D	G	S	M	C	A	T	I	D	G	S	M	C	DL	A	D	S	M	C	A
	+	+												+[1]		+	+[1]		+[1]				+	+															+[1]				

A, aneuploidy; C, chromosomal aberrations; D, DNA damage; DL, dominant lethal mutations; G, gene mutation; I, inihibition of intercellular communication; M, micronuclei; R, mitotic recombination and gene conversion; S, sister chromatid exchange; T, cell transformation

In completing the tables, the following symbols indicate the consensus of the Working Group with regard to the results for each endpoint:

+ considered to be positive for the specific endpoint and level of biological complexity
+[1] considered to be positive, but only one valid study was available to the Working Group; sperm abnormality, mouse
- considered to be negative
-[1] considered to be negative, but only one valid study was available to the Working Group
? considered to be equivocal or inconclusive (e.g., there were contradictory results from different laboratories; there were confounding exposures; the results were equivocal)

Summary table of genetic and related of ultraviolet B radiation

Nonmammalian systems													Mammalian systems																													
Proka-ryotes		Lower eukaryotes				Plants			Insects				*In vitro*																*In vivo*													
													Animal cells								Humans cells								Animals							Humans					
D	G	D	R	G	A	D	G	C	R	G	C	A	D	G	S	M	C	A	T	I	D	G	S	M	C	A	T	I	D	G	S	M	C	DL	A	D	S	M	C	A
	+							+[1]					+	+	+[1]				+		+	+					+[1]		+							+					

A, aneuploidy; C, chromosomal aberrations; D, DNA damage; DL, dominant lethal mutation; G, gene mutation; I, inhibition of intercellular communication; M, micronuclei; R, mitotic recombination and gene conversion; S, sister chromatid exchange; T, cell transformation

In completing the tables, the following symbols indicate the consensus of the Working Group with regard to the results for each endpoint:

+ considered to be positive for the specific endpoint and level of biological complexity

+[1] considered to be positive, but only one valid study was available to the Working Group; sperm abnormality, mouse

- considered to be negative

-[1] considered to be negative, but only one valid study was available to the Working Group

? considered to be equivocal or inconclusive (e.g., there were contradictory results from the different laboratories; there were confounding exposures; the results were equivocal)

Summary table of genetic and related effects of ultraviolet C radiation

Nonmammalian systems													Mammalian systems																													
Proka-ryotes		Lower eukaryotes				Plants			Insects				*In vitro*												*In vivo*																	
													Animals cells								Human								Animals							Humans					
D	G	D	R	G	A	D	G	C	R	G	C	A	D	G	S	M	C	A	T	I	D	G	S	M	C	A	T	I	D	G	S	M	C	DL	A	D	S	M	C	A
+	+	+		+	+[1]		+[1]	+[1]					+[1]	+	+		+		+		+	+	+	+[1]	+		+		+[1]							+[1]				

A, aneuploidy; C, chromosomal aberrations; D, DNA damage; DL, dominant lethal mutation; G, gene mutation; I, inhibition of intercellular communication; M, micronuclei; R, mitotic recombination and gene conversion; S, sister chromatid exchange; T, cell transformation

In completing the tables, the following symbols indicate the consensus of the Working Group with regard to the results for each endpoint:

+ considered to be positive for the specific endpoint and level of biological complexity
+[1] considered to be positive, but only one valid study was available to the Working Group; sperm abnormality, mouse
- considered to be negative
-[1] considered to be negative, by only one valid study was available to the Working Group
? considered to be equivocal or inconclusive (e.g., there were contradictory results from different laboratories; there were confounding exposures; the results were equivocal)

Solar and 'solar-simulated' radiation and radiation from sunlamps (UVA and UVB) are mutagenic to prokaryotes and plants, induce DNA damage in fish and in amphibian cells *in vitro,* are mutagenic to and induce sister chromatic exchange in amphibian cells, induce micronucleus formation and transformation in mammalian cells *in vitro* are mutagenic to and induce DNA damage and sister chromatic exchange in human cells *in vitro* and induce DNA damage in mammalian skin cells irradiated *in vivo.*

UVA radiation is mutagenic to prokaryotes and induces DNA damage in fungi. It is mutagenic to and induces DNA damage, chromosomal aberrations and sister chromatic exchange in mammalian cells and induces DNA damage and mutation in human cells *in vitro.*

UVB radiation is mutagenic to prokaryotes and induces chromosomal aberrations in plants. It is mutagenic to and induces DNA damage, sister chromatic exchange and transformation in mammalian cells, is mutagenic and induces DNA damage and transformation in human cells *in vitro* and induces DNA damage in mammalian skin cells irradiated *in vivo.*

UVC radiation induces DNA damage in and is mutagenic to prokaryotes, fungi and plants and induces DNA damage in insects and aneuploidy in yeast. It induces sister chromatic exchange in amphibian and avian cells *in vitro;* it is mutagenic to and induces DNA damage, chromosomal aberrations, sister chromatic exchange and transformation in mammalian and human cells *in vitro;* and it induces DNA damage in mammalian skin cells irradiated *in vivo.*

UVR in the three wavelength ranges can induce or enhance cellular and viral gene expression.

5.5 Evaluations[1]

There is *sufficient evidence* in humans for the carcinogenicity of solar radiation. Solar radiation causes cutaneous malignant melanoma and nonmelanocytic skin cancer.

There is *limited evidence* in humans for the carcinogenicity of exposure to ultraviolet radiation from sunlamps and sunbeds.

There is *inadequate evidence* in humans for the carcinogenicity of exposure to fluorescent lighting.

There is *inadequate evidence* in humans for the carcinogenicity of other sources of artificial ultraviolet radiation.

There is *sufficient evidence* for the carcinogenicity of solar radiation in experimental animals.

There is *sufficient evidence* for the carcinogenicity of broad-spectrum ultraviolet radiation in experimental animals.

There is *sufficient evidence* for the carcinogenicity of ultraviolet A radiation in experimental animals.

[1] For definition of the italicized terms, see Preamble.

There is *sufficient evidence* for the carcinogenicity of ultraviolet B radiation in experimental animals.

There is *sufficient evidence* for the carcinogenicity of ultraviolet C radiation in experimental animals.

Overall evaluation

Solar radiation *is carcinogenic to humans* (Group 1).

Ultraviolet A radiation *is probably carcinogenic to humans* (Group 2A).

Ultraviolet B radiation *is probably carcinogenic to humans* (Group 2A).

Ultraviolet C radiation is *probably carcinogenic to humans* (Group 2A).

Use of sunlamps and sunbeds entails exposures that are probably carcinogenic to humans (Group 2A).

Exposure to fluorescent lighting is not classifiable as to its carcinogenicity to humans (Group 3)

CONTINUED

6. References

Aberer, W., Schuler. G., Stingl, G., Hönigsmann, H. & Wolff, K. (1981) Ultraviolet light depeletes surface markers of Langerhans cells. *J. invest. Dermatol*., **76**, 202-210

Adam, S.A., Sheaves, J.K., Wright, N.H., Mosser, G., Harris, R.W. & Vessey, M.P (1981) A case-control study of the possible association between oral contraceptives and malignant melanoma. *Br. J. Cancer,* **44**, 45-50

Agin, P.P., Rose, A.R, III, Lane, C.C.. Akin, F.J. & Sayre, R.M. (1981a) Changes in epidermal forward scattering absorption after UVA or UVA-UVB irradiation. *J. invest. Dermatol.,* **76**, 17-177

Agin, P.P, Lane. C.C. & Sayre, R.M. (1981b) Ultraviolet irradiation induces optical and structural changes in the skin of hairless mice. *Photochem. Photobiophys.,* **3**, 185-194

Alcalay, J., Freeman, S.E., Goldberg, L.H. & Wolf, J.E. (1990) Excision repair of pyrimidine dimers induced by simulated solar radiation in the skin of patients with basal cell carcinoma. *J. invest. Dermatol*., **95**, 506-509

Alter, B.J., Schendel, D.J., Bach, M.L., Bach, F.H., Klein, J. & Stimpfling, J.H. (1973) Cell-mediated lympholysis. Importance of serologically defined *H*-2 regions. J. *exp. Med*., **137**, 1303-1309

Ambach, W & Rehwald, W. (1983) Measurements of the annual variation of the erythema dose of global radiation. *Radiat. environ. Biophys.,* **21**, 295-303

American Conference of Governmental Industrial Hygienists (1991) *1991-1992 Threshold Limit Va/ues for C'hernical Substances and Physical Agents and Biological Exposure Indices,* Cincinnati, OH, pp. 123-128

Ananthaswamy, H.N. (1984a) Lethality and transformation of 10T1/2 mouse embryo fibroblast cell line by various wavelengths of ultraviolet radiation. *Photodermatology,* **1**, 265-176

Ananthaswamy, H.N. (1984b) Neoplastic transformation of neonatal mouse skin fibroblasts in culture after a single exposure to ultraviolet radiation *in* vivo. *Photodermatology,* **1**,10-113

Ananthaswamy, H.N. & Fisher, M.S. (1981) Photoreactivation of ultraviolet radiation-induced pyrimidine dimers in neonatal BALB/c mouse skin. *Cancer Res.,* **41**, 1829-1833

Ananthaswamy, H.N. & Kripke, M.L. (1981) In vitro transformation of primary cultures of neonatal BALB/c mouse epidermal cells with ultraviolet-B radiation. *Cancer Res.,* **41**, 2882-2890

Ananthaswamy, H.N. & Pierceall, W.E. (1990) Molecular mechanisms of ultraviolet radiation carcinogenesis. *Photochem. Photobiol.,* **52**, 1119-1136

Ananthaswamy, H.N., Price, J.E., Goldberg, L.H. & Bales, E.S. (1988) Detection and identification of activated oncogenes in human skin cancers occurring on sun-exposed bodysites. *CancerRes.,* **48**, 3341-3346

Anderson, D.E. (1963) Effect of pigment on bovine ocular squamous carcinoma. *Ann. N.Y.Acad. Sci.,* **100**, 436-446

Anderson, R.R. & Parrish. J.A. (1981) The optics of human skin. *J. invest.* ***Derrnatol.,*** **77**, 13-19

Anderson, R.R. & Parrish, J.A. (1982) Optical properties of human skin. In: Regan, J.D. & Parrish, J.A., eds, *The Science of Photo-medicine,* New York, Plenum, pp. 147-194

Anderson. L.M. & Rice, J.M. (1987) Tumorigenesis in athymic nude mouse skin by chemical carcinogenesis and ultraviolet light. *J. natl Cancer Inst.,* **78**, 125-134

Andley, U.P. (1987) Yearly review. Photodamage to the eye. *Photochem. Photobiol.,* 46, 1057-1066

Anon. (1979) *Sun-lamps, Solariums, Sunbeds and Health Lamps,* London, Which? Consumer Association, pp. 268-272

Anon. (1987) The *Truth About Tanning,* London, Which? Consumer Association, pp. 21-216

Ansel, J.C., Luger, T.A. & Green, I. (1983) The effect of in vitro and in vivo UV irradiation on the production of ETAF [epidermal cell derived thymocyte-activating factor] activity by human and murine keratinocytes. *J. invest. Dermatol*., **81**, 519-523

Applegate, L.A. & Ley, R.D. (1988) Ultraviolet radiation-induced lethality and repair of pyrimidine dimers in fish embryos. *Mutat. Res*., **198**, 85-92

Applegate, L.A. & Ley. R.D. (1991) DNA damage is involved in the induction of opacification and neovascularization of the cornea by ultraviolet radiation. *Exp. Eye Res*., **52**, 493-497

Applegate, L.A., Ley, R.D., Alcalay, J. & Kripke, M.L. (1989) Identification of the molecular target for the suppression of contact hypersensitivity by ultraviolet radiation. *J. exp. Med*., **170**, 1117-1131

Arlett, C.F. & Harcourt, S.A. (1983) Variation in response to mutagens amongst normal and repair-defective human cells. In: Lawrence, C.W., ed., *Induced Mutagenesis*: *Molecular Mechanisms and their Implications for Environmental Protection*, New York, Plenum, pp. 249-267

Arlett, C.F., Harcourt, S.A., Cole, J., Green, M.H. & Anstey, A.V (1992) A comparison of the response of unstimulated and stimulated T-lymphocytes and fibroblasts from normal, xeroderma pigmentosurn and trichothiodystrophy donors to the lethal action of UV-C. *Mutat. Res*., **273**, 127-135

Armstrong, B.K. (1984) Melanoma of the skin. *Br. med. Bull*., **40**, 346-350

Armstrong, R.B. (1986) Solar urticaria. *Dermatol. Clin*., **4**, 253-259

Armstrong, B.K. (1988) Epidemiology of malignant melanoma: intermittent or total accumulated exposure to the sun? *J. Dermatol. surg. Oncol*., **14**, 835-849

Armstrong, B.K., Woodings, T.L., Stenhouse, N.S. & McCall, M.G. (1983) *Mortality from Cancer in Migrants to Australia 1962 to 1971*, Perth, University of Western Australia, pp. 21, 81-83

Armstrong, B.K., Heenan, P.J., Caruso, V., Glancy, R.J. & Flolman, C.D.J. (1984) Seasonal variation in the junctional component of pigmented naevi (Letter to the Editor). *Int. J. Cancer*, **34**, 441-442

Armstrong, B.K., de Klerk, N.H. & Holman, C.D.J. (1986) Etiology of common acquired melanocytic nevi: constitutional variables, sun exposure, and diet. *J. natl Cancer Inst*., **77**, 329-335

Athas, W.F., Hedayati, M.A.. Matanoski, G.M., Farmer, E.R. & Grossman, L. (1991) Development and field-test validation of an assay for DNA repair in circulating human lymphocytes. *Cancer Res*., **51**, 5786-5793

Atkin, M., Fenning, J., Heady, J.A., Kennaway. E.L. & Kennaway, N.M. (1949) The mortality from cancer of the skin and lip in certain occupations. *Br. J. Cancer*, **3**, 1-15

Aubry, F. & MacGibbon, B. (1985) Risk factors of squamous cell carcinoma of the skin. A case-control study in the Montreal region. *Cancer*, **55**, 907-911

Auerbach, H. (1961) Geographic variation in incidence of skin cancer in the United States. *Public Health Rep*., **76**, 345-348

Augustsson, A., Stierner, U., Rosdahl, I. & Suurküla, M. (19903 Melanocytic naevi in sun-exposed and protected skin in melanoma patients and controls. *Acta derm. venereol.,* **71**, 512-517

Azizova, A.O., Islomov. A.I., Roshchupkin, D.I., Predvoditelev, D.A., Remizov, A.N. & Vladimirov, Y.A. (1980) Free radicals formed on ultraviolet irradiation of the lipids of biological membranes. *Biophysics,* **24**, 407-414

Baadsgaard, O., Fox, D.A. & Cooper, K.D. (1988) Human epidermal cells from ultraviolet light-exposed skin preferentially activate autoreactive $CD4^+$ $2H4^+$ suppressor-inducer lymphocytes and $CD8^+$ suppressor/cytotoxic lymphocytes. *J. Immunol.,* **140**, 1738-1744

Bach, F.H., Grillot-Courvalin, C., Kuperman, O.J., Sollinger, H.W., Hayes, C., Sondel, RM., Alter, B.J. & Bach, M. L. (1977) Antigenic requirements for triggering of cytotoxic T lymphocytes . *Immunol. Rev.,* **35**, 76-96

Bachem, A. (1956) Ophthalmic ultraviolet action spectra. *Ann. J. C)phthalmol.,* 41, 969-975

Baden, H.P & Pathak, M.A. (1967) The metabolism and function of urocanic acid in skin. *J. invest. Dermatol.,* **48**, 11-17

Balshi, J.D., Francfort, J.W. & Perloff, L.J. (1985) The influence of ultraviolet irradiation on the blood transfusion effect. *Surgery,* **98**, 243-249

Banerjee, S.K., Christensen. R.B., Lawrence, C.W. & LeClerc, J.E. (1988) Frequency and spectrum of mutations produced by a single cis-syn thymine-thymine cyclobutane dimer in a single-stranded vector. *Proc. natl Acad. Sci. USA*, **85**, 8141-8145

Banerjee, S.K., Borden, A., Christensen, R.B., LeClerc, J.E. & Lawrence, C.W. (1990) SOS-Dependent replication past a single *trans-syn* T-T cyclobutane dimer gives a different mutation spectrum and increased error rate compared to replication past this lesion in uninduced cells. *J. Bacteriol.,* **172**, 2105-2112

Barrett, J.C., Tsutsui, T. & Ts'o, P.O.P (1978) Neoplastic tranforn1ation induced by a direct perturbation of DNA. *Nature,* **274**, 229-232

Barrett, S.F., Robbins. J.H., Tarone, R.E. & Kraemer, K.H. (1991) Evidence fist defective repair of cyclobutane pyrimidine dimers with normal repair and other DNA photoproducts in a transcriptionally active gene transfectcd into Cockayne syndrome cells. *Mutat. Res.,* **255**, 281-291

Barth, C., Knuschke, P. & Barth, J. (1990) Examination of welders exposed to UV radiation (Ger.). *Z. ges. Hyg.,* **36**, 654-55

Baturay, N.Z., Targovnik, H.S., Reynolds, R.J. & Kennedy, A.R. (1985) Induction of in vitro transformation by near-uv light and its interaction with ß-propiolactone. *Carcinogenesis,* **6**, 465-468

Beadle, PC. & Burton, J.L. (1981) Absorption of ultraviolet radiation by skin surface lipid. *Br J. Dermatol.,* **104**, 549-551

Beardmore, G.L. (1972) The epidemiology of malignant melanoma in Australia. In: McCarthy, W.H., ed., *Melanoma anal Skin Cancer,* Sydney, V.C.N. Blight (Goverment Printer). pp. 39-4

Bech-Thomsen. N., Wulf, H.C., Poulsen, T. & Lundgren, K. (1988a) Pretreatment with long-wave ultraviolet light inhibits ultraviolet-induced skin tumor development in hairless mice. *Arch. Dermatol.,* **124**, 1215-1218

Bech-Thomsen, N., Wulf, H.C. & Lundgren, K. (1988b) Pre-treatment with UVA influences broad-spectrum UV photocarcinogencsis in hairless mice (Abstract). In: Rikles, E., ed., *Proceedings of the 10th International Congress on Photobiology Jerusalem,* Jerusalem, International Association of Biology, p. 34

Beer, J.Z. & Zmudzka, B.Z. (1991) Activation of human immunodeficiency virus by radiation. In: Seymour. C.B. & Mothersill. C., eds, *New Developments in Fundamental and Applied Radiology,* London. Taylor & Francis, pp. 113-123

Beer, J.Z., Olvey, K.M., Miller, S.A. & Zmudzka, B.Z. (1991) Studies on the human immunodeficiency virus promoter induction by UVA and UVB radiation (Abstract). *Photochem. Photobiol.,* **53**, 25S

Beitner, H. (1986) The effect of high dose long-wave ultraviolet radiation (UVA) on epidermal melanocytes in human skin: a transmission electron microscopic study. *Photodermatology*, **3**, 133-139

Beitner, H. & Wennersten, G. (1983) The immediate action of long-wave ultraviolet radiation (UVA) on suprabasal melanocytes in human skin: a transmission electron microscopical study. *Acta denmatol. venereol.,* **63**, 328-334

Beitner, H., Norell, S.E., Ringborg, U., Wennersten, G. & Mattson, B. (1990) Malignant melanoma: aetiologieal importance of individual pigmentation and sun exposure. *Br. J. Dermatol.,* **122**, 43-51

Bender, M.A., Griggs, H.G. & Walker, P.L. (1973) Mechanisms of chromosomal aberration production. I. Aberration induction by ultraviolet light. *Mutat.* Res., **20**, 387-402

Ben-Hur, E. & Ben-lshai, R. (1968) *Trans-syn* thymine dimers in ultraviolet-irradiated denatured DNA: identification and photoreactivability. *Biochim. biophys. Acta,* **166**, 9-15

Beral, V. & Robinson, N. (1981) The relationship of malignant melanoma, basal and squamous skin cancers to indoor and outdoor work. *Br J. Cancer,* **44**, 886-891

Beral, V., Evans, S., Shaw, H. & Milton, G. (1982) Malignant melanoma and exposure to fluorescent lighting at work. *Lancet*, **ii**, 290-293

Berg, M. (1987) Ultraviolet radiation in operation rooms. In: Passchier, WF. & Bosnjakovic, B.F.M., eds, *Human exposure to Ultraviolet Radiation: Risk and Regulations, Amsterdam,* Elsevier, pp. 359-363

Berger, D.S. (1976) The sunburning ultraviolet meter: design and performance. Photochem. Photo-*biol*., **24**, 587-593

Berger, H. & Kaase, H. (1983) Risk for carcinoma from sources of UVA radiation (Ger.). Z. *Hautkr.,* **58**, 63

Berger, D.S. & Urbach. F. (1982) A climatology of sunburning ultraviolet radiation. *Photochem. Photobiol.,* **35**, 187-192

Berger, H., Tsambaos, D. & Mahrle, G. (1980a) Experimental elastosis induced by chronic ultraviolet exposure. Light and electron-microsccypic study. *Arch. dermatol. Res*., **269**, 39-49

Berger, H., Tsambaos, D. & Kaase, H. (1980b) Experimental actinic elastosis by chronic exposure to filtered UVA radiation (Ger.). Z. *Hautkr,* **55**, 1510-1527

Bergstresser, P.R. (1986) Ultraviolet B radiation induces 'local immunosuppression'. Currenl *Probl. Dermatol.,* **15**, 205-218

Bernhard, J.D., Pathak, M.A., Kochevar, I.E. & Parrish, J.A. (1987) Abnorinal reactions to ultraviolet radiation. In: Fitzpatrick, T.B., Eisen, A.Z., Wolff, K., Freedberg. I.M. & Austen, K.F., eds, *Dermatology in General Medicine,* 3rd ed., New York, McGraw-Hill, pp. 1481-l507

Beukers, R. & Berends, W. (1960) Isolation and identification of the irradiation product of thymine. *Biochim. biophys. Acta,* **41**, 550-551

Beukers, R., Ylstra, J. & Berends, W. (1958) The effect of ultraviolet 1ight on some components of the nucleic acids. II. In rapidly frozen solutions. *Recl. Trav chim.* Pays-Bas, **77**, 729-732

Bielfeld, V., Weichenthal, M., Roser, M., Breithart, E., Berger, J., Seemanova, E. & Rüdiger. H.W. (1989) Ultraviolet-induced chromosomal instability in cultured fibroblasts of heterozygote carriers for xeroderma pigmentosum. *Cancer Genet. Cytogenet .,* **43**, 219-226

Bissett, D.L., Flannon. D.R. & Orr, TV (1987) An animal model of solar-aged skin: histological, physical, and visible changes in UV-irradiated hairless mouse skin. *Photochem. Photobiol*., **46**, 367-378

Bissett, D.L., Hannon, D.P & Orr, TV. (1989) Wavelength dependence of histological, physical, and visible changes in chronically UV-irradiated hairless mouse skin. *Photochem. Photobiol.,* **50**, 763-769

Blum, H.F. (1948) Sunlight as a causal factor in cancer of the skin of man. *J. natl Inst. Cancer*, **9**, 247-258

Blum, H.F. (1959) *Carcinogenesis by Ultraviolet Light,* Princeton, NJ, Princeton University Press

Blum, H.F. & Lippincott, S.W. (1942) Carcinogenic effectiveness of ultraviolet radiation of wavelength 2537 Å. *J. natl Cancer lnst.,* **3**, 211-216

Blum, H.F., Butler, E.G., Dailey, T.H., Daube, J.R., Mawe, R.C. & Soffen, G.A. (1959) Irradiation of mouse skin with single doses of ultraviolet light. *J. natl Cancer /nst*., **22,** 979-993

Blumthaler, M., Canaval, H. & Ambach, W. (1983) Measurement of erythemally active doses of solar UVB radiation (Ger.). *Z. Med.-Meteorol*., **2**,14-17

Blumthaler, M., Ambach, W. Ac Daxecker, F. (1985a) Computation of radiation doses from different solar UVB radiations producing photoelectric keratosis (Ger.). *Klin. Mbl. Augenheilk.,* **186,** 275-278

Blumthaler, M., Ambach, W. & Canaval, H. (1985b) Seasonal variation of solar UV-radiation at a high mountain station. *Photochem. Photobiol.,* **42,** 147-152

Boettner, E.A. & Wolter, J.R. (1962) Transmission of the ocular media. *Invest. Ophthalmol.,* **l**, 776-783

Bootsma, D. & Hoeijmakers, J.H.J. (1991) The genetic basis of xeroderma pigmentosum. Ann. *Genet.,* **34**, 143-150

Borek, C., Ong, A. & Mason, H. (1989) Ozone and ultraviolet light act as additive cocarcinogens to induce in vitro neoplastic transformation. *Teratog. Carcinog. Mutag.,* **9**, 71-74

Bos, A.J.J. & de Haas, M.P (1987) On the safe use of a high power ultraviolet laser. In: Passchier, W.F. & Bosnjakovic, B.F.M., eds, *Human Exposure to Ultraviolet Radiation: Risks and Regulations,* Amsterdam, Elsevier, pp. 377-382

Bose, B., Agarwal, S. & Chatterjee, S.N. (1989) UVA induced lipid peroxidation in liposomal membrane. *Radiat. environ. Biophys.,* **28**, 59-65

Bouissou, H., Pieraggi, M.-T., Julian, M. & Savit, T. (1988) The elastic tissue of the skin. A comparison of spontaneous and actinic (solar) aging. *Int. J. Dermatol.,* **27**, 327-335

Bowden, G.T., Trosko, J.E., Shapas, B.G. & Boutwell, R.K. (1975) Excision of pyrimidine dimers from epidermal DNA and nonsemiconservative epidermal DNA synthesis following ultraviolet irradiation of mouse skin. *Cancer Res.,* **35**, 3599-3607

Bowker, K.W. & Longford, A.R (1987) Ultraviolet radiation hazards from the use of solaria. In: Passchier, W.F. & Bosnjakovic, B.F.M., eds, *Human Exposure to Ultraviolet Radiation: Risks and Regulations,* Amsterdam, Elsevier, pp. 365-369

Boyd, R.W. (1983) *Radiometry and the Detection of Optical Radiation,* New York, John Wiley & Sons

Boyle, J., MacKie, R.M., Briggs, J.D., Junor, B.J.R. & Aitchison, T.C. (1984) Cancer, warts and sunshine in renal transplant patients. A case-control study. *Lancet, i,* 702-705

Bradley, M.O. & Sharkey, N.A. (1977) Mutagenicity and toxicity of visible fluorescent light to cultured mammalian cells. *Nature*, **266**, 724-726

Bradley, M.O., Hsu, I.C. & Harris, C.C. (1979) Relationships between sister chromatic exchange and mutagenicity, toxicity and DNA damage. *Nature*, **282,** 318-320

Brash, D.E. & Haseltine, W.A. (1982) UV-Induced mutation hotspots occur at DNA damage hot-spots. *Nature*, **298**, 189-192

Brash, D.E., Rudolph. J.A., Simon, J.A., Lin, A., McKenna, G.J., Baden. H.P, Halperin, A.J. & Pontén, J. (1991) A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc. natl Acad. Sci. USA*, **88**, 10124-10128

Bredberg. A., Kraerner, K.H. & Seidman, M.M. (1986) Restricted ultraviolet mutational spectrum in a shuttle vector propagated in xeroderma pigmentosum cells. *Proc. natl Acad. Sci. USA*, **83**, 8273-8277

Bridges, B.A. (1988) Mutagenic DNA repair in *Escherichia coli*. XVI. Mutagenesis by ultraviolet light plus delayed photoreversal in *rec*A strains. *Mutat. Res.*, **198**, 343-350

Bridges, B.A. (1990) Sunlight, DNA damage and skin cancer: a new perspective. *Jpn J. Cancer Res.*, **81**, 105-107

Bridges, B.A. & Bates, H. (1990) Mutagenic DNA repair in *Escherichia coli*. VIII. Involvement of DNA polymerase III α-subunit (DnaE protein) in mutagenesis alter exposure to UV light, *Mutagenesis*, **5**, 35-38

Bridges, B.A. & Brown. G.M. (1992) Mutagenic repair in *Escherichia coli*. XXI. A stable SOS-inducing signal persisting after excision repair of ultraviolet damage. *Mutat. Res.* (in press)

Bridges, B.A., Woodgate, R., Ruiz-Rubio, M., Sharif, F., Sedgwick, S.G. & Hübscher. U. (1987) Current understanding of UV-induced base pair substitution mutation in *E. coli* with particular reference to the DNA polymerase III complex. *Mutat. Res.*, **181**, 219-226

Broughton, B.C., Lenmann. A.R., Harcourt, S.A., Arlett, C.F., Sarasin, A., Kleijer W.J., Beemer, F.A., Nairn, R. & Mitchell, D. L. (1990) Relationship between pyrimidine dimers, 6-4 photoproducts, repair synthesis and cell survival: studies using cells from patients with trichothiodystrophy. *Mutut. Res.*, **235**, 33-40

Brown, L.R. & Wüthrich, K. (1977) A spin label study of lipid oxidation catalyzed by heme proteins. *Biochim. biophys. Acta*, **464**, 356-369

Brown, J., Kopf, A.W., Rigel, D.S. & Fridmai1, R.J. (1984) Malignant melanoma in World War II veterans. *Int. J. Dermatol.*, **23**, 661-663

Bruggers, J.H.A., de Jong, W.E., Bosnjakovic. B.F.M. & Passchier, W.F. (1ti87) Use of artificial tanning equipment in the Netherlands. In: Passchier, WE & Bosnjakovic, B.F.M., eds, *Human Exposure to Ultraviolet Radiation*: Risk and Regulations, Amsterdam, Elsevier, pp. 235-239

Bruls, W.A.G., Slaper. H., van der Leun, J.C. & Berrens, L. (1984a) Transmission of human epidermis and stratum corneum as a function of thickness in the ultraviolet and visible wavelengths. *Photochem. Photohiol.*, **40**, 485-494

Bruls, W.A.G., van Weelden, H. & van der Leun, J.C. (1984b) Transmission of UV-radiation through human epidermal layers as a factor influencing the minimal erytherna dose. *Photochem. Photobiol.*, **39**, 63-67

Bruyneel-Rapp, F., Dorsey, S.B. & Guin, J.D. (1988) The tanning salon: an area survey of equipment, procedures, and practices. *J. Am. Acad.* Dermatol, **18**, 1030-1038

Burki, H.J. & Lam, C.K. (1978) Comparison of the lethal and mutagenic effects of gold and white fluorescent lights on cultured mammalian cells. *Mutat. Res.*, **54**, 373-377

Burnet, F.M. (1971) Implications of immunological surveillance for cancer therapy. *Isr. J. med. Sci.*, **7**, 9-16

Calkins, J., Selby, C. & Enoch, H.G. (1987) Comparison of UV action spectra for lethality and mutation in Salmonella typhimurium using a broad band source and monochromatic radiations. *Photochem. Photobiol.*, **45**, 631-636

Cameron, L.L., Vitasa, B.C., Lewis, P.G., Taylor, H.R. & Emmett, E.A. (1988) Visual assessment of facial elastosis using photographs as a measure of cumulative ultraviolet exposure. *Photodermatology*, **5**, 277-282

Caplan, R.M. (1967) Medical uses of the Wood's lamp. *J. Am. med. Assoc*., **202**, 1035-1038

Cavard, C., Zider, A., Vernet, M., Bennoun, M., Saragosti, S., Grimber, B. & Briand, P. (1990) In vivo activation by ultraviolet rays of the human immunodeficiency virus type 1 long terminal repeat. *J. clin. Invest*., **36**, 1369-1374

Cerutti, PA. (1981) Measurement of thymine damage induced by oxygen radical species. In: Friedberg, E.C. & Hanawalt, PC., eds, *DNA Repair. A laboratory, Manual of Research Procedures*. Vol. 1, Part A, New York, Marcel Dekker, pp. 57-68

Cerutti, PA. & Netrawali, M. (1979) Formation and repair of DNA damage induced by indirect action of ultraviolet light in normal and xeroderma pigmentosum skin fibroblasts. *Radiat. Res*., Suppl., 423-432

Cesarini, J.-P & Muel, B. (1989) Erythema induced by quartz-halogen sources. *Photodermatology*, **6**, 222-227

Challoner, A.V.J., Corless, D., Davis, A., Deane, G.H.W., Diffey, B.L., Gupta, S.P. & Magnus, I.A. (1976) Personnel monitoring of exposure to ultraviolet radiation. *Clin. exp. Dermatol*., **1**, 175-179

Challoner, A.V.J., Corbett, M.F., Davis, A., Diffey, B.L., Leach, J.F. & Magnus, I.A. (1978) Description and application of a personal ultraviolet dosimeter: a review of preliminary studies. *Natl Cancer Inst. Monogr*., **50**, 97-100

Chamberlain, J. & Moss, S.H. (1987) Lipid pcroxidation and other membrane damage produced in Eschenchia cold EC1060 by near-UV radiation and deuterium oxide. *Photochem. Photobiol*., **45**, 625-630

Chan, G.L. & Little, J.B. (1976) Induction of oncogenic transformation *in vitro* by ultraviolet light. *Nature*, **264**, 442-444

Chan, G.L. & Little, J.B. (1979) Correlation of in vitro transformation with in vivo tumorigenicity in 10T1/2 mouse cells exposed to UV light. *Br. J. Cancer*, **39**, 590-593

Chan, G.L., Peak, M.J., Peak, J.G. & Haseltine, W.A. (1986) Action spectrum for the formation of endonuclease-sensitive sites and (6-4) photoproducts induced in a DNA fragment by ultraviolet radiation. *Int. J. Radiat. Biol*., **50**, 641-648

Chao, C.C.-K. & Rosenstein, B.S. (1985) Induction of sister-chromatic exchanges in ICR 2A frog cells exposed to 254 nm and solar UV wavelengths. *Photochem. Photobiol*., **41**, 625-627

Chao, C.C.-K. & Rosenstein, B.S. (1986) Use of metabolic inhibitors to investigate the excision repair of pyrimidine dimers and non-dimer DNA damages induced in human and ICR 2A frog cells by solar ultraviolet radiation. *Photochem. Photobiol*., **43**, 165-170

Chu, E.H.Y. (1965a) Effects of ultraviolet radiation on mammalian cells. I. Induction of chromosome aberrations. *Mutat. Res.,* **2**, 75-94

Chu, E.H.Y. (1965b) Effects of ultraviolet radiation on mammalian cells. II. Differential UV and x-ray sensitivity of chromosomes to breakage in 5-aminouracil synchronized cell populations. *Genetics*, **52**, 1279-1294

Chung, H.-T., Burnham, D.K., Robertson, B., Roberts, L.K. & Daynes, R.A. (1986) Involvement of prostaglandins in the humane alterations caused by the exposure of mice to ultraviolet radiation. *J. Immunol.,* **137**, 2478-2484

Churchill, M.E., Peak, J.G. & Peak, M.J. (1991) Correlation between cell survival and DNA single-strand break repair proficiency in the Chinese hamster ovary cell lines AA8 and EM9 irradiated with 365-nm ultraviolet A radiation. *Photochem. Photobiol.,* **53**, 229-236

Cieminis, K.G.K., Rančelienė, V.M., Prijalgauskienė, A.J., Tiunaitienė, N.V., Rudzianskaitė, A.M. & Jančys, Z..J. (1987) Chromosome and DNA damage and their repair in higher plants irradiated with short-wave ultraviolet light. *Mutat. Res.,* **181**, 9-16

Claas, F.H.J., Rothert, M., Havinga, I., Schothorst, A.A., Vermeer, B.-J. & van Rood, J.J. (1985) Influence of ultraviolet radiation treatment on the survival of heterotopic skin grafts in the mouse. *J. invest. Dermatol.,* **84**, 31-32

Clark, J.H. (1964) The effect of long ultraviolet radiation in the development of tumors induced by 20-methylcholanthrene. *Cancer Res.,* **24**, 207-211

Cleaver, J.E. (1968) Defective repair replication of DNA in xeroderma pigmentosuin. *Nature,* 218, 652-656

Cleaver, J.E. & Kraemer, K.H. (1989) Xeroderma pigmentosum. In: Scriver. C.R., Beaudet, A.L., Sly, W.S. & Valle, D., eds, T*he Metabolic Basis of Inherited Disease,* New York, McGraw-Hill, pp. 2949-2971

Clemmesen, J. (1965) *Statistical Studies in theAetiology of Malignant Neoplasms. I. Review and Results,* Copenhagen, Munksgaard, p. 409

Cole, C.A., Forbes. P.D., Davies, R.E. & Urbach, F. (1985) Effect of indoor lighting on normal skin. *Ann. N.Y. Acad. Sci.,* **453**, 305-316

Cole, C.A., Forbes, P.D. & Davies, R.E. (1986) An action spectrum for UV photocarcinogenesis. *Photochem. Photobiol.,* **43**, 275-284

Colella, C.M., Bogani, P. Agati, G. & Fusi, E (1986) Genetic effects of UVB: mutagenicity of 308 nm light in Chinese hamster V79 cells. *Photochem. Photobiol.,* **43**, 437-442

Commission lnternationale de l'Eclairage (International Comn1ission on Illumination) (1987) *Vocabulaire International de l'Eclairage* [International Lighting Vocabularyl (CIE Publication No. 17.4), 4th ed., Geneva, Bureau Central de la Commission Electrotechique lnternationale, p. 3

Coohill, T.P., Peak, M.J. & Peak, J.G. (1987) The effects of the ultraviolet wavelengths of radiation present in sunlight on human cells *in vitro. Photochem. Photobiol.,* **46**, 1043-1050

Cooke, K.R. & Fraser, J. (1985) Migration and death from malignant melanoma. *Int. J. Cancer,* **36**, 175-178

Cooke, A. & Johnson, B.E. (1978) Dose response, wavelength dependence and rate of excision of ultraviolet radiation induced pyrimidine dimers in mouse skin DNA. Biochim. *biophys. Acta,* **517**, 24-30

Cooke, K.R., Skegg, D.C.G. & Fraser, J. (19S4) Socio-economic status, indoor and outdoor work, and malignant melanoma. *Int. J. Cancer,* **34**, 7-62

Cooper, K.D., Fox, P., Neises, G. & Katz, S.I. (1955) Effects of ultraviolet radiation on human epidermal cell alloantigen presentation: initial depression of' Langerhans cell-dependent function is followed by the appearance of $T6^{-}Dr^{+}$ cells that enl1ance epidermal alloantigen presentation. J. *Immunol.,* **134**, 129-137

Cooper, K.D., Neises, G.R. & Katz. S.I. (1986) Antigen-presenting OKM5 $^{+}$ melanophages appear in human epidermis after ultraviolet radiation. *J. invest. Dermatol.,* **86**, 363-370

Corominas. M., Kamino. H., L.eon, J. & Pellicer, A. (1989) Oncogene activation in human benign tumors of the skin (keratoacanthon1as): Is H-ras involved in dii'ferentiation as well as proliferation? *Proc. natl Acad. Sci. USA,* **86**, 6372-6376

Cox, C.W.J. (1987) Ultraviolet irradiance levels in welding processes. In: Passchier. W.F-. & Bosnjakovic. B.FM., eds. *Human Exposure to Ultraviolet Racticition: Risks und Regulations,* Amsterdam, Elsevier, pp. 383-386

Cripps, D.J., Horowitz, S. & Hong, R. (1978) Spectrum of ultraviolet radiation on human B and T lymphocyte viability. *Clin. exp. Dermatol.,* 3, 43-50

Cristofolini, M., Franceschi, S., Tasin, L., Zumiani, G., Piscioli, F., Talamini, R. & La Vecchia, C. (1987) Risk factors for cutaneous malignant melanoma in a northern Italian population. *Int. J. Cancer,* **39**, 150-154

Crombie, I.K. (1981) Distribution of malignant melanoma on the body surface. *Br. J. Cancer,* **43**, 842-849

Cullen, A.P (1980) Additive effects of ultraviolet radiation. *Am. J. Optometry physiol. Optics.* **57**, 808-814

Cunningham, M.L., Johnson, J.S., Giovanazzi, S.M. & Peak, M.J. (1985) Photosensitized production of superoxide anion by monochromatic (290-405 nm) ultraviolet irradiation of NADH and NADPH coenzymes. *Photochem. Photobiol.,* **42,** 125-128

Czernielewski, J.M., Masouye, l., Pisani, A., Ferracin, J., Auvolat, D. & Ortonne, J.-P (1988) Effect of chronic sun exposure on human Langerhans cell densities. *Photodermatology* **5**, 116-120

Czochralska, B., Kawczynski, W., Bartosz, G. & Shugar, D. (1984) Oxidation of excited-state NADH and NAD dimer in aqueous medium—involvement of O_2^- as a mediator in the presence of oxygen. *Biochim. biophys. Acta,* **801**, 403-409

D'Ambrosio, S.M., Slazinski. L., Whetstone, J.W. & Lowney, E. (1981) Excision repair of UV-induced pyrimidine dimers in human skin *in vivo. J. invest. Dermatol.,* **77**, 311-313

D'Ambrosio, S.M., Bisaccia, E., Whetstone, J.W., Scarborough, D.A. & Lowney, E. (1953) DNA repair in skin of lupus erythematosus following in vivo exposure to ultraviolet radiation *J. invest. Dermatol.,* **81**, 452-454

Danpure, H.J. & Tyrrell, R.M. (1976) Oxygen-dependence of near-UV (365 nm) lethality and the interaction of near-UV and x-rays in two mammalian cell lines. *Photochetn Photohiol.,* **23**, 171-177

Dardanoni, L.. Gafá. L.. Paterno, R. & Pavone, G. (1984) A case-control study on lip cancer risk factors in Ragusa (Sicily). *Int. J. Cancer,* **34**, 335-337

Davies, R.E. & Forbes. P. D. (1988) Retinoids and photocarcinogenesis: a review. *J. Toxicol. cutaneous ocul. Toxicol.,* **7**, 241-253

Davies, R.E., Dodge, H.A. & DeShields, L.H. (1972) Alteration of thc carcinogenic activity of 7,12-dirnethylbenz(a)anthracene (DMBA) by light (Abstract no. 54). *Proc. Am. Assoc. Cancer Res.,* **13**, 14

Davis, A. & Sims. D. (1983) *Weathering of Polymers,* London, Applied Science

Daynes, R.A., Spellman, C.W, Woodward, J.G. & Stewart, D.A. (1977) Studies into the transplantation biology of ultraviolet light-induced tumors. *Transplantation,* **23**, 343-348

Daynes, R.A., Spikes. J.D. & Krueger, G. (1983) *Experimental and C.linical Photoimmunology,* Vols I and II, Boca Raton, FL, CRC Press

Dearden, S.J., Hunter, T.F. & Philp, J. (1981) Bilayer microviscosity changes due to O_2 ($^1\Delta_g$) peroxidation in lipid vesicles. *Chem. Phys. Lett.,* **81**, 606-609

Dearden, S.J.. Hunter, TE & Philp, J. (1985) Fatty acid analysis as a function of photo-oxidation in egg yolk lecithin vesicles. *Photochetn. Photobiol.,* **41**, 213-215

De Fabo, E.C. & Kripke, M.L. (1980) Wavelength dependence and dose-rate independence of UV radiation-induced immunologic unresponsiveness of mice to a UV-induced fibrosarcoma. *Photochem. Photobiol..* **32**, 183-188

De Fabo, E.C. & Noonan, F.P. (1983) Mechanism of immune suppression by ultraviolet irradiation *in vivo*. I. Evidence for the existence of a unique photoreceptot in skin and its role in photo-immunology. *J. exp. Med.,* **157**, 84-98

De Flora, S., Camoirano. A., Izzotti, A. & Bennicelli, C. (1990) Potent genotoxicity of halogen lamps, compared to fluorescent light and sunlight. *Carciriogenesis,* **11**, 2171-2177

Denkins, Y., Fidler, I.J. & Kripke, M.L. (1989) Exposure of mice to UVB radiation suppresses delayed hypersensitivity to *Candida albicans. Photochem. Photobiol*., **49,** 615-619

Desai, I.D., Sawant, P.L. & Tappel, A.L. (1964) Peroxidative and radiation damage to isolated Iysosomes. *Biochim. biophys. Acta,* **86,** 277-285

De Weerd-Kastelein, E.A., Keijzer, W., Rainaldi, G. & Bootsma, D. (1977) Induction of sister chromatid exchanges in xeroderma pigmentosum cells after exposure to ultraviolet light. *Mutat. Res.,* **45,** 253-261

Diffey, B.L. (1982) The consistency of studies of ultraviolet erytherna in normal human skin. *Phys. med. Biol.,* **27,** 715-720

Diffey, B.L. (1986) Use of UVA sunbeds for cosmetic tanning. *Br. J. Derrnatol.,* **ll5**, 67-76

Diffey, B. (1987a) A comparison of dosimeters used for solar ultraviolet radiometry. *Photochem. Photobiol.,* **46**, 55-60

Diffey, B.L. (1987b) Analysis of the risk of skin cancer from sunlight and solaria in subjects living in northern Europe. *Photodermatology*, **4**, 118-126

Diffey, B.L. (1987c) Cosmetic and medical applications of ultraviolet radiation: risk evaluation and protection techniques. In: Passchier, W.F. & Bosnjakovic, B.F.M., eds, *Human Exposure to Ultraviolet Radiation: Risks and Regulations,* Amsterdam, Elsevier, pp. 305-315

Diffey, B.L. (1988) The risk of skin cancer from occupational exposure to ultraviolet radiation in hospitals. *Phys. med. Biol.,* **33**, 1187-1193

Diffey, B.L. (1989a) Ultraviolet radiation and skin cancer. Are physiotherapists at risk? *Physiotherapy,* **75**, 615-616

Diffey, B.L. (1989b) Ultraviolet radiation dosimetry with polysulphone film. In: Diffey. B.L., ed., *Radiation Measurement in Photobiology,* London, Academic Press, pp. 135-159

Diffey, B.L. (1990a) Human exposure to ultraviolet radiation. *Semin. Dermatol.,* **9**. 2-10

Diffey, B.L. (1990b) Ultraviolet radiation lainps for the phototherapy and photochemotherapy of skin disease. In: Champion. R.H. & Pye, R.J., eds, *Recent Advances in Dermatology,* Vol. 8. Edinburgh, Churchill Livingstone, pp. 21-40

Diffey, B.L. (1991) Solar ultraviolet radiation effects on biological systems. *Phys. med. Biol*., **36,** 299-328

Diffey, B.L. & Farr, PM. (1987) An appraisal of ultraviolet lamps used for the photoytherapy of psoriasis. *Br. J. Dermatol.,* **117**, 49-56

Diffey, B.L. & Farr, P.M. (1989) The normal range in diagnostic phototesting. *Br J. Dermatol.,* **120**, 517-524

Diffey, B.L. & Farr, PM. (1991a) Quantitative aspects of ultraviolet erythema. *Clin. phys. physiol. Meas.*, **12**, 311 -325

Diffey, B.L . & Farr, P.M. (1991b) Tanning with UVB or UVA: an appraisal of risks. *J. Photochem. Photobiol. B. Biol.,* **8**, 219-223

Diffey, B.L. & Langley, F.C. (1986) *Evaluation of Ultraviolet Radiation Hazards in Hospitals* (Report No. 49), London, institute of Physical Sciences in Medicine

Diffey, B.L. & McKinlay, A.E (1983) The UVB content of UVA fluorescent lamps' and its erythernal effectiveness in human skin. *Phys. med. Biol.,* **28**, 351-358

Diffey, B.L., Kerwin, M. & Davis, A. (1977) The anatomical distribution of sunlight. *Br. J. Dermatol.,* **97**, 407-410

Diffey, B.L., Tate, T.J. & Davis, A. (1979) Solar dosimetry of the face: the relationship of natural ultraviolet radiation exposure to basal cell carcinoma localization. *Phys. med. Biol.,* **24**, 931-939

Diffey, B.L., Challoner, A.V.J. & Key, P.J. (1980) A survey of the ultraviolet radiation emissions of photochemotherapy units. *Br. J. Dermatol*., **102**, 301-306

Diffey. B.L., Larkö, O., Meding, B., Edeland, H.G. & Wester, U. (1986) Personal monitoring of exposure to ultraviolet radiation in the car manufacturing industry. *Ann. occup. Hyg*., **30**, 163-170

Diffey, B.L., Farr, PM. & Oakley, A.M. (1987) Quantitative studies on UVA-induced erythema in human skin. *Br. J. Dermatol*., **117**, 57-66

DiPaolo, J.A. & Donovan, P.J. (1976) In vitro morphologic transtonnation of Syrian hamster cells by UV-irradiation is enhanced by X-irradiation and unaffected by chemical carcinogens. *Int. J. radiat. Biol*., **30**, 41-53

Doda, D.D. & Green. A.E.S. (198()) Surface reflectance measurements in the UVA from an airborne platform. Part 1. *Appl. Optics*, **19**, 2140-2145

Doll, R. (1991) Urban and rural factors in the aetiology of cancer. *Int. J. Cancer*, **47**, 803-810

Doll, R., Muir, C. & Waterhouse, J., eds (1970) Cancer Incidence in Five Continents, Vol. II, Berlin, Springer

Doniger, J., Jacobson, E.D., Krell, K. & DiPaolo, J.A. (1981) Ultraviolet light action spectra for neoplastic transformation and lethality of Syrian hamster embryo cells correlate with spectrum for pyrimidime dimer formation in cellular DNA. *Proc. natl Acad. Sci.* USA, **78**., 2378-2382

Dorado, G., Steingrimsdottir, H., Arlett, C.F. & Lehmann, A.R. (1991) Molecular analysis of ultra-violet-induced mutations in a xeroderma pigmentosum cell line. *J. mol. Biol*., **217**, 217-222

Dorn, H.F. (1944a) Illness from cancer in the United States. Public Health Rep., **59**, 33-48

Dorn, H.F. (1944b) Illness front cancer in the United States: IV Illness from cancer of specific sites classed in broad groups. *Public Health Rep*., **59**, 65-77

Dorn, H.F. (1944c) Illness from cancer in the United States: VI. Regional differences in illness from cancer. *Public Health Rep*., **59**, 97-ll4

Dorn, C.R., Taylor, D.O.N. & Schneider, R. (1971) Sunlight exposure and risk of developing cutaneous and oral squamous cell carcinomas in white cats. *J. natl Cancer Inst*., **46**, 1073-1078

Doudney, C.O. (1976) Mutation in ultraviolet light-damaged microorganisms. In: Wang, S.Y., ed., *Photochemistry and Photobiology of Nucleic Acids,* Vol. 2, New York, Academic Press, pp. 309-374

Dougherty, M.A., McDermott, R.J. & Hawkins, M.J. (1988) A profile of users of commercial tanning salons. *Health Values,* **12**, 21-28

Dreosti. I.E., Baghurst, PA., Partick, E.J. & Turner, J. (1990) Induction of micronuclei in cultured marine splenocytes exposed to elevated levels of ferrous ions, hydrogen peroxide and ultraviolet irradiation. *Mutat. Res*., **244**, 337-343

Drobetsky, E.A. & Glickman, B.W. (1990) The nature of ultraviolet light-induced mutations at the heterozygous *aprt* locus in Chinese hamster ovary cells. *Mutat. Res*., **232**, 281-289

Dubin, N., Moseson, M. & Pasternack, B.S. (1986) Epidemiology of malignant melanoma: pigmentary traits, ultraviolet radiation, and the identify cation of high-risk populations. *Recent Results Cancer Res*., **102**, 56-75

Dubin, N., Moseson, M. & Pasternack, B.S. (1989) Sun exposure and malignant melanoma among susceptible individuals. *Environ. Health Perspectives*, **81**, 139-151

Eaton, G.J., Custer, R.P & Crane, A.R. (1978) Effects of ultraviolet light on nude mice. Cutaneous carcinogenesis and possible leukemogenesis. *Cancer*, **42**, 182-188

Ebbesen, P. (1981) Enhanced lymphoma incidence in BALB/c mice after ultraviolet light treatment. *J. natl Cancer Inst*., **67**, 1077-1078

Eggset, G., Volden. G. & Krokan, H. (1983) UV-Induced DNA damage and its repair in human skin *in vivo* studied by sensitive immunohistochemical methods. *Carcinogenesis,* **4**, 745-750

Eggset, G., Krokan, H. & Volden, G. (1986) UV-Induced DNA damage and its repair in tanned and untanned human skin *in vivo. Photobiochem. Photobiophys.,* **10**, 181-187

Eisenstark, A. (1987) Mutagenic and lethal effects of near-ultraviolet radiation (290-400 nm) on bacteria and phage. *Environ. mol. Mutag.,* **10**, 317-337

Eklund, G. & Malec, E. (1978) Sunlight and incidence of cutaneous malignant melanoma. Effect of latitude and domicile in Sweden. *Scand. J. plast. reconstr. Surg.,* **12**, 231-241

Elkind, M.M. & Han, A. (1978) DNA single-strand lesions due to 'sunlight' end UV light: a comparison of their induction in Chinese hamster and human cells, and their fate in Chinese hamster cells. *Photochem. Photobiol.,* **27**, 717-724

Ellison, M.J. & Childs, J.D. (1981) Pyrimidine dimers induced in *Escherichia coli* DNA by ultraviolet radiation present in sunlight. *Photochem. Photobiol*., **34**, 465-469

Elmets, C.A., Bergstresser, P.R., Tigelaar, R.E., Wood, P.J. & Streilein, J.W. (1983) Analysis of the mechanism of unresponsiveness produced by haptens painted on skin exposed to low dose ultraviolet radiation. *J. exp. Med.,* **158**, 781-794

Elmets, C.A., LeVine, M.J. & Bickers, D.R. (1985) Action spectrum studies for induction of immunologic unresponsiveness to dinitrofluorobenzene following in vivo low dose ultraviolet radiation. *Photochem. Photobiol.,* **42**, 391-397

Elmets, C.A., Larson, K., Urda, G.A. & Schacter, B. (1987) Inhibition of postbinding target cell lysis and of lymphokine-induced enhancement of human natural killer cell activity by in vitro exposure to ultraviolet B radiation. *Cell. Immunol.,* **104**, 47-58

Elwood, J.M. (1989a) Epidemiology and control of melalloma in white populations and in Japan. *J. invest. Dennatol.,* **92**, 214S-221S

Elwood, J.M. (1989b) Epidemiology of melanoma: its relationship to ultraviolet radiation and ozone depletion. In: Jones, R.R. & Wigley, T., eds, *Ozone Depletion. Health and Environmental Consequences,* New York, John Wiley & Sons, pp. 169-189

Elwood, J.M. & Gallagher, R.P (1983) Site distribution of malignant melanoma. *Can. med. Assoc. J.,* **128**, 1400-1404

Elwood, J.M., Lee, J.A.H., Walter, S.D., Mo, T. & Green, A.E.S. (1974) Relationship of melanoma and other skin cancer mortality to latitude and ultraviolet radiation in the United States and Canada. *Int. J. Epidemiol.,* **3**, 325-332

Elwood, J.M., Gallagher, R.P, Hill, G.B., Spinelli, J.J., Pearson, J.C.G. & Threlfall, W. (1984) Pigmentation and skin reaction to sun as risk factors for cutaneous melanoma: Western Canada Melanoma Study. *Br. med. J.,* **288**, 99-102

Elwood, J.M., Gallagher, R.P, Davison, J. & Hill, G.B. (1985a) Sunburn, suntan and the risk of cutaneous malignant melanoma: the Western Canada Melanoma Study. *Br. J. Cancer*, **51**, 543-549

Elwood, J.M., Gallagher, R.P, Hill, G.B. & Pearson, J.C.G. (1985b) Cutaneous melanoma in relation to intermittent and constant sun exposure: the Western Canada Melanoma Study. *Int. J. Cancer,* **35**, 427-433

Elwood, J.M., Williamson, C. & Stapleton, P.J. (1986) Malignant melanoma in relation to moles, pigmentation, and exposure to fluorescent and other lighting sources. *Br J. Cancer,* **53**, 65-74

Elwood, J.M., Gallagher, R.P, Worth, A.J., Wood, W.S. & Pearson. J.C.G. (1987) Etiological differences between subtypes of cutaneous malignant melanoma: Western Canada Melanoma Study. *J. natl Cancer Inst.,* **78**, 37-44

Elwood, J.M., Whitehead, S.M., Davison, J., Stewart, M. & Galt, M. (1990) Malignant melanoma in England: risk associated with naevi, freckles, social class, hair colour, and sunburn. *Int. J. Epidemlol*., **19**, 801-810

Emmett, E.A. (1973) Ultraviolet radiation as a cause of skin tumors. *Crit. Rev. Toxicol*., **2**, 211-255

Emmett, E.A. & Horstman, S.W (1976) Factors influencing the output of ultraviolet radiation during welding. *J. occup. Med*., **18**, 41-44

Engel, A., Johnson, M.-L. & Haynes, S.G. (1988) Health effects of sunlight exposure in the United States. Results from the first National Health and Nutrition Examination Survey, 1971-1974. *Arch. Derrnatol*., **124**, 72-79

English, D.R., Rouse, I.L., Xu, Z., Watt, J.D., Holman, C.D.J., Heenan. P.J. & Armstrong, B.K. (1985) Cutaneous malignant melanoma and fluorescent lighting. *J. natl Cancer Inst.,* **74**, 1191-1197

Enninga, I.C., Groenendijk, R.T.L., Filon, A.R., van Zeeland, A.A. & Simons. J.W.I.M. (1986) The wavelength dependence of UV-induced pyrimidine dimer formation, cell killing and mutation induction in human diploid skin fibroblasts. *Carcinogenesis*, **7**, 1899-1836

Epstein, J.H. (1965) Comparison of the carcinogenic and cocarcinogenic effects of ultraviolet light on hairless mice. *J. natl Cancer Inst.,* **34**, 741-745

Epstein, J.H. (1985) Animal models for studying photocarcinogenesis. In: Maibach, H. & Lowe, N., eds, *Models in Dermatology.* Vol.2, Basel, Karger, pp. 303-312

Epstein, J.H. (1988) Photocarcinogenesis promotion studies with benzoyl peroxide (BPO) and croton oil. *J. invest. Dermatol*., **91**, 114-116

Epstein, J.H. (1990) Induction of melanomas in experimental animals. *Photodermatol. Photo-immunol. Photomed*., **7**, 95-97

Epstein, J.H. & Epstein, W.L. (1962) Cocarcinogenic effect of ultraviolet light on DMBA tumor initiation in albino mice. J. *invest. Dermutol*., 39, 455-460

Epstein, J.H. & Epstein, W.L. (1963) A study of tumor types produced by ultraviolet light in hairless mice and hairy mice. *J. invest. Dermatol*., **41**, 463-73

Epstein, J.H. & Roth, H.L. (1968) Experimental ultraviolet light catcinogenesis. A study of croton oil promoting effects. J *invest. Dermatol*., **50**, 387-389

Epstein, J.H., Epstein. W.L. & Nakai, T. (1967) Production of melanomas from DMBA-induced 'blue nevi' in hairless mice with ultraviolet light. *J. natl Cancer Inst*., **38**, 19-30

Epstein, W.L., Fukuyama, K. & Epstein, J.H. (1969) Early effects of ultraviolet light on DNA synthesis in human skin *in vivo. Arch. Dermatol.,* **100**, 84-89

Epstein, J.H., Fukuyama. K., Reed, W.B. & Epstein, W.L. (1970) Defect in DNA synthesis in skin of patients with xeroderma pigmentosum demonstrated *in vivo. Science*, **168**, 1477-1478

Eriksen, P. (1987) Occupational applications of ultraviolet radiation: risk evaluation and protection techniques. In: Passchier, W.F. & Bosnjakovic, B.F.M., eds, *Human Exposure to Ultraviolet Radiation. Risks and Regulations,* Amsterdam, Elsevier, pp. 317-331

Eriksen, P., Moscato, P.M., Franks, J.K. & Sliney, D.H. (1987) Optical hazard evaluation of dental curing lights. *Community Dent. ora/ Epidemiol*., **15**, 197-201

Everett, M.A., Yeargers, E., Sayre, R.M. & Olson, R.L. (1966) Penetration of epidermis by ultraviolet rays. *Photochem. Photobiol*., **5**, 533-542

Everett, M.A., Nordquist, J. & Olson, R.L. (1970) Ultrastructure of human epidermis following chronic sun exposure. *Br. J. Dermatol*., **84**, 248-257

Fan, J., Schoenfeld, R.J. & Hunter, R. (1959) A study of the epidermal clear cells with special reference to their relationship to the cells of Langerhans. *J. invest. Dermatol*., **32**, 445-50

Farr, PM. & Diffey, B.L. (1985) The erythemal response of human skin to ultraviolet radiation. *Br. J. Dermatol*., **113**, 65-76

Fears, T.R., Scotto, J. & Schneiderman, M.A. (1976) Skin cancer, melanoma, and sunlight. *Am. J. public Health*, **66**, 461-464

Fears, T.R., Scotto, J. & Schneiderman, M.A. (1977) Mathematical models of age and ultraviolet effects on the incidence of skin cancer among whites in the United States. *Am. J. Epidemiol.,* **105**, 42-427

Fincham, S. & Hill, G.B. (1989) Risk factors for non-melanocytic skin cancer in Alberta males (Abstract). *Am. J. Epidemiol*., **130**, 841

Findlay, G.M. (1928) Ultra-violet light and skin cancer. *Lancet*, **ii**, 1070-1073

Findlay, C.M. (1930) Cutaneous papillomata in the rat following exposure to ultra-violet light. *Lancet,* **i**, 1229-1231

Fisher, M.S. & Cifone, M.A. (1981) Enhanced metastatic potential of murine fibrosarcomas treated in *vitro* with ultraviolet radiation. *Cancer Res*., **41**, 3018-3023

Fisher, G.J. & Johns, H.E. (1976) Pyrimidine photohydrates. In: Wang, S., ed., *Photochemistry and Photobiology of Nucleic Acids,* Vol. 1, New York, Academic Press. pp. 169-224

Fisher, M.S. & Kripke, M.L. (1977) Systemic alteration induced in mice by ultraviolet light irradiation and its relationship to ultraviolet carcinogenesis. *Proc. natl Acad. Sci. USA*, **74**, 1688-1692

Fisher, M.S. & Kripke, M.L. (1978) Further studies on the tumor-specific suppressor cells induced by ultraviolet radiation. *J. Immunol*., **121**, 1139-1144

Fisher, M.S. & Kripke, M.L. (1982) Suppressor T lymphocytes control the development of primary skin cancers in ultraviolet-irradiated mice. *Science,* **216**, 1133-1134

Fix, D.F. (19S6) Thermal resistance of UV-mutagenesis to photoreactivation in *E. coli* B/r *uvrA ung*: estimates of activation energy and further analysis. *Mol. gen. Genet.,* **204**, 452-456

Foley, P., Lanzer, D. & Marks, R. (1986) Are solar keratoses more common on the driver's side? *Br. med. J*., **293**, 18

Forbes, P.D. & Urbach, F. (1975) Experimental modification of photocarcinogenesis. I. Fluorescent whitening agents and short-wave UVR. *Food Cosmet. Toxicol*., **13**, 335-337

Forbes, P.D., Davies, R.E. & Urbach, E. (1978) Experimental ultraviolet photocarcinogenesis: wavelength interactions and time-dose relationships. *Nat1* Cancer *Inst. Monogr*., **50**, 31-38

Forbes, P.D., Blum, H.F. & Davies, R.E. (1981) Photocarcinogenesis in hairless mice: dose-response and the influence of dose-delivery. *Photochem. Photobiol.,* **34**, 361-365

Forbes, P.D., Davies, R.E., Urbach, F., Berger, D. & Cole, C. (1982) Simulated stratospheric ozone depletion and increased ultraviolet radiation: effects on photocarcinogenesis in hairless mice. *Cancer* Res., **42**, 2796-2803

Forbes, P.D., Davies, R.E., Urbach, E. & Dunnick, J.K. (1990) Long-term toxicity of oral 8-methoxypsoralen plus ultraviolet radiation in mice. *J. Toxicol. cutaneous ocul*. Toxicol., **9**, 237-250

Fornace, A.J., Jr, Schalch, H. & Alamo, I., Jr (1988) Coordinate induction of metallothioneins I and II in rodent cells by UV irradiation. *Mol. cell. Biol.,* **8**, 4716-4720

F'ortner, G.W. & Kripke, M.L. (1977) In vitro reactivity of splenic lymphocytes from normal and UV irradiated mice against syngeneic UV-induced tumors. *J. Immunol*., **118**, 1483-1487

Fortner, G.W. & Lill, P.H. (1985) Immune response to ultraviolet-induced tumours. I. Transplantation immunity developing in syngeneic mice in response to progressor ultraviolet-induced tumors. *Transplantation*, **39**, 44-49

Foukal, P. (1990) *SolarAstrophysics*, New York, John Wiley & Sons, pp. 6-75

Fox, I.J., Sy, M.-S., Benacerraf, B. & Greene, M.I. (1981) Impairment of antigen-presenting cell function by ultraviolet radiation. II. Effect of in vitro ultraviolet irradiation on antigenpresenting cells. *Transplantation,* **31**, 262-265

Francis, A.J. & Giannelli, F. (1991) Cooperation between human cells sensitive to USA radiations: a clue to the mechanism of cellular hypersensitivity associated with different clinical conditions. *Exp. Cell Res*., **195,** 47-52

Franklin, W.A. & Haseltine, W.A. (1986) The role of the (6-4) photoproduct in ultraviolet light-induced transition mutations in *E. coli. Mutat. Res.,* **165**, 1-7

Franklin, S.A., Lo, K.M. & Haseltine, W.A. (1982) Alkaline lability of fluorescent photoproducts produced in ultraviolet light-irradiated DNA. *J. biol. Chem.,* **257**, 13535-13543

Frederick, J.E. (1990) Trends in atmospheric ozone and ultraviolet radiation: mechanisms and observations for the northern hemisphere. *Photochem. Photobiol*., **51**, 757-763

Freeman, R.G. (1975) Data on the action spectrum for ultraviolet carcinogenesis. *J. **natl Cancer Inst***., **55**, 1119-1122

Freeman, R.G. (1978) Action spectrum for ultraviolet carcinogenesis. *Natl Cancer Inst. Monogr*., **50**, 27-29

Freeman, S.E. (1988) Variations in excision repair of UVB-induced pyrimidine dimers in DNA of human skin *in situ. J. invest. Dermatol*., **90**, 814-817

Freeman, R.G. & Knox, J.M. (1964) Ultraviolet-induced corneal tumors in different species and strains of animals. *J. invest. Dermatol*., **43**, 431-436

Freeman, S.E., Gange, R.W., Matzinger, E.A. & Sutherland, B.M. (1986) Higher pyrimidine dimer yields in skin of normal humans with higher UVB sensitivity. *J. invest. Dermutol*., **86**, 34-36

Freeman, S.E., Gange. R.W., Sutherland, J.C., Matzinger, E.A. & Sutherland, B.M. (1987) Production of pyrimidine dimers in DNA of human skin exposed *in situ* to UVA radiation. *J. invest. Dermatol.,* **88**, 430-433

Freeman, S.E., Applegate, L.A. & Ley, R.D. (1988a) Excision repair of UVR-induced pyrimidine dimers in corneal DNA. *Photochem. Photobiol*., **47**, 159-163

Freeman, S.E., Ley, R.D. & Ley, K.D. (1988b) Sunscreen protection against UV-induced pyrimidine dimers in DNA of human skin *in situ. Photodermatology*, **5**, 243-247

Freeman, S.E., Hacham, H., Gange, R.W., Maytum, D.J., Sutherland, J.C. & Sutherland, B.M. (1989) Wavelength dependence of pyrimidine dimer formation in DNA of human skin irradiated *in situ* with ultraviolet light. *Proc. natl Acad. Sci. USA*, **86**, 5605-5609

Friedburg, E. (1984) *DNA Repair*, New York, W.H. Freeman & Co.

Frucht, D.M., Lamperth, L., Vicenzi, E., Belcher, J.H. & Martin, M.A. (1991) Ultraviolet radiation increases HIV-long terminal repeat-directed expression in transgenic mice. *AIDS Res. hum. Retroviruses*, **7**, 729-733

Fujiwara, Y., Ichihashi, M., Kano, Y., Goto, K. & Shimizu, K. (1981) A new human photosensitive subject with a defect in the recovery of DNA synthesis after ultraviolet-light irradiation. *J. invest. Dermatol*., **77**, 256-263

Gafá, L., Filippazzo, M.G., Tumino. R., Dardanoni, G., Lanzarone, F. & Dardanoni, L. (1991) Risk factors of nonmelanoma skin cancer in Ragusa, Sicily: a case-control study. *Cancer Causes Control,* **2**, 395-399

Gahring, L., Baltz, M., Pepys, M.B. & Daynes, R. (1984) Effect of ultraviolet radiation on production of epidermal cell thymocyte-activating factor/interleukUl 1 *in vivo* and *in vitro. Immunology*, **81**, 1198-1202

Gallagher, R.P. (1988) Ocular melanoma in farmers (Letter to the Editor). *Am. J. ind. Med.*, **13**, 523-525

Gallagher, P.E. & Duker, N.J. (1986) Detection of UV purine photoproducts in a defined sequence of human DNA. *Mol. cell. Biol.,* **6**, 707-709

Gallagher, P.E. & Duker, N.J. (1989) Formation of purine photoproducts in a defined human DNA sequence. *Photochem. Photobiol*., **49**, 599-605

Gallagher, C.H., Path, F.R.C., Canfield, P.J., Greenoak, G.E. & Reeve, VE. (1984a) Characterization and histogenesis of tumors in the hairless mouse produced by low-dosage incremental ultraviolet radiation. *J. invest. Dermatol*., **83**, 169-174

Gallagher, C.H., Greenoak, G.E., Reeve, V.E., Canfield, P.J., Baker, R.S.U. & Bonin, A.M. (1984b) Ultraviolet carcinogenesis in the hairless mouse skin. Influence of the sunscreen 2-ethylhexyl-p-methoxycinnamate. *Aust. J. exp. Biol. med. Sci.,* **62**, 577-588

Gallagher, R.P, Threlfall, W.J., Jeffries, E., Band, P.R., Spinelli, J. & Coldman, A.J. (1984) Cancer and aplastic anemia in British Columbia farmers. *J. natl Cancer Inst.,* **72**, 1311-1315

Gallagher, R.P, Elwood, J.M., Rootman, J., Spinelli, J.J., Hill, G.B., Threlfall, W.J. & Birdsell, J.M. (1985) Risk factors for ocular melanoma: Western Canada Melanoma Study. *J. natl Cancer Inst*., **74**, 775-778

Gallagher, R.P, Elwood, J.M. & Hill, G.B. (1986) Risk factors for cutaneous malignant melanoma: the Western Canada Melanoma Study. *Recent Results Cancer Res.,* **102**, 38-55

Gallagher, R.R, Elwood, J.M., Threlfall, W.J., Spinelli, J.J., Fincham, S. & Hill, G.B. (1987) Socio-economic status, sunlight exposure, and risk of malignant melanoma: the Western Canada Melanoma Study. *J. natl Cancer Inst.,* **79**, 647-652

Gallagher, P.E., Weiss, R. B., Brent, T.P. & Duker, N.J. (1989) Wavelength dependence of DNA incision by a human ultraviolet endonuclease. *Photochem. Photobiol.,* **49**, 363-367

Gallagher, R.P, McLean, D.I., Yang, C.P, Coldman, A.J., Silver, H.K.B., Spinelli, J.J. & Beagrie, M. (1990a) Anatomic distribution of acquired melanocytic nevi in white children. A comparison with melanoma: the Vancouver mole study. *Arch. Dermatol.,* 126, 466-471

Gallagher, R.P, McLean, D.I., Yang, C.P., Coldman, A.J., Silver, H.K.B., Spinelli, J.J. & Beagrie, M. (1990b) Suntan, sunburn and pigmentation factors and the frequency of acquired melanocytic nevi in children. Similarities to melanoma: the Vancouver mole study. *Arch. Dermatol.,* **126**, 770-776

Gange, R.W. (1987) Acute effects of ultraviolet radiation in the skin. In: Fitzpatrick, T.B., Eisen. A.Z., Wolff, K., Freedberg, I.M. & Austen, K.F., eds, *Dermatology in General Medicine,* 3rd ed., New York, McGraw-Hill, pp. 1451-1457

Gange, R.W., Blackett, A.D., Matzinger, E.A., Sutherland, B.M. & Kochevar, I.E. (1985) Comparative protection efficiency of UVA- and UVB-induced tans against erythema and formation of endonuclease-sensitive sites in DNA by UVB in human skin. *J. invest Dermatol.,* **85**, 362-364

Garbe, C., Krüger, S., Stadler, R., Guggenmoos-Holzmann, I. & Orfanos, C.E. (1989) Markers and relative risk in a German population for developing malignant melanoma. *Int. J. Dermatol*., **28**, 517-523

Gardiner, B.G. & Kirsch, P.J. (1991) *European Intercomparison of Ultraviolet Spectrometers, Panorama*, *Greece, 3-12 July 1991* (Report to the Commission of the European Communities [STEP Project 76], Science and Technology for Enviromnental Protection), Luxembourg, Commission of the European Communities

Garland, F.C., White, M.R.. Garland, C.F., Shaw, E. & Gorham, E.D. (1990) Occupational sunlight exposure and melanoma in the US Navy. *Arch. environ. Health.* **45**, 261-267

Garrison, L.M., Murray, L.E., Doda, D.D. & Green, A.E.S. (1978) Diffuse-direct ultraviolet ratios with a compact double monochromator. *Appl. Optics*, **17**, 827-836

Gellin, G.A., Kopf, A.W. & Garfinkel, L. (1965) Basal cell epithelioma. A controlled study of associated factors. *Arch. Dermatol*., **91**, 38-45

Gellin, G.A., Kopf, A.W. & Garfinkel, L. (1969) Malignant melanoma. A controlled study of possibly associated factors. *Arch. Dermatol*., **99**, 43-48

Gensler, H.L. (1988a) Enhancement of chemical carcinogenesis in mice by systemic effects of ultraviolet radiation. *Cancer Res*., **48**, 620-623

Gensler, H.L. (1988b) Prevention of chemically induced two-stage skin carcinogenesis in mice by systemic effects of ultraviolet irradiation. *Carcinogenesis*, **9**, 767-769

Gensler, H.L. & Bowden, G.T. (1987) UVB-lnduced modulation of mouse skin tumor induction by benzo[a]pyrene (Abstract no. 546). *Proc. Am. Assoc. Cancer Res*., **28**, 137

Gensler, H.L. & Welch, K. (1992) Prevalence of tumor prevention rather than tumor enhancement when repetitive UV radiation treatments precede initiation and promotion. *Carcinogenesis*, **13**, 9-13

Giam, Y.C. (1987) Cutaneous gerontology: solar degeneration of the skin. *Ann. Acad. Med. Singapore*, **16**, 94-97

Giannini, M.S.H. (1986) Suppression of pathogenesis in cutaneous leishmaniasis by UV irradiation. *Infect. Immun*., **51**, 838-843

Gibbs, N.K., Young, A.R. & Magnus, I.A. (1985) Failure of UVR dose reciprocity for skin tumorigenesis in hairless mice treated with 8-methoxypsoralen. *Photochem. Photobiol*., **42**, 39-42

Gibson, P. & Diffey, B.L. (1989) Techniques for spectroradiometry and broadband radiometry. In: Diffey, B.L., ed., *Radiation Measurement in Photobiology,* London, Academic Press, pp. 135-159

Gies, P., Roy, C. & Elliott, G. (1988) The anatomical distribution of solar UVR with emphasis on the eye. In: *Radiation Protection Practice,* Vol. 1. Sydney, Pergamon Press, pp. 341-344

Gilchrest, B.A., Soter, N.A., Stoff, J.S. & Mihm, M.C., Jr (1981) The human sunburn reaction: histologic and biochemical studies. *J. Am. Acad. Dermatol*., **5**, 411-422

Gilchrest, B.A., Murphy, G.F. & Soter, N.A. (1982) Effect of chronologic aging and ultraviolet irradiation on Langerhans cells in human epidermis. *J. invest. Dermatol*., **79**, 85-88

Giles, G.G., Marks, R. & Foley, P. (1988) Incidence of non-melanocytic skin cancer treated in Australia. *Br med. J*., **296**, 13-17

Glazier, A., Morison, W.L., Bucana, C., Hess, A.D. & Tutschka, P.J. (1984) Suppression of epidermal graft-*versus*-host disease with ultraviolet radiation. *Transplantation*, **37**, 211-213

Glickman, B.W., Schaaper, R.M., Haseltine, W.A., Dunn, R.L. & Brash, D.E. (1986) The C-C (6-4) UV photoproduct is mutagenic in *Escherichia coli. Proc. natl Acad. Sci. USA*, **83**, 6945-6949

Goldberg, L.H. & Altman, A. (1984) Benign skin changes associated with chronic sunlight exposure. *Cutis*, **34**, 33-39

Goñi, F.M., Ondarroa, M., Azpiazu, I. & Macarulla, J.M. (1985) Phospholipid oxidation catalysed by cytochrome *c* in liposomes. *Biochim. biophys. Acta*, **835**, 549-556

Goodman, G.J., Marks, R., Selwood, T.S., Ponsford, M.W. & Pakes, W. (1984) Non-melanocytie skin cancer and solar keratoses in Victoria—clinical studies II. *Aust. J. Derm*., **25**, 103-106

Gordon, D. & Silverstone, H. (1976) Worldwide epidemiology of premalignant and malignant cutaneous lesions. In: Andrade, R., Gumport, S.L., Popkin, G.L. & Rees, R.D., eds, *Cancer of the Skin,* Vol. 1, London, W.B. Saunders, pp. 405-434

Gorlin, R.J. (1987) Nevoid basal-cell carcinoma syndrome. *Medicine*, **66**, 98-113

Grabner, G. & Brenner, W. (1981) Unscheduled DNA repair in the human cornea following solar simulating radiation. *Acta ophthalmol*., **59**, 847-853

Grady, H.G., Blum, H.F. & Kirby-Smith, J.S. (1941) Pathology of tumors of the external ear in mice induced by ultraviolet radiation. J. *natl Cancer Inst*., **2**, 269-276

Grady, H.G., Blum, H.F. & Kirby-Smith, J.S. (1943) Types of tumor induced by ultraviolet radiation and factors influencing their relative incidence. J. *natl Cancer Inst*., **3**, 371-378

Graham, S., Marshall, J., Haughey, B., Stoll, H., Zielezny, M., Brasure, J. & West, D. (1985) An inquiry into the epidemiology of melanoma. *Am. J. Epidemiol*., **122**, 606-619

Granstein, R.D. (1985) Epidermal I-J-bearing cells are responsible for transferable suppressor cell generation after immunization of mice with ultraviolet radiation-treated epidermal cells. *J. invest. Dermatol.,* **84**, 206-209

Granstein, R.D. & Sauder, D.N. (1987) Whole-body exposure to ultraviolet radiation results in increased serum interleukin-1 activity in humans. *Lymphokine Res*., **6**, 187-193

Granstein, R.D., Lowy, A. & Greene, M.I. (1984) Epidermal antigen-presenting cells in activation of suppression: identification of a new functional type of ultraviolet radiation-resistant epidermal cell. *J. Immunol.,* **132**, 563-565

Granstein, R.D., Askari, M., Whitaker, D. & Murphy, G.F. (1987) Epidermal cells in activation of suppressor lymphocytes: further characterization. *J. Immunol.,* 138, 4055-4062

Greaves, M.W., Hensby, C.N., Black, A, K., Plummer, N.A., Fincham, N., Warin, A.P. & Camp, R. (1978) Inflammatory reactions induced by ultraviolet irradiation. *Bull. Cancer*, **65**, 299-304

Green, A.C. (1984) Sun exposure and the risk of melanoma. *Aust. J. Dermatol.,* **25**, 99-102

Green, A.C. (1991) Premature ageing of the skin in a Queensland population. *Med. J. Aust*., **155**, 473-478

Green, A.C. & Battistutta, D. (1990) Incidence and determinants of skin cancer in a high-risk Australian population. *Int. J. Cancer*, **46**, 356-361

Green, A. & O'Rourke, M.G.E. (1985) Cutaneous malignant melanoma in association with other skin cancers. *J. natl Cancer Inst.,* **74**, 977-980

Green, A. & Siskind, V. (1983) Geographical distribution of cutaneous melanoma in Queensland. *Med. J. Aust.,* **1**, 407-410

Green, A.E.S., Findley, G.B., Jr, Klenk, K.F., Wilson, W.M. & Mo, T. (1976) The ultraviolet dose dependence of non-melanoma skin cancer incidence. *Photochem. Photobiol*., **24**, 353-362

Green, A.C., Siskind, V., Bain, C. & Alexander, J. (1985a) Sunburn and malignant melanoma. *Br J. Cancer*, **51,** 393-397

Green, A.C., McLennan, R. & Siskind, V. (1985b) Common acquired naevi and the risk of malignant melanoma. *Int. J. Cancer*, **35**, 297-300

Green, A.C., Bain, C., McLennan, R. & Siskind, V. (1986) Risk factors for cutaneous melanoma in Queensland. *Recent Results Cancer Res*., **102**, 76-97

Green, A.C., Beardmore, G., Hart, V., Leslie, D., Marks, R. & Staines, D. (1988a) Skin cancer in a Queensland population. *J. Am. Acad. Dermatol*., **19**, 1045-1052

Green, A.C., Sorahan, T., Pope, D., Siskind, V., Hansen, M., Hanson, L., Leech, P., Ball, P.M. & Grimley, R.P. (1988b) Moles in Australian and British schoolchildren (Letter to the Editor). *Lancet,* **ii**, 1497

Greene, M.I., Sy, M.S., Kripke, M. & Benacerraf, B. (1979) Impairment of antigen-presenting cell function by ultraviolet radiation. *Proc. natl Acad. Sci. USA*, **76**, 6591-6595

Griggs, H.G. & Bender, M.A. (1973) Photoreactivation of ultraviolet-induced chromosomal aberrations. *Science*, **179**, 86-88

Grob, J.J., Gouvernet, J., Aymar, D., Mostaque, A., Romano, M.H., Collet, A.M., Noe, M.C., Diconstanzo, M.P. & Bonerandi, J.J. (1990) Count of benign melanocytic nevi as a major indicator of risk for nonfamilial nodular and superficial spreading mclarloma. *Cancer*, **66**, 387-395

de Gruijl, F.R. & van der Leun, J.C. (1982a) Effect of chronic UV exposure on epidermal transmission in mice. *Photochem. Photobiol*., 36, 433-438

de Gruijl, F.R. & van der Leun. J.C. (1982b) Systemic influence of pre-irradiatior1 of a limited skin area on UV-tumorigenesis. *Photochem. Photobiol*., **35**, 379-383

de Gruijl, F.R. & van der Leun, J.C. (1983) Follow up on systemic influence of partial pre-irradiatior on UV-tumorigenesis. *Photochern. Photobiol*., **38**, 381-383

de Gruijl, F.R., van der Meer, J.B. & van der Leun, J.C. (1983) Dose-time dependency of tumor formation by chronic UV exposure. *Photochem. Photobiol*., **37**, 53-62

Gupta, A.K. & Anderson, T.F. (1987) Psoralen photochemotherapy. *J. Am. Acad. Dermatol*., **17**, 703-734

Gurish, M.F., Lynch, D.H. & Daynes, R.A. (1982) Changes in antigen-presenting cell function in the spleen and lyrnph nodes of ultraviolet-irradiated mice. *Transplantation*, **33**, 280-284

Gurish, M.F, lynch, D.H., Yowell, R. & Daynes, R.A. (1983) Abrogation of epiderrnal antigen-presenting cell function by ultraviolet radiation administered *in vivo*. *Transplantation*, **36**, 304-309

Haenszel, W. (1963) Variations in skin cancer incidence within the United States. *Natl Cancer Inst. Monogr*., **10**, 225-243

Halasz, C.L.G., Leach, E.E., Walther, R.R. & Poh-Fitzpatrick, M.B. (1983) Hydroa vacciniforme: induction of lesions with ultraviolet A. *J. Am. Acad. Dermatol*., **8**, 171-176

Hall, J.D. & Mount, D.W. (1981) Mechanisms of DNA replication and mutager1esis in ultraviolet-irradiated bacteria and man1malian cells. *Prog. nucleic Acid* Res. *mol.* Biol., **25**, 53-126

Halprin, K.M., Comerford, M., Presser, S.E. & Taylor, J.R. (1981) Ultraviolet light treatment delays contact sensitization to nitrogen mustard. *Br. J. Dermatol*., **105**, 71-76

Haniszko, J. & Suskind, R.R. (1963) The effect of ultraviolet radiation on experimental cutaneous sensitization in guinea pigs. *J. invest. Dermatol*., **40**, 183-191

Hannan, M.A., Paul, M., Amer, M.H. & Al-Watban, F.H. (1984) Study of ultraviolet radiation and genotoxic effects of natural sunlight in relation to skin cancer in Saudi Arabia. *Cancer Res*., **44**, 2192-2197

Hanson, D.L. & DeLeo, VA. (1989) Long wave ultraviolet radiation stimulates arachidonic acid release and cyclooxygenase activity in mammalian cells in culture. *Photochem. Photobiol*., **49**, 423-430

Harber, L.C. & Bickers, D.R. (1981) *Photosensitivity Diseases. Principles of Diagnosis and Treatment*, Philadelphia, PA, W.B. Saunders

Hardie, I.R., Strong, R.W, Hartley, L.C.J., Woodruff, P.W.H. & Clunie, C.J.A. (1980) Skin cancer in Caucasian renal allograft recipients living in a subtropical climate. *Surgery*, **87**, 177-183

Hariharan, P.V. & Cerutti, P.A. (1976) Excision of ultraviolet and gamma ray products of the 5,6-dihydroxy-dihydrothymine type by nuclear preparations of xeroderma pigmentosum cells. *Biochim. biophys. Acta*, **447**, 375-378

Hariharan, P.V & Cerutti, P.A. (1977) Formation of products of the 5,6-dihydroxydibydrothymine type by ultraviolet light in HeLa cells. *Biochemistry,* **16**, 2791-2795

Hartman, Z., Hartman, P.E. & McDermott, W.L. (1991) Mutagenicity of coolwhite fluorescent light for Salmonella. *Mutat. Res*., **260**, 25-38

Hawk, J.L.M. & Parrish, J.A. (1982) Responses of normal skin to ultraviolet radiation. In: Reegan, J.D. & Parrish, J.A., eds, *The Science of Photomedicine,* New York, Plenum, pp. 219-260

Hayashi, Y. & Aurelian, L. (1986) Immunity to herpes simple virus type 2: viral antigen-presenting capacity of epidermal cells and its impairment by ultraviolet irradiation. *J. Immunol*., **136**, 1087-1092

Health Council of the Netherlands (1986) *UV Radiation: Human Exposure to Ultraviolet Radiation* (Report 1986/93), The Hague

Hefferren, J.J., Cooley, R.O., Hall, J.B., Olsen, N.H. & Lyon, H.W. (1971) Use of ultraviolet illumination in oral diagnosis. *J. Am. dent. Assoc*., **82**, 1353-1360

Henderson, S.T (1970) *Daylight and Its Spectrum*, New York, American Elsevier

Henderson, L.M., Arlett, C.F., Harcourt, S.A., Lehmann, A.R. & Broughton, B.C. (1985) Cells from an immunodeficient patient (46BR) with a defect in DNA ligation are hypomutable but hypersensitive to the induction of sister chromatic exchanges. *Proc. natl Acad. Sci. USA*, **82**, 2044-2048

Henseler, T., Wolff, K., Hönigsmann, H. & Christophers, E. (1981) Oral 8- methoxypsoralen photochemotherapy of psoriasis. The European PUVA study: a cooperative study among 18 European centres. Lancet, **i**, 853-857

Herity, B., O'Loughlin, G., Moriarty, M.J. & Conroy, R. (1989) Risk factors for non-melanoma skin cancer. *Irish med. J*., **82**, 151-152

Hersey, P., Bradley, M., Hasic, E., Haran, G., Edwards, A. & McCarthy, W.H. (1983a) Immunological effects of solarium exposure. *Lancet*, **i**, 545-548

Hersey, P., Haran, G., Hasic, E. & Edwards, A. (1983b) Alteration of T cell subsets and induction of suppressor T cell activity in normal subjects after exposure to sunlight. *J. Immunol*., **31**, 171-174

Hersey, P. MacDonald, M., Burns, C., Schibeci, S., Matthews, H. & Wilkinson, F.J. (1987) Analysis of the effect of a sunscreen agent on the suppression of natural killer cell activity induced in human subjects by radiation from solarium lamps. *J. invest Dermatol*., **88**, 271-276

Hersey, P., MacDonald, M., Henderson, C., Schibeci, S., D'Alessandro, G., Pryor, M. & Wilkinson, E.J. (1988) Suppression of natural killer cell activity in humans by radiation from solarium lamps depleted of UVB. *J. invest. Dermatol*., **90**, 305-310

Hietanen, M. (1990) *Spectroradiometic and Photometric Studies on Ocular Exposure to Ultraviolet and Visible Radiation from Light Sources*, PhD Thesis, Helsinki, University of Helsinki, Department of Physics

Higgins, S.A., Frenkel, K., Cummings, A. & Teebor, G.W. (1987) Definitive characterisation of human thymine glycol *N*-glycosylase activity. *Biochemistry*, **26**, 1683-1688

Hinds, M.W. & Kolonel, L.N. (1980) Malignant melanoma of the skin in Hawaii, 1960-1977. *Cancer*, **45**, 811-817

Hitchins, V.M., Beer, J.Z., Strickland, A.G. & Olvey, K.M. (1987) Lethal and mutagenic effects of UVA radiation in six strains of L5178Y mouse lymphoma cells. In: Passchier, W.F. & Bosnjakovic, B.F.M., eds, *Humun Exposure to Ultraviolet Radiation: Risk and Regulations*, Amsterdam, Elsevier, pp. 65-69

Hoeijmakers, J.H.J. & Bootsma, D. (1990) Molecular genetics of eukaryotic DNA excision repair. *Cancer Cells*, **2**, 311-320

Hoffman, J.S. (1987) Ultraviolet Radiation and Melanoma (with a Special Focus on Assessing the Risks of Stratospheric Ozone Depletion) (EPA 400/1-87-001D), Washington DC, Office of Air and Radiation. US Environmental Protection Agency

Hogan, D.J., To, T., Gran, L., Wong, D. & Lane, P.R. (1989) Risk factors for basal cell carcinoma. *Int. J. Dermatol.*, **28**, 591-594

Holick, M.F., MacLaughlin, J.A., Clark, M.B., Holick, S.A., Potts, J.T., Jr, Anderson, R.R., Blank, I.H., Parrish, J.A. & Elias, P. (1980) Photosynthesis of previtamin D3 in human skin and the physiologic consequences. *Science,* **210**, 203-205

Hollaender, A. (1943) Effect of long ultraviolet and short visible radiation (3500 to 4900 A) on *Eschenchia coli. J. Bacteriol.*, **46**, 531-541

Hollander, M.C. & Fornace, A.J., Jr (1989) Induction of *fos* RNA by DNA-damaging agents. ***Cancer** Res.*, **49**, 1687-1692

Hollis, D.E. & Scheibner, A. (1988) Ultrastructural changes in epidermal Langerhans cells and melanoeytes in response to ultraviolet irradiation, in Australians of aboriginal and Celtic descent. *Br. J. Dermatol.,* **119**, 21-31

Holly, E.A., Kelly, J.W., Shpall, S.N. & Chiu, S.-H. (1987) Number of melanocytic nevi as a major risk factor for malignant melanoma. *J. Am. Acad. Dermatol.,* **17**, 459-468

Holly, E.A., Aston, D.A., Char, D.H., Kristiansen, J.J. & Ahn, D.K. (1990) Uveal melanoma in relation to ultraviolet light exposure and host factors. *Cancer Res.*, **50**, 5773-5777

Holly, E.A., Aston, D.A., Ahn, D.K., Kristiansen, J.J. & Char, D.H. (1991) No excess prior cancer in patients with uveal melanoma. O*phthalmology*, **98**, 608-611

Holman, C.D.J. & Armstrong, B.K. (1984a) Pigmentary traits, ethnic origin, benign nevi, and family history as risk factors for cutaneous malignant melanoma. *J. natI Cancer Inst.*, **72**, 257-266

Holman, C.D.J. & Armstrong, B.K. (1984b) Cutaneous malignant melanoma and indicators of total accumulated exposure to the sun: an analysis separating histogenetic types. *J. natl Cancer Inst.,* **73**, 75-82

Holman, C.D.J., Gibson, I.M., Stephenson, M. & Armstrong, B.K. (1983a) Ultraviolet irradiation of human body sites in relation to occupation and outdoor activity: field study using personal UVR dosimeters. *Clin. exp. Dermatol.*, **8**, 269-277

Holman, C.D.J., Heenan, P.J., Caruso, V., Glancy, R.J. & Armstrong, B.K. (1983b) Seasonal variation in the junctional component of pigmented naevi. *Int. J. Cancer*, **31**, 213-215

Holman, C.D.J., Armstrong, B.K., Evans, P.R., Lumsden, G.J., Dallimore, K.J., Meehan, C.J., Beagley, J. & Gibson, I.M. (1984a) Relationship of solar keratosis and history of skin cancer to objective measures of actinic skin damage. *Br. J. Dermatol.,* **110**, 129-138

Holman, C.D., Evans, P.R., Lumsden, G.J. & Armstrong, B.K. (1984b) The determinants of actinic skin damage: problems of confounding among environmental and constitutional variables. *Am. J. Epidemiol.*, **120**, 414-422

Hohnan, C.D.J., Armstrong, B.K. & Heenan, P.J. (1986a) Relationship of cutaneous malignant melanoma to individual sunlight-exposure habits. *J. natl Cancer Into.*, **76**, 403-414

Holman, C.D.J., Armstrong, B.K., Heenan, P.I., Blackwell, J.B., Cumming, F.J., English, D.R., Holland, S., Kelsall, G.R.H., Matz, L.R., Rouse, I.L., Singh, A., Ten Seldam, R.E.J., Watt, J.D. & Xu, Z. (1986b) The causes of malignant melanoma: results froth the West Australian Lions Melanoma Research Project. *Recent Results Cancer Res.*, **102**, 18-37

Holmberg, M. & Gumauskas, E. (1990) Chromosome-type exchange aberrations are induced by inhibiting repair of UVC-induced DNA lesions in quiescent human lymphocytes. *Mutat. Res.,* **232**, 261-266

Hönigsmann, H., Brenner, W. Tanew, A. & Ortel, B. (1987) UV-lnduced unscheduled DNA synthesis in human skin: dose response, correlation with erythema, time course and split dose exposure *in vivo*. *J. Photochem. Photobiol. B Biol.,* **1**, 33-43

Hoover, T.L., Morison, W.L. & Kripke, M.L. (1987) Ultraviolet carcinogenesis in athymic nude mice. *Transplantation*, **44**, 693-695

Howie, S.E.M., Norval, N., Maingay, J. & Ross, J.A. (1986a) Two phenotypically distant T cells ($Ly1+2^-$ and Lyl^-2^+) are involved in ultraviolet-B light-induced suppression of the efferent DTH response to HSV-1 *in vivo. Immunology*, **58**, 653-658

Howie, S.E.M., Norval, M. & Maingay, J.P. (1986b) Alterations in epidermal handling of HSV-1 antigens *in vitro* induced by in vivo exposure to UVB light. ***Immunology***, **57**, 225-230

Howie, S., Norval, M. & Maingay, J. (1986c) Exposure to low-dose ultraviolet radiation suppresses delayed-type hypersensitivity to herpes simplex virus in mice. *J. invest. Dermatol*., **86**, 125-128

Hsia, H.C., Lebkowski, J.S., Leong, P.-M., Calos, M.P. & Miller, J.H. (1989) Comparison of ultraviolet irradiation-induced mutagenesis of the *lac*I gene in *Escherichia coli* and in human 293 cells. *J. mol. Biol*., **205**, 103-113

Hsie, A.W., Li, A.P & Machanoff, R. (1977) A fluence response study of lethality and mutagenicity of white, black, and blue fluorescent light, sunlamp, and sunlight irradiation in Chinese hamster ovary cells. *Mutat. Res*., **45**, 333-342

Hsu, J., Forbes, P.D., Harber, L.C. & Lakow, E. (1975) Induction of skin tumors in hairless mice by a single exposure to UV radiation. *Photochem. Photobiol.,* **21**, 185-188

Hueper, W.C. (1942) Morphological aspects of experimental actinic and arsenic carcinomas in the skin of rats. *Cancer Res.,* **2**, 551-559

Huldschinsky, K. (1933) Eye sarcoma in rats caused by abnormally long UV (Ger.). *Dtsch. med. Wochenschr.,* **59**, 530-531

Hunter, D.J., Colditz, G.A., Stampfer, M.J., Rosner, B., Willett, W.C. & Speizer, F.E. (1990) Risk factors for basal cell carcinoma in a prospective cohort of women. *Ann. Epidemiol.,* **1**, 13-23

Husain, Z., Yang, Q. & Biswas, D.K. (1990) cHa-*ras* Proto oncogene. Amplification and over-expression in UVB-induced mouse skin papillomas and carcinomas. *Arch. Dermatol.,* **126**, 324-330

Husain, Z., Pathak, M.A., Flotte, T. & Wick, M.M. (1991) Role of ultraviolet radiation in the induction of melanocytic tumors in hairless mice following 7,12-dimethylbenz(a)anthracene application and ultraviolet irradiation. *Cancer Res.,* **51**, 4964-4970

Huselton, C.A. & Hill, H.Z. (1990) Melanin photosensitizes ultraviolet light (UVC) DNA damage in pigmented cells. *Environ. mol. Mutag.*, **16**, 37-43

Hutchinson, E. (1987) A review of some topics concerning mutagenesis by ultraviolet light. *Photochem. Photobiol*., **45**, 897-903

Hutchinson, F. & Wood, R.D. (1986) Mechanisms of mutagenesis of *E. coli* by ultraviolet light. *Basic* ***Life Sci.,*** **38**, 377-383

Hutchinson, E. Yamamoto, K., Stein, J. & Wood, R.D. (1988) Effect of photoreactivation on mutagenesis of lambda phage by ultraviolet light. *J. mol. Biol*., **202**, 593-601

IARC (1980) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans,* Vol. 24, *Some Pharmaceuticul Drugs,* Lyon, pp. 101-124

IARC (1985) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans,* Vol. 37, *Tobacco Habits Other than Smoking; Betel Quid and Areca-nut Chewing; and Some Related Nitrosamines,* Lyon. pp. 37-136

IARC (1986a) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans,* Vol. 40, *Some Naturally Occurring und Synthetic Food Compounds, Furocoumarins and Ultraviolet Radiation.* Lyon, pp. 317-371

IARC (1986b) *IARC Monographs on the Evalaution of the Carcinogenic Risk of Chemicals to Humans.* Vol. 38, *Tobacco Smoking,* Lyon

IARC (1987a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes* 1 to 42, Lyon, pp. 175-176

IARC (1987b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating o*f IARC Monographs Volumes 1 to 42, Lyon, pp. 242-245

IARC (1988) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 44, *Alcohol Drinking*, Lyon

IARC (1990) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 49, *Chromium, Nickel and Welding*, Lyon, pp. 447-525

Ikushima, T. & Wolff, S. (1974) UV-Induced chromatic aberrations in cultured Chinese hamster cells after one, two, or three rounds of DNA replication. *Mutat. Res*., **22**, 193-201

International Electrotechnical Commission (1987) *Safety of Household and Similar Electrical Appliances*, Part 2, *Particular Requirements for Ultra-violet and Infra-red Radiation Skin Treatment Appliances for Household Use* (Publication 335-2-27: 1987), (Geneva, Bureau Central de la Commission Electrotechnique Internationale

International Electrotechnical Commission (1989) *Amendment*, Geneva, Bureau Central de la Commission Electrotechnique Internationale

International Non-ionizing Radiation Committee of the International Radiation Protection Association (1985) Guidelines on limits of exposure to ultraviolet radiation of wavelengths between 180 nm and 400 nm (incoherent optical radiation). *Health Phys*., **49**, 331-340

International Non-ionizing Radiation Committee of the International Radiation Protection Association (1989) Proposed change to the IRPA 1985 guidelines on limits of exposure to ultraviolet radiation. *Health Phys*., **56**, 971-972

Iqbal, M. (1983) *An Introduction to Solar Radiation*, New York, Academic Press, pp. 335-373

Ito, M. (1966) The photodynamic effect of acridine orange and ultraviolet on the mouse skin carcinogenesis by 20-methylcholanthrene. *Nagoya med. J*., **12**, 247-259

Ito, A. & Ito, T. (1983) Possible involvement of membrane damage in the inactivation by broad-band near-UV radiation in *Saccharomyces cerevisiae* cells. *Photochem. Photobiol*., **37**, 395-401

Iversen, O.H. (1986) Carcinogenesis studies with benzoyl peroxide (Panoxyl gel 5%). J. *invest. Dermatol*., **86**, 442-448

Iversen, O.H. (1988) Skin tumorigenesis and carcinogenesis studies with 7,12-dimethylbenz[a]-anthracene, ultraviolet light, benzoyl peroxide (Panoxyl gel 5%) and ointment gel. Carcinogenesis, **9**, 803-809

Jacobson, E.D., Krell, K., Dempsey, M.J., Lugo, M.H., Ellingson, O. & Hench, C.W., II (1978) Toxicity and mutagenicity of radiation from fluoreceent lamps and a sunlamp in L5178Y mouse lymphoma cells. *Mutat. Res*., **51**, 61-75

Jacobson, E.D., Krell, K. & Dempsey, M.J. (1981) The wavelength dependence of ultraviolet light-induced cell killing and mutagenesis in L5178Y mouse lymphoma cells. *Photochem. Photobiol*., **33**, 257-260

Jagger, J. (1981) Near-UV radiation effects on microorganisms. *Photochem. Photobiol*., **34**, 761-768

Jagger, J. (1985) *Solar-UV Actions on Living Cells*, New York, Praeger

Jessup, J.M., Hanna, N., Palaszynski, E. & Kripke, M.L. (1978) Mechanisms of depressed reactivity to dinitrochlorobenzene and ultraviolet-induced tumors during ultraviolet carcinogenesis in BALB/c mice. *Cell. Immunol*., **38**, 105-115

Johns, H.E., Rapaport, S.A. & Delbrück, M. (1962) Photochemistry of thymine dimers.*J. mol. Biol.*, **4**, 104-114

Jones, C.A., Huberman, E., Cunningham, M.L. & Peak, M.J. (1987) Mutagenesis and cytotoxicity in human epithelial cells by far- and near-ultraviolet radiations: action spectra. *Radiat. Res.*, **110**, 244-254

Jones, S.K., Moseley, H. & Mackie, R. (1987) UVA-lnduced melanocytic lesions. *Br J. Dermatol.,* **117**, 111-115

Jose, J.G. & Pitts, D.G. (1985) Wavelength dependency of cataracts in albino mice following chronic exposure. *Exp. Eye Res.,* **41**, 545-563

Joshi, S.D., Shrikhande, S.S. & Ranade, S.S. (1984) Studies on UV-induced skin tumors in experirnental animals. *Photobiochem. Photobiophys.,* **7**, 235-243

Joshi, S.D., Shrikhande, S.S., Naik, S.N. & Ranade, S.S. (1986) Multiplicity of tumours induced in the laboratory animals by ultraviolet (UVC) irradiation. *Indian J. anim. Sci.,* **56**, 736-743

Jun. B.-D., Roberts, L.K., Cho, B.-H., Robertson. B. & Daynes, R.A. (1988) Parallel recovery of epidermal antigen-presenting cell activity and contact hypersensitivity responses in mice exposed to ultraviolet irradiation: the role of a prostaglandin-dependent mechanism. *J. invest. Dermatol.,* **90**, 311-316

Kaase, H., Zidowitz, B. & Berger, H. (1984) Spectral radiation measurements of UV-irradiation apparatus and experiments to estimate the risk of photocarcinogenesis (Ger.). *Lichtforschung,* **1**, 43-47

Kaidbey, K.H. (1988) Wavelength dependence for DNA synthesis inhibition in hairless mouse epidermis. *Photodermatology*, **5**, 65-70

Kaidbey, K.H., Agin, P.P, Sayre, R.M. & Kligman, A.M. (1979) Photoprotection by melanin—a comparison of black and Caucasian skin. *J. Am. Acad Dermatol.*, **1**, 249-260

Kalthoff, K. & Jäckle, H. (1982) Photoreactivation of pyrimidine dimers generated by a photosensitized reaction in RNA of insect embryos *(Smittia* spec.). In: Hélène, C., Charlier, M., Montenay-Garestier, T. & Laustriat, G., eds, *Trends in Photobiology,* New York, Plenum, pp.173-188

Kantor, G.J. (1985) Effects of sunlight on mammalian cells. *Photochem. Photobiol.,* **41**, 741-746

Kawada, A. (1986) UVB-Induced erythema, delayed tanning, and UVA-induced immediate tanning in Japanese skin. *Photodermatology,* **3**, 327-333

Keijzer, W., Mulder, M.P., Langeveld, J.C.M., Smit, E.M.E., Bos, J.L., Bootsma, D. & Hoeijmakers, J.H.J. (1989) Establishment and characterization of a melanoma cell line from a xeroderma pigmentosum patient: activation of N-*ras* at a potential pyrimidine dimer site. *Cancer Res.,* **49**, 1229-1235

Kelfkens, G., de Gruijl, F.R. & van der Leun, J.C. (1991a) Tumorigenesis by short-wave ultraviolet A: papillomas *versus* squamous cell carcinomas. *Carcinogenesis*, **12**, 1377-1382

Kelfkens, G., van Weelden, H., de Gruijl, F.R. & van der Leun, J.C. (199lb) Influence of dose rate in ultraviolet tumorigenesis. *J. Photochem. Photobiol. B Biol.,* **l0**, 41-50

Keller, A.Z. (1970) Cellular types, survival, race, nativity, occupations, habits and associated diseases in the pathogenesis of lip cancers. *Am. J. Epidemiol.*, **91**, 486-499

Kelly, G.E., Meikle, W.D. & Sheil, A.G.R. (1987) Effects of immunosuppressive therapy on the induction of skin tumors by ultraviolet irradiation in hairless mice. *Transplantation,* **44**, 429-434

Kelly, G.E., Meikle, W.D. & Moore, D.E. (1989) Enhancement of UV-induced skin carcinogenesis by azathioprine: role of photochemical sensitisation. *Photochem. Photobiol.,* **49**, 59-65

Kennedy, A.R., Ritter, M.A. & Little, J.B. (1980) Fluorescent light induces malignant transformation in mouse embryo cell cultures. *Science,* 207, 1209-1211

Keyse, S.M. & Tyrrell, R.M. (1989) Heme oxygenase is the major 32-kDa stress protein induced in human skin fibroblasts by UVA radiation, hydrogen peroxide and sodium arsenite. *Proc. natl Acad. Sci USA,* **86**, 99-103

Keyse, S.M., Moss, S.H. & Davies, D.J.G. (1983) Action spectra for inactivation of normal and xeroderma pigmentosum human skin fibroblasts by ultraviolet radiations. *Photochem. Photobiol.,* **37**, 307-312

Keyse, S.M., Applegate, L.A., Tromvoukis, Y. & Tyrrell, R.M. (1990) Oxidant stress leads to transcriptional activation of the human heme oxygenase gene in cultured skin fibroblasts. *Mol. cell. Biol.,* **10**, 4967-4969

Khlat, M., Vail, A., Parkin, M. & Green, A. (1992) Mortality from melanoma in migrants to Australia: variation by age at arrival and duration of stay. *Am. J. Epidemiol.,* **135**, 1103-1113

Kim, T.-Y., Kripke, M.L. & Ullrich, S. E. (1990) Immunosuppression by factors released from UVirradiated epidermal cells: selective effects on the generation of contact and delayed hypersensitivity after exposure to UVA or UVB radiation. *J. invest. Dermatol.,* 94, 26-32

Kinlen, L.J., Sheil, A.G.R., Peto, J. & Doll, R. (1979) Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. *Br. med. J.,* **ii**, 1461-1466

Kinsey, V.E. (1948) Spectral transmission of the eye to ultraviolet radiatioris. *Arch. Opthalmol*., **39**, 508-5 13

Kirby-Smith, J.S. & Craig, D.L. (1957) The induction of chromosome aberrations in *Tradescantia* by ultraviolet radiation. *Genetics*, **42**, 176-187

Kirkpatrick, C.S., Lee, J.A.H. & White, E. (1990) Melanoma risk by age and socio-economic status. *Int. J. Cancer*, **46**, 1-4

Kjeldstad, B. & Johnsson, A. (1986) An action spectrum for blue and near ultraviolet inactivation of *Propionibacterium acnes;* with emphasis on a possible porphyrin photosensitization. *Photochem. Photobiol*., **43**, 67-70

Klamen, D.L. & Tuveson, R.W. (1982) The effect of membrane fatty acid composition on the near-UV (300-400 nm) sensitivity of *Eschenchia coli* K1060. *Photochem. Photobiol*., **35**, 167-173

Klein, K.L. & Linnemann, C.C., Jr (1986) Induction of recurrent genital herpes simplex virus type 2 infection by ultraviolet light (Letter to the Editor). *Lancet*, **i**, 796-797

Klepp, O. & Magnus, K. (1979) Some environmental and bodily characteristics of melanoma patients. A case-control study. *Int. J. Cancer*, **23**, 482-486

Kligman, A.M. (1969) Early destructive effect of sunlight on human skin. *J. Am. med. Assoc*., **210**, 2377-2380

Kligman, L.H. (1988) UVA enhances low dose UVB tumorigenesis (Abstract). *Photochem. Photobiol*., **47**, 8S

Kligman, L.H. (1989) The ultraviolet-irradiated hairless mouse: a model for photoaging. *J. Am. Acad. Dermatol.,* **21**, 623-631

Kligman, L.H. & Kligman, A.M. (1981) Histogenesis and progression of ultraviolet light-induced tumors in hairless mice. *J. natl Cancer Inst*., **67**, 1289-1297

Kligman, L.H. & Sayre, R.M. (1991) An action spectrum for ultraviolet induced elastosis in hairless mice: quantification of elastosis by image analysis. *Photochem. Photobiol*., 53, 237-242

Kligman, L.H., Akin, F.J. & Kligman, A.M. (1985) The contributions of UVA and UVB to connective tissue damage in hairless mice. *J. invest. Dermatol*., **84**, 272-276

Kligman, L.H., Kaidbey, K.H., Hitchins, V.M. & Miller, S.A. (1987) Long wavelength (> 340 nm) ultraviolet-A induced skin damage in hairless mice is dose dependent. Im Passchier, W.F. & Bosnjakovic, B.F.M., eds, *Human Exposure to Ultraviolet Radiation. Risks and Regulations,* Amsterdam, Elsevier, pp. 77-81

Kligman, L.H., Crosby, M.J., Miller, S.A., Hitchins, V.M. & Beer, J.Z. (1990) Skin cancer induction in hairless mice by long-wavelength UVA radiation: a progress report (Abstract). *Photochem. Photobiol.,* **51**, 18S-19S

Kligman, L.H., Crosby, M.J., Miller, S.A., Hitchins, V.M. & Beer, J.Z. (1992) Carcinogenesis by long wavelength UVA and failure of reciprocity. In: Urbach, F., ed., *Biological Responses to Ultraviolet A Radiation,* Overland Park, KS, Valdenmar, pp. 301-308

Knees-Matzen, S., Roser, M., Reimers, U., Ehlert, U., Weichenthal, M., Breitbart, E.W. & Rüdiger, H.W. (1991) Increased UV-induced sister-chromatic exchange in cultured fibroblasts of first-degree relatives of melanoma patients. *Cancer Genet. Cytogenet*., **53**, 265-270

Kocsard, E. & Ofner, F. (1964) Contact eczematous sensitization and sensitivity of the solar elastotic skin. *Aust. J. Dermatol*., **7**, 203-205

Kolari. P.J., Lauharanta, J. & Hoikkala, M. (1986) Midsummer solar UV-radiation in Finland compared with the UV-radiation from phototherapeutic devices measured by different techniques. *Photodermatology*, **3**, 340-345

Kopecky, K.E., Pugh, G.W., Jr, Hughes, D.E., Booth, G.D. & Cheville, N.F. (1979) Biological effect of ultraviolet radiation on cattle: bovine ocular squamous cell carcinoma. *Am. J. vet. Res.,* **40**, 1783-1788

Kopf, A.W, Lindsay, A.C., Rogers, G.S., Friedman, R.J., Rigel, D.S. & Levenstein, M. (1985) Relationship of nevocytic nevi to sun exposure in dysplastic nevus syndrome. *J. Am Acad. Dermatol.,* **12**, 656-662

Kostkowski, H.J., Saunders, R., Ward, J., Popenoe, C. & Green, A. (1982) *Measurement of Solar Terrestrial Spectral Irradiance in the Ozone (Cut-off Region, Self-studyManual on Optical Radiation Meusurements.* Part III, Applications (NBS Technical Note 910-5; PB 83-184382), Washington DC, National Bureau of Standards

Koval, T.M. (1987) Photoreactivation of UV damage in cultured *Drosophila* cells. *Experientia,* **43**, 445-446

Kraerner, K.H. (1980) Xeroderma pigmentosum. A prototype disease of enviromental-genetic interaction. *Arch. Dermatol.,* **116**, 541-542

Kraemer, K.H. Greene, M.H. (1985) Dysplastic nevus syndrome. Familial and sporadic precursors of cutaneous melanoma. *Dermatol. Clin.,* **3**, 225-237

Kraemer, K.H. & Slor, H. (1984) Xeroderma pigmentosum. *Clin Dermatol.,* **2**, 33-69

Kraemer, K.H. & Weinstein, G.D. (1977) Decreased thymidine incorporation in circulating leukocytes after treatment of psoriasis with psoralen and long-wave ultraviolet light. *J. invest. Dermatol.,* **69**, 211-214

Kraemer, K.H., Lee, M.M. & Scotto, J. (1987) Xeroderma pigmentosum. Cutaneous. Ocular, and neurologic abnormalities in 830 published cases. *Arch. Dermatol*., **123**, 241-250

Kraemer, K.H., Seetharam, S., Protić-Sabljić, M., Brash, D.E., Bredberg, A. & Seidman, M.M. (1988) Defective DNA repair and mutagenesis by dimer and non-dimer photoproducts in xeroderma pigmentosum measured with plasmid vectors. In: Friedberg, E.C. & Hanawalt, P.C., eds, *Mechanisms and Consequences of DNA Damage Processing,* New York, Alan R. Liss, pp. 325-335

Kramer, G.F. & Ames, B.N. (1987) Oxidative mechanisms of toxicity of low-intensits near- UV light in *Salmonella typhimurium. J. Bactenol*., **169**, 2259-2266

Krepinsky, A.B., Rainbow, A.J. & Heddle, J.A. (1980) Studies on the ultraviolet light sensitivity of Bloom's syndrome fibroblasts. *Mutat. Res*., **69**, 357-368

Kricker, A., English, D.R., Randell, P.L., Heenan, P.J., Clay, C.D., Delaney, T.A. & Armstrong, B.K. (1990) Skin cancer in Geraldton, Western Australia: a survey of incidence and prevalence. *Med. J. Aust.,* **152**, 399-407

Kricker, A., Armstrong, B.K., English, D.R. & Heenan, P.J. (1991a) Pigmentary and cutaneous risk factors for non-melanocytic skin cancer—a case-control study. *Int. J. Cancer*, **48,** 650-662

Kricker, A., Armstrong, B.K., English, D., Heenan, P.J. & Randell, P.L. (1991b) A case-control study of non-melanocytic skin cancer and sun exposure in Western Australia (Abstract No. III, P2). ***Cancer Res.*** *clin. Oncol.,* **117** (Suppl. II), S75

Kripke, M.L. (1974) Antigenicity of murine skin tumors induced by ultraviolet light. *J.* ***natl Cancer Inst.,*** **53**, 1333-1336

Kripke, M.L. (1977) Latency, histology, and antigenicity of tumors induced by ultraviolet light in three inbred mouse strains. *Cancer Res.,* **37**, 1395-1400

Kripke, M.L. & Fisher, M.S. (1976) Immunologic parameters of ultraviolet carcinogenesis. *J. natl Cancer Inst.,* **57**, 211-215

Kripke, M.L. & McClendon, E. (1986) Studies oil the role of antigen-presenting cells in the systemic suppression of contact hypersensitivity by UVB radiation. *J. Immunol.,* 137, 443-447

Kripke, M. L. & Morison, W.L. (1985) Modulation of immune function by UV radiation. *J. invest Dermatol.,* **85**, 625-665

Kripke, M.L. & Morison, W.L. (1986a) Studies on the mechanism of systemic suppression of contact hypersensitivity by ultraviolet B radiation. *Photodermatology,* **3**, 4-14

Kripke, M.L. & Morison, W.L. (1986b) Studies on the mechanism of systemic suppression of contact hypersensitivity by UVB radiation. II. Differences in the suppression of delayed and contact hypersensitivity in mice. *J. invest. Dermatol.,* **86**, 543-549

Kripke, M.L. & Sass, E.R., eds (1978) International conference on ultraviolet carcinogenesis. *Natl Cancer Inst. Monogr*., **50**

Kripke, M.L.. Lofgreen, J.S., Beard, J., Jessup, J.M. & Fisher, M.S. (1977) In vivo immune responses of mice during carcinogenesis by ultraviolet irradiation. *J. natl Cancer Inst*., **59**, 1227-1230

Kromberg, J.G.R., Castle, D., Zwane, E.M. & Jenkins, T. (1989) Albinism and skin cancer in southern Africa. *Clin. Genet*., **36**, 43-52

Krutmann, J. & Elmets, C.A. (1988) Recent studies on mechanisms in photoimmunology. *Photochem. Photobiol.,* **48**, 787-798

Kubitschek, H.E. (1967) Mutagenesis of near-visible light. *Science,* **155**, 1545-1546

Kumar, S., Joshi, P.C., Sharma, N.D., Bose, S.N., Davies, R.J.H, Takeda, N. & McCloskey, J.A. (1991) Adenine photodimerization ill deoxyadenylate sequences: elucidation of the mechanism through structural studies of a major d(ApA) photoproduct. *Nucleic Acids Res*., **19**, 2841-2847

Kunkel, T.A. (1984) Mutational specificity of depurination. *Proc. natl Acad. Sci. USA*, **81**, 1494-1498

Kupper, T.S., Chua, A.O., Flood, P., McGuire, J. & Gubler, U. (1987) Interleukin 1 gene expression in cultured human keratinocytes is augmented by ultraviolet irradiation. *J. clin. Invest.,* **80**, 430-436

Kurihara, T., Tatsumi, K., Takahashi, H. & Inoue, M. (1987) Sister-chromatid exchanges induced by ultraviolet light in Bloom's syndrome fibroblasts. *Mutat Res.,* **183**, 197-202

Lai, L.-W & Rosenstein, B.S. (1990) Induction of DNA strand breaks and DNA-protein cross-links in normal human skin fibroblasts following exposure to 254 nm UV radiation. *J. Photochem. Photobiol. B Biol*., **6**, 395-404

Lancaster, H.O. (1956) Some geographical aspects of the mortality from melanoma in Europeans. *Med. J. Aust*., **1**, 1082-1087

Lancaster, H.O. & Nelson, J. (1957) Sunlight as a cause of melanoma: a clinical survey. *Med. J. Aust*., **1**, 452-456

Larcom, L.L., Morris, T.E. & Smith, M.E. (1991) Tanning salon exposure suppression of DNA repair capacity and mitogen-induced DNA synthesis. *Photochem. Photobiol*., **53**, 511-516

Larkö, O. & Diffey, B.L. (1983) Natural UV-B radiation received by people with outdoor, indoor and mixed occupations and UV-B treatment of psoriasis. *Clin. exp. Dermatol*., **8**, 279-285

Larkö, O. & Diffoy, B.L. (1986) Occupational exposure to ultraviolet radiation in dermatology departments. *Br. J. Dermatol.,* **114**, 479-484

Lau, H., Reemtsma, K. & Hardy, M.A. (1983) Pancreatic islet allograft prolongation by donor-specific blood transfusions treated with ultraviolet irradiation. *Science*, **221**, 754-756

Lau, H., Reemtsma, K. & Hardy, M.A. (1984) Prolongation of rat islet allograft survival by direct ultraviolet irradiation of the graft. *Science,* **223**, 607-609

Leach, J.F., McLeod, V.E., Pingstone, A.R., Davis, A. & Deane, C.H.W. (1978) Measurement of the ultraviolet doses received by office workers. *Clin. exp. Dermatol*., **3**, 77-79

LeClerc, J.E., Borden, A. & Lawrence C.W. (1991) The thymine-thymine pyrimidine-pyrimidone (6-4) ultraviolet light photoproduct is highly mutagenic and specifically induces 3'-thymine-to-cytosine transitions in *Escherichia coli. Proc. natl Acad. Sci. USA,* **88**, 9685-9689

Lee, J.A.H. (1982) Melanoma and exposure to sunlight. *Epidemiol. Rev*., **4**, 110-136

Lee, J.A.H. & Storer, B.E. (1980) Excess of malignant melanomas in women in the British Isles. *Lancet,* **ii**, 1337-1339

Lee, J.A.H. & Strickland, D. (1980) Malignant melanoma: social status and outdoor work. *Br. J. Cancer*, **41**, 757-763

Lee, G.S.-F., Savage, E.A., Ritzel, R.G. & von Borstel, R.C. (1988) The base-alteration spectrum of spontaneous and ultraviolet radiation-induced forward mutations in the *URA3* locus of *Saccharomyces cerevisiae. Mol. gen. Genet.,* **214**, 396-404

Lehmann, A.R., Arlett, C.F., Broughton, B.C., Harcourt, S.A., Steingrimsdottir, H., Stefanini, M., Taylor, A.M.R., Natarajan, A.T, Green, S., King, M.D., MacKie, R.M., Stephenson, J.B.P & Tolmie, J.L. (1988) Trichothiodystrophy, a human DNA repair disorder with heterogeneity in the cellular response to ultraviolet light. *Cancer Res.,* **48**, 6090-6096

Lerman, S. (1980) *Radiant Energy and the Eye,* New York, MacMillan

Lerman. S. (1988) Ocular phototoxicity. *New Engl. J. Med.,* **319**, 1475-1477

Letvin, N.L., Greene, M.I., Benacerraf, B. & Germain, R.N. (1980a) Immunologic effects of whole-body ultraviolet irradiation: selective defect in splenic adherent cell function *in vitro. Proc. natl Acad. Sci.* USA, **77**, 2881-2885

Letvin, N.L., Nepom, Jar, Greene, M.I., Benacerraf, B. & Germain, K.N. (1980b) Loss of Ia-bearing splenic adherent cells after whole body ultraviolet irradiation J. *Immunol.,* **125**, 2550-2554

van der Leun, J.C. (1984) Yearly review: UV-carcinogenesis. *Photochem. Photobiol*., **39**, 861-868

van der Leun, J.C. (1987a) Principles of risk reduction and protection. In: Passchier, W.F. & Bosnjakovic, B.E.M., eds, *Human Exposure to Ultraviolet Radiation: Risks and Regulations.* Amsterdam. Elsevier, pp. 293-303

van der Leun, J.C. (l987b) Interactions of different wavelengths in effects of UV radiation on skin. *Photodermatology*, **4**, 257-264

van der Leun, J.C. (1992) Interactions of UVA and UVB in photodermatology: what was photo-augmentation? In: Urbach, F., ed, *The Biological Responses to Ultraviolet A* ***Radiation,*** Overland Park, KS, Valdenmar, pp. 309-319

van der Leun, J.C. & van Weelden, H. (1986) UVB phototherapy: principles, radiation sources, regimens. *Curr. Probl. Dermatol*., **15**, 39-51

Levi, F., La Vecchia, C., Te, V.-C. & Mezanotte, G. (1988) Descriptive epidemiology of skin cancer in the Swiss canton of Vaud. *Int. J. Cancer,* **42**, 811-816

Lew, R.A., Sober, A.J., Cook, N., Marvell, R. & Fitzpatrick, T.B. (1983) Sun exposure habits in patients with cutaneous melanoma: a case control study. *J. Dermatol. surg. Oncol*., **9**, 981-986

Ley, R.D. (1985) Photoreactivation of UV-Induced pyrimidine dimers and erythema in the marsupial *Monodelphis domestica. Proc. natl Acad. Sci. USA,* **82**, 2409-2411

Ley, R.D. & Applegate, L.A. (1989) Photodermatological studies with the marsupial *Monodelphis domestica.* In: Maibach, H.I. & Lowe, N.J., eds, *Models in Dermatology,* Vol.4, Basel, Karger, pp. 265-275

Ley, R.D., Sedita, B.A. & Boye, E. (1978) DNA polymerase I-mediated repair of 365 nm-induced single-strand breaks in the DNA of *Escherichia coli. Photochem. Photobiol.,* **27**, 323-327

Ley, R.D., Peak, M.J. & Lyon, L.L. (1983) Induction of pyrimidine dimers in epidennal DNA of hairless mice by UVB: an action spectrum. *J. invest. Dermatol.,* **80**, 188-191

Ley. R.D., Applegate, L.A., Stuart, T.D. & Fry, R.J.M. (1987) UV radiation-induced skin tumors in *Monodelphis domestica. Photodermatology,* 4, 144-147

Ley, R.D., Applegate, L.A. & Freeman, S.E. (1988) Photorepair of ultraviolet radiation-induced pyrimidine dimers in corneal DNA. *Mutat. Res.,* **194**, 49-55

Ley, R.D., Appiegate, L.A., Padilla, R.S. & Stuart, T.D. (1989) Ultraviolet radiation-induced malignant melanoma in *Monodelphis domestica. Photochem. Photobiol*., **50**, 1-5

Ley, R.D., Applegate, L.A., Fry, R.J.M. & Sanchez, A.B. (1991) Photoreactivation of ultraviolet radiation-induced skin and eye tumors of *Monodelphis domestica. Cancer Res*., **51**, 6539-6542

Lightfoote, M.M., Zmundzka, B.Z., Olvey, K.M., Miller, S.A. & Beer, J.Z. (1992) Effects of UVB radiation on human immunodeficiency virus. In: Houck, M. & Kligman, A., eds, *Biological Effects of Light* (in press)

Lill, P.H. (1983) Latent period and antigenicity of murine tumors induced in C3H mice by short-wavelength ultraviolet radiation. *J. invest. Dermatol.,* **81**, 342-346

Lin, C.S., Goldthwait, D.A. & Samols, D. (1990) Induction of transcription from the long terminal repeat of Moloney murine sarcoma provirus by UV-irradiation, x-irradiation, and phorbol ester. *Proc. natl Acad. Sci. USA*, **87**, 36-40

Lindahl-Kiessling, K. & Safwenberg, J. (1971) Inability of UV-irradiated lymphocytes to stimulate allogenic cells in mixed Iymphocyte cultures. *Int. Arch. Allergy,* **41**, 670-678

Lindqvist, C. (1979) Risk factors in lip cancer: a questionnaire survey. Am. J. *Epidemiol.,* **109**, 521-530

Lippincott, S.W. & Blum, H.F. (1943) Neoplasms and other lesions of the eye induced by ultraviolet radiation in strain A mice. *J. natl Cancer Inst*., **3**, 545-554

Lippke, J.A., Gordon, L.K., Brash, D.E. & Haseltine, W.A. (1981) Distribution of UV light-induced damage in a defined sequence of human DNA: detection of alkaline-sensitive lesions at pyri-midine nucleoside-cytidine sequences. *Proc. natl Acad. Sci USA*, **78**, 3388-3392

Lischko, A.M., Seddon, J.M., Gragoudas, E.S., Egan, KM. & Glynn, R.J. (1989) Evaluation of prior primary malignancy as a determinant of uveal melanoma. A case-control study. *Ophthalmology,* 96, 1716-1721

Livingston, W. (1983) Landscape as viewed in the 320-nm ultraviolet. *J. opt. Soc. Am*., **73**, 1653-1657

Logani, M.K, Sambuco, C.P., Forbes, P.D. & Davies, R.E. (1984) Skin-tumour promoting activity of methyl ethyl ketone peroxide—a potent lipid-peroxidizing agent. *Food chem. Toxicol*., **22**, 879-882

Luande, J., Henschke, C.I. & Mohammed, N. (1985) The Tanzanian human albino skin. *Cancer*, **55**, 1823-1828

van der Lubbe, J.L.M., Rosdorff, H.J.M., Bos, J.L. & van der Eb, A.J. (1988) Activation of N-ras induced by ultraviolet irradiation *in vitro. Oncogene Res*., **3**, 9-20

Lucke-Huhle, C., Mai, S. & Herrlich, P. (1989) UV-lnduced early-domain binding factor as the limiting component of simian virus 40 DNA amplification in rodent cells. *Mol. cell. Biol*., **9**, 4812-4818

Lundgren, K & Wulf, H.C. (1988) Cytotoxicity and genotoxicity of UVA irradiation in Chinese hamster ovary cells measured by specific locus mutations, sister chromatic exchanges and chromosome aberrations. *Photochem. Photobiol*., **47**, 559-563

Lunnon, R.J. (1984) Ultraviolet photography. In: Williams, R., ed., *Medical Photography Study Guide.* Lancaster, MTP Press, pp. 225-233

Lynch, D.H., Gurish, M.F. & Haynes, R.A. (1983) The effects of high-dose UV exposure on murine Langerhans cell function at exposed and unexposed sites as assessed using in vivo and in vitro assays. *J. invest. Dermatol*., **81**, 336-341

Lynge, E. & Thygesen, L. (1990) Occupational cancer in Denmark. Cancer incidence in the 1970 census population. *Scand. J. Work Envuon. Health,* **16** (Suppl. 2), 1-35

Machta, L., Cotton, G., Hass, W. & Komhyr, W. (1975) *CIAP Measurements of Solar Ultraviolet Radiation* (Final Report, Interagency Agreement DOT-A5-20082), Washington DC, US Department of Transportation

Mack, T.M. & Floderus, B. (1991) Malignant melanoma risk by nativity, place of residence at diagnosis, and age at migration. *Cancer Causes Control*, **2**, 401-411

MacKie, R.M. & Aitchison, T (1982) Severe sunburn and subsequent risk of primary cutaneous malignant melanoma in Scotland. B. *J. Cancer*, **40**, 955-960

MacKie, R.M., Freudenberger, T. & Aitchison, T.C. (1989) Personal risk-factor chart for cutaneous melanoma. *Lancet*, **ii**, 487-490

MacLaughlin, J. ~ Holick, M.F. (1985) Aging decreases the capacity of human skin to produce vitamin D3. *J. clin. Invest*., **76**, 1536-1538

Madewell, B.R., Conroy, J.D. & Hodgkins, E.M. (1981) Sunlight-skin cancer association in the dog: a report of three cases. *J. cutaneous Pathol*., **8**, 434 -443

Magee, M.J., Kripke, M.L. & Ullrich, S.E. (1989a) Suppression of the elicitation of the immune response to alloantigen by ultraviolet radiation. *Transplantation*, **47**, 1008-1013

Magee, M.J., Kripke, M.L. & Ullrich, S.E. (1989b) Inhibition of the immune response to alloantigen in the rat by exposure to ultraviolet radiation. *Photochem. Photobiol*., **50**, 193-199

Magnus, K. (1973) Incidence of malignant melanoma of the skin in Norway, 1955-1970. Variations in time and space and solar radiation. *Cancer*, **32**, 1275-1286

Magnus, K. (1991) The Nordic profile of skin cancer incidence. A comparative epidemiological study of the three main types of skin cancer. *Int. J. Cancer*, **47**, 12-19

Maher, V.M., Dorney, D.J., Mendrala, A.L., Konze-Thomas, B. & McCormick, J.J. (1979) DNA excision-repair processes in human cells can eliminate the cytotoxic and mutagenic consequences of ultraviolet irradiation. *Mutat. Res*., **62**, 311-323

Maher, V.M., Rowan, L.A., Silinskas, K.C., Kateley, S.A. & McCormick, J.J. (1982) Frequency of UV induced neoplastic transformation of diploid human fibroblasts is higher in xeroderma pigmentosum cells than in normal cells. *Proc. natl Acad. Sc. USA*, **79**, 2613-2617

Maltzman, W. & Czyzyk, L. (1984) UV-lrradiation stimulates levels of p53 cellular tumor antigen in nontransformed mouse cells. *Mol. cell. Biol*., **4**, 1689-1694

Mandal, T.K. & Chatterjee, S.N. (1980) Ultraviolet- and sunlight-induced lipid peroxidation in liposomal membrane. *Radiat. Res*., **83**, 290-302

Mariutti, G. & Matzeu, M. (1987) Measurement of ultraviolet radiation in welding processes and hazard evaluation. In: Passchier, W.F. & Bosnjakovic, B.F.M., eds, *Human Exposure to Ultraviolet Radiation: Risks and Regulations,* Amsterdam, Elsevier, pp. 387-390

Marks, R. & Selwood, T.S. (1985) Solar keratoses. The association with erythemal ultraviolet radiation in Australia. *Cancer,* **56**, 2332-2336

Marks, R., Ponsford, M.W., Selwood, T.S., Goodman, G. & Mason, G. (1983) Non-melanocytic skin cancer and solar keratoses in Victoria *Med. J. Aust*., **2**, 619-622

Marks, R., Rennie, G. & Selwood, T.S. (1988) Malignant transformation of solar keratoses to squamous cell carcinoma. *Lancet*, **i**, 795-797

Marks, R., Jolley, D., Dorevitch, A.P. & Selwood, T.S. (1989) The incidence of non-melanocytic skin cancers in an Australian population: results of a five-year prospective study. *Med. J. Aust.,* **150**, 475-478

Marshall, R.R. & Scott, D. (1976) The relationship between chromosome damage and cell killing in UV-irradiated normal and xeroderma pigmentosum cells. *Mutat. Res*., **36**, 397-400

Marshall, R.R., Arlett, C.F., Harcourt, S.A. & Broughton, B.A. (1980) Increased sensitivity of cell strains from Cockayne's syndrome to sister-chromatic exchange induction and cell killing by UV light. *Mutat. Res.,* **69**, 107-112

Matsumoto, K., Sugiyama, M. & Ogura, R. (1991) Non-dimer DNA damage in Chinese hamster V-79 cells exposed to ultraviolet-B light. *Photochem. Photobiol.,* **54**, 389-392

Matsunaga, T., Hieda, K. & Nikaido, O. (1991) Wavelength dependent formation of thymine dimers and (6-4)photoproducts in DNA by monochromatic ultraviolet light ranging from 150 to 365 nm. *Photochem. Photobiol.,* **54**, 403-410

Matsuoka, L.Y., Ide, L., Wortsman, J., MacLaughlin, J.A. & Holick, M.F. (1987) Sunscreens suppress cutaneous vitamin D3 synthesis. *J. clin. Endocnnol. Metab.,* **64**, 1165-1168

Mayne, L.V., Mullenders, L.H.F. & van Zeeland, A.A. (1988) Cockayne's syndrome: a UV sensitive disorder with a defect in the repair of transcribing DNA but normal overall excision repair. In: Friedberg, E.C. & Hanawalt, PC., eds, *Mechanisms and Consequences of DNA Damage Processing,* New York, Alan R. Liss, pp. 349-353

McCormick, J.P., Fisher, J.R., Pachlatko, J.P. & Eisenstark, A. (1976) Characterisation of a cell-lethal product from the photooxidation of tryptophan: hydrogen peroxide. *Science,* **191**, 468-669

McCredie, M. & Coates. M.S. (1989) *Cancer Incidence in Migrants to New South Wales. 1972 to 1984,* New South Wales Central Cancer Registry, Woolloomooloo, NSW, New South Wales Cancer Council, pp. 22-23, 62-63

McGovern, V.J., Shaw, H.M., Milton, G.W. & Farago, G.A. (1980) Is malignant melanoma arising in a Hutchinson's melanotic freckle a separate disease entity? *Histopathology,* **4**, 235-242

McGrath, H., Wilson, W.A. & Scopelitis, E. (1986) Acute effects of low-fluence ultraviolet light on human T-lymphocyte subsets. *Photochem. Photobiol.,* **43**, 627-631

McGregor, W.G., Chen, R.-H., Lukash, L., Maher, V.M. & McCormick, J.J. (1991) Cell cycle-dependent strand bias for UV-induced mutations in the transcribed strand of excision repair-proficient human fibroblasts but not in repair-deficient cells. *Mol. cell. Biol.,* **11**, 1927-1934

McKinlay, A.F. & Diffey, B.L. (1987) A reference action spectrum for ultraviolet induced erythema in human skin. *CIE* (*Commission Internationale de l'Eclairage) J.,* **6**, 17-22

McKinlay, A.F. & Whillock, M.J. (1987) Measurement of ultra-violet radiation from fluorescent lamps used for general lighting and other purposes in the UK In: Passchier, W.F. & Bosnjakovic, B.F.M., eds, *Human Exposure to Ultraviolet Radiation: Risks and Regulations,* Amsterdam, Elsevier, pp. 253-258

McKinlay, A.F., Whillock, M.J. & Meulemans, C.C.E. (1989) *Ultraviolet Raduation and Blue-light Emissions from Spotlights Incorporating Tungsten Halogen Lamps* (Report NRPB-R228), Didcot, National Radiological Protection Board

McLennan, A.G. (1987) The repair of ultraviolet light-induced DNA damage in plant cells. *Mutat. Res.,* **181**, 1-7

Mecherikunnel, A.T. & Richmond, J.C. (1980) *Spectral Distribution of Solar Radiation* (NASA Technical Memorandum 82021), Greenbelt, MD, Goddard Space Flight Center

Melski, J.W., Tanenbaum, L., Parrish, J.A., Fitzpatrick, T.B. & Bleich, H.L. (1977) Oral methoxsalen photochemotherapy for the treatment of psoriasis: a cooperative clinical trial. *J. invest. Dermatol,* **68**, 328-335

Menzies, S.W., Greenoak, G.E., Reeve, V.E. & Gallagher, C.H. (1991) Ultraviolet radiation-induced murine tumors produced in the absence of ultraviolet radiation-induced systemic tumor immunosuppression. *Cancer Res.*, **51**, 2773-2779

Miguel, A.G. & Tyrrell, R.M. (1983) Induction of oxygen-dependent lethal damage by monochromatic UVB (313 nm) radiation: strand breakage, repair and cell death. *Carcinogenesis*, **4**, 375-380

Milham, S., Jr (1983) *Occupational Mortality in Washington State 1950-1979* (DHSS (NIOSH) Publ. No. 83-116), Cincinnati, OH, National Institute for Occupational Safety and Health

Miller, J.H. (1985) Mutagenic specificity of ultraviolet light. *J. mol. Biol.*, **182**, 45-68

Miskin, R. & Ben-Ishai, R. (1981) Induction of plasminogen activator by UV light in normal and xeroderma pigmentosum fibroblasts. *Proc. natl Acad. Sci USA,* **78**, 6236-6240

Mitchell, D.L. (1988) The relative cytotoxicity of (6-4)photoproducts and cyclobutane dimers in mammalian cells. *Photochem. Photobiol.,* **48**, 51-57

Mitchell, D.L., Haipek, C.A. & Clarkson, J.M. (1985) (6-4)Photoproducts are removed from the DNA of UV-irradiated mammalian cells more efficiently than cyclobutane pyrimidine dimers. *Mutat. Res.*, **143**, 109- 112

Mitchell, D.L., Jen, J. & Cleaver, J.E. (1991) Relative induction of cyclobutane dimers and cytosine photohydrates in DNA irradiated *in vitro* and *in vivo* with ultraviolet-C and ultraviolet-B light. *Photochem. Photobiol.,* **54**, 741-746

Moan, J., Dahlback, A., Henriksen, T & Magnus, K. (1989) Biological amplification factor for sunlight-induced nonmelanoma skin cancer at high latitudes. *Cancer Res.,* **49**, 5207-5212

Molina, M.J. & Rowland, F.S. (1974) Stratospheric sink for chlorofluoromethanes: chlorine atom-catalyzed destruction of ozone. *Nature,* **249**, 810-812

Mondal, S. & Heidelberger, C. (1976) Transformation of C3H/lOT1/2 CL8 mouse embryo fibroblasts by ultraviolet irradiation and a phorbol skin. *Nature,* **260**, 710-711

Morgun, V.V., Logvinenko, V.F., Dvernyakov, V.S. & Timoshenko, VM. (1988) Mutagenic activity of pulsed concentrated sunlight. *Sov. Genet.*, **24**, 189-193

Morison, W.L. (1983a) *Phototherapy and Photochemotherapy of Skin Disease,* New York, Praeger

Morison, W.L. (1983b) Solar urticaria. In: Parrish, J.A., Kripke, M.L. & Morison, W.L., eds, ***Photo****immunology,* New York, Plenum, pp. 215-226

Morison, W.L. (1983c) Autoimmune disease. In: Parrish, J.A., Kripke, M.L. & Morison, W.L., eds, *Photoimmunology,* New York, Plenum, pp. 255-266

Morison, W.L. (1986) The effects of UVA radiation on immune function. In: Urbach, F. & Grange**,** R.W., eds, *The Biological Effects of UVA Radiation,* New York, Praeger, pp. 202-209

Morison, W.L. (1989) Effects of ultraviolet radiation on the immune system in humans. *Photochem. Photobiol*., **50**, 515-524

Morison, W.L. & Kelley, S.P. (1985) Sunlight suppressing rejection of 280 to 320 nm UV-radiationinduced skin tumors in mice. *J. natl Cancer Inst*., **74**, 525-527

Morison, W.L. & Kochevar, I.E. (1983) Photoallergy. In: Parrish, J.A., Kripke, M.L. & Morison, W.L., eds, *Photoimmunology,* New York, Plenum, pp. 227-253

Morison, W.L. & Kripke, M.L. (1984) Systemic suppression of contact hypersensitivity by ultraviolet B radiation or methoxsalen/ultraviolet A radiation in the guinea pig. *Cell. Immunol.,* **85**, 270-277

Morison, W.L., Parrish, J.A., Bloch, K.J. & Krugler, J.I. (1979a) In vivo effect of UVB on lymphocyte function. *Br.* J. *Dermatol.,* **101**, 513-519

Morison, W.L., Parrish. J.A., Anderson, R.R. & Bloch, K.J. (1979b) Sensitivity of mononuclear cells to UV radiation. *Photochem. PhotobioI.,* **29**, 1045-1047

Morison, W.L., Bucana, C. & Kripke, M.L. (1984) Systemic suppression of contact hypersensitivity by UVB radiation is unrelated to the UVB-induced alterations in the morphology and number of Langerhans cells. *Immunology,* **52**, 299-306

Morison, W.L., Pike, R.A. & Kripke, M.L. (1985) Effect of sunlight and its component wavebands on contact hypersensitivity in mice and guinea pigs. *Photodermatology,* **2**, 195-204

Morison, W. L. , Jerdan, M.S. , Hoover, T L. & Farmer, E.R. (1986) UV radiation-induced tumors in haired mice: identification as squamous cell carcinomas. *J. natl Cancer Inst*., **77**, 1155-1162

Mørk, N.-J. & Austad, J. (1982) Short-wave ultraviolet light (UVB) treatment of allergic contact dermatitis of the hands. *Acta dermatovenereol.,* **63**, 87-89

Morrison, H. (1985) Photochemistry and photobiology of urocanic acid. *Photodermatology,* **2**, 158-165

Moseley, H. (1988) *Non-ionising Radiation: Microwaves, Ultraviolet and Laser Radiation* (Medical Physics Handbooks 18), Bristol, Adam Hilger, pp. 110-154

Moss, S.H. & Smith, K.C. (1981) Membrane damage can be a significant factor in the inactivation of *Escherichia coli* by near-ultraviolet radiation. *Photochem. Photobiol.,* **33**, 203-210

Muir, C., Waterhouse, J., Mack, T., Powell, J. & Whelan, S., eds (1987) *Cancer Incidence in Five Continents, Vol. V* (IARC Scientific Publications No. 88), Lyon, IARC

Munakata, N. (1989) Genotoxic action of sunlight upon *Bacillus subtilis* spores: monitoring studies at Tokyo, Japan. *J. Radiat. Res.,* **30**, 338-351

Murthy, P.B., Rahiman, M.A. & Tulpule, P.G. (1982) UV-Induced chromosome aberrations, sister-chromatid exchanges and cell survival in cultured lymphocytes from malnourished children. *Pediatr Res.,* **16**, 663-664

Musk, P. Campbell, R., Staples, J., Moss, D..J. & Parsons, R.G. (1989) Solar and UVC-induced mutation in human cells and inhibition by deoxynucleosides. *Mutat. Res.,* **227**, 25-30

Mutzhas, M.F. (1986) UVA-Emitting light sources. In: Urbach, F. & Grange, R.W., eds. *The Biological Effects of UVA Radiation,* New York, Praeger, pp. 10-23

Myhr, B.C., Turnbull, D. & DiPaolo, J.A. (1979) Ultraviolet mutagenesis of normal and xeroderma pigmentosum variant human fibroblasts. *Mutat. Res.,* **62**, 341-353

Natarajan, A.T., van Zeeland, A.A., Verdegaal-Immerzeel, E.A.M. & Filon, A.R. (1980) Studies on the influence of photoreactivation on the frequencies of UV-induced chromosomal aberrations, sister-chronlaticl exchanges and pyrimidine dimers in chicken embryonic fibroblasts. *Mutat. Res.,* **69**, 307-317

Nathanson, R.B., Forbes, P.D. & Urbach, F. (1976) Modification of photocarcinogenesis by two immunosuppressive agents. *Cancer Lett.,* **1**, 243-247

Nelson, E.W., Eichwald, E.J. & Shelly, J. (1987) Increased ultraviolet radiation-induced skin cancers in cyclosporine-treated mice. *Transplant. Proc*., **19**, 526-527

Nikula, K.J., Benjamin, S.A., Angleton, G.M., Saunders, W.J. & Lee, A.C. (1992) Ultraviolet radiation, solar dermatosis, and cutaneous neoplasia in beagle dogs. *Radiat. Res.,* **129**, 11-18

Nishi, Y., Hasegawa, M.M., Taketomi, M., Ohkawa, Y. & Inui, N. (1984) Comparison of 6-thio-guanine-resistant mutation and sister chromatic exchanges in Chinese hamster V79 cells with forty chemical and physical agents. *Cancer Res*., **44**, 3270-3279

Noonan, F.P. & De Fabo, E.C. (1985) Immune suppression by ultraviolet radiation and its role in ultraviolet radiation induced carcinogenesis in mice. *Aust. J. Dermatol.,* **26**, 4-8

Noonan, F.P., De Fabo, E.C. & Kripke, M.L. (1981a) Suppression of contact hypersensitivity by UV radiation and its relationship to UV-induced suppression of tumor immunity. *Photochem. Photobiol.,* **34**, 683 689

Noonan, F.P, Kripke, M.L., Pedersen, G.M. & Greene, M.I. (1981b) Suppression of contact hyper-sensitivity in mice by ultraviolet irradiation is associated with defective antigen presentation. *Immunology,* **43**, 527-533

Noonan, F.P, Bucana, C., Sauder, D.N. & De Fabo, E.C. (1984) Mechanism of systemic immune suppression by UV irradiation *in vivo.* II. The UV effects on number and morphology of epi-dermal Langerhans cells and the UV-induced suppression of contact hypersensitivity have different wavelength dependencies. *J. Immunol.,* **132**, 2408-2416

Noonan, F.P, De Fabo, E.C. & Morrison, H. (1988) cis-Urocanic acid, a product formed by ultraviolet B irradiation of the skin, initiates an antigen presentation defect in splenic dendritic cells *in vivo. J. invest. Dermatol*., **90**, 92-99

Norbury, K.C. & Kripke, M. L. (1978) Ultraviolet carcinogenesis in T-cell depleted mice . *J. natl Cancer Inst.,* **61**, 917-921

Norimura, T., Maher, V.M. & McCormick, J.J. (1990) Cytotoxic and mutagenic effect of UV, ethylnitrosourea and (±)-7ß,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene in diploid human T lymphocytes in culture: comparison with fibroblasts. *Mutagenesis*, **5**, 447-451

Norval, M., Mclutyre, C.R., Simpson, T.J., Howie, S.E.M. & Bardshiri, E. (1988) Quantification of urocanic acid isomers in murine skin during development and after irradiation with UVB light. *Photodermatology*, **5**, 179-186

Nusbaum, B.P, Edwards, E.K., Jr, Horwitz, S.N. & Frost, P. (1983) Psoriasis therapy. The effect of UV radiation on sensitization to mechlorethamine. *Arch. Dermatol*., **119**, 117-121

O'Beirn, S.F., Judge, P. Urbach, F., MacCon, C.F. & Martin, F. (1970) Skin cancer in County Galway, Ireland. *Proc. natl Cancer Conf.,* **6**, 489-500

O'Dell, B.L., Jessen., R.T, Becker, L.E., Jackson, R.T. & Smith, E.B. (19801 Diminished immune response in sun-damaged skin. *Arch. Dermatol.,* **116**, 559-561

Oettlè, A.G. (1963) Skin cancer in Africa. *Natl Cancer Inst. Monogr*., **10**, 197-214

Office of Population Censuses and Surveys (1986) *Occupationul Mortality: the Registar General's Decennial Supplement for Great Britain 1979-80, 1982-83* (Series DS No. 6), London, Her Majesty's Stationery Office

Okamoto, H. & Kripke, M.L. (1987) Effector and suppressor circuits of the immune response are activated *in vivo* by different mechanisms. *Proc. natl Acad. Sci.* USA, **84**, 3841-3845

O'Loughlin, C., Moriarty, M.J., Herity, B. & Daly, L. (1985) A re-appraisal of risk factors for skin carcinoma in Ireland: a case control study. *Irish J. med. Sci.,* **154**, 61-65

Olsen, J.H. & Jensen. O.M. (1987) Occupation and risk of cancer in Denmark. An analysis of 93 810 cancer cases, 1970-1979. *Scand. J. Work Environ. Health,* **13** (Suppl. 1), 1-91

Olsen, W.M., Huitfeldt, H.S. & Eggset, G. (1989) UVB-Induced (6-4) photoproducts in hairless mouse epidermis studied by quantitative immunohistochemistry. *Carcinogenesis,* **10**, 1669-1673

Onuigbo, W.I.B. (1978) Lip lesions in Nigerian Igbos. *Int. J. oral Surg*., **7**, 73-75

Østerlind, A. (1987) Trends in incidence of ocular malignant melanoma in Denmark 1943-1982. *Int. J. Cancer,* **40**, 161-164

Østerlind, A. (1990) Malignant melanoma in Denmark. Occurrence and risk factors. *Acta oncol.,* **29**, 1-22

Østerlind, A., Olsen, J.H., Lynge, E. & Ewertz, M. (1985) Second cancer following cutaneous melanoma and cancers of the brain, thyroid, connective tissue, bone, and eye in Denmark, 1943-80. *Natl Cancer Inst. Monogr*., **68**, 361-388

Østerlind, A., Hou-Jensen, K. & Jensen, O.M. (1988a) Incidence of cutaneous malignant melanoma in Denmark 1978-1982. Anatomic site distribution, histologic types, and comparison with non-melanoma skin cancer. *Br. J. Cancer*, 58, 385-391

Østerlind, A., Tucker, M.A., Stone, B.J. & Jensen, O.M. (1988b) The Danish case-control study of cutaneous malignant melanoma. II. Importance of UV-light exposure. *Int. J. Cancer*, **42**, 319-324

Østerlind, A., Tucker, M.A., Hou-Jensen, K., Stone, B.J., Engholm, G. & Jensen, O.M. (198&) The Danish case-control study of cutaneous malignant melanoma. I. Importance of host factors. *Int. J. Cancer*, **42**, 200-206

Otani, T & Mori, R. (1987) The effects of ultraviolet irradiation of the skin on herpes simplex virus infection: alterations in immune function mediated by epidermal cells and in the course of infection. *Arch. Virol*., **96**, 1-15

Oxholm, A., Oxholm, P., Staberg, B. & Bendtzen, K. (1988) Immunohistological detection of interleukin I-like molecules and tumour necrosis factor in human epidermis before and after UVB-irradiation *in vivo*. *Br. J. Dermatol.,* **118**, 369-376

Paffenbarger, R.S., Jr, Wing, A.L. & Hyde, R.T. (1978) Characteristics in youth predictive of adult-onset malignant lymphomas, melanomas, and leukemias: brief communication. *J. natl Cancer Inst*., **60**, 89-92

Parrington, J.M. (1972) Ultraviolet-induced chromosome aberrations and mitotic delay in human fibroblast cells. *Cytogenetics,* **11**, 117-131

Parrington, J.M., Delhanty, J.D.A. & Baden, H.P. (1971) Unscheduled DNA synthesis, UV-induced chromosome aberrations and SV40 transformation in cultured cells from xeroderma pigmentosum. *Ann. hum. Genet*., **35**, 149-160

Parrish, J.A. (1983) *The Effect of Ultraviolet Radiation on the Immune System,* New Brunswick, NJ, Johnson & Johnson

Parrish, J.A. & Jaenicke, K.F. (1981) Action spectrum for phototherapy of psoriasis. *J. invest. Dermatol*, **76**, 359-362

Parrish, J.A., Fitzpatrick, T.B., Tanenbaum, L. & Pathak, M.A. (1974) Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. *New Engl. J. Med*., **291**, 1207-1211

Parrish, J.A., Zaynoun, S. & Anderson, R.R. (1981) Cumulative effects of repeated subthreshold doses of ultraviolet radiation. *J. invest. Dermatol*., **76**, 356-358

Parrish, J.A., Kripke, M.L. & Morison, W.L., eds (1983) *Photoimmunology,* New York, Plenum

Parry, J.M., Sharp, D., Tippins, R.S. & Parry, E.M. (1979) Radiation-induced mitotic and meiotic aneuploidy in the yeast *Saccharomyces cerevisiae. Mutat. Res*., **61**, 37-55

Parshad, R., Taylor, W.G., Sanford, K.K., Camalier, R.F., Gantt, R. & Tarone, R.E. (1980a) Fluorescent light-induced chromosome damage in human IMR-90 fibroblasts. Role of hydrogen peroxide and related free radicals. *Mutat. Res*., **73**, 115-124

Parshad, R., Sanford, K.K. , Jones, G..M., Tarone, R.E., Hoffman, H.A. & Grier, A.H. (1980b) Susceptibility to fluorescent light-induced chromatic breaks associated with DNA repair deficiency and malignant transfonnalion in culture. *Cancer Res*., **40**, 4415-4419

Pathak, M.A., Fitzpatrick, T.B., Greiter, F. & Kraus, E.W. (1987) Preventive treatment of sunburn, dermatoheliosis, and skin cancer with sun-protective agents. In: Fitzpatrick, T.B., Eisen, A.Z., Wolff, K., Freedberg, I.M. & Austen, K.F., eds, *Dermatology in General Medicine,* 3rd ed., New York, McGraw-Hill, pp. 1507-1522

Patrick, M.H. (1977) Studies on thymine-derived UV photoproducts in DNA—I. Formation and biological role of pyrimidine adducts in DNA. *Photochem. Photobiol.,* **25**, 357-372

Patton, J.D., Rowan, L.A., Mendrala, A.L., Howell, J.N., Maher, V.M. & McCormick, J.J. (1984) Xeroderma pigmentosum fibroblasts including cells from XP variants are abnormally sensitive to the mutagenic and cytotoxic action of broad spectrum simulated sunlight. *Photochem. Photobiol.,* **39**, 37-42

Pauw, H. & Meulemans, C.C.E. (1987) Occupational exposure to artificial UV-A radiation within the Philips factories in the Netherlands. In: Passchier, W.F. & Bosnjakovic, B.F.M., eds, *Human Exposure to Ultraviolet Radiation: Risks and Regulations,* Amsterdam, Elsevier, pp. 265-268

Peak, M.J. & Peak, J.G. (1982) Single-strand breaks induced in Bacillus *subtilis* DNA by ultraviolet light: action spectrum and properties. *Photochem. Photobiol.,* **35**, 675-680

Peak, J.G. & Peak, M.J. (1990) Ultraviolet light induces double-strand breaks in DNA of cultured human P3 cells as measured by neutral filter elusion. *Photochem. Photobiol.,* **52**, 387-393

Peak, J.G. & Peak, M.J. (1991) Comparison of initial yields of DNA-to-protein crosslinks and singlestrand breaks induced in cultured human cells by far- and near-ultraviolet light, blue light, and x-rays. *Mutat. Res.,* **246**, 187-191

Peak, M.J., Peak, J.G., Moehring, M.P. & Webb, R.B. (1984) Ultraviolet action spectra for DNA dimer induction, lethality, and mutagenesis in *Escherichia coli* with emphasis on the UVB region. *Photochem. Photobiol.,* **40**, 613-620

Peak, J.G., Peak, M.J., Sikorski, R.S. & Jones, C.A. (1985) Induction of DNA-protein crosslinks in human cells by ultraviolet and visible radiations: action spectrum. *Photochem. Photobiol.,* **41**, 295-302

Peak, M.J., Peak, J.G. & Carnes, B.A. (1987) Induction of direct and indirect single-strand breaks in human cell DNA by far- and near-ultraviolet radiations: action spectrum and mechanisms. *Photochem. Photobiol.,* **45**, 381-387

Peak, J.G., Woloschak, G.E. & Peak, M.J. (1991a) Enhanced expression of protein kinase C gene caused by solar radiation. *Photochem. Photobiol.,* **53**, 395-397

Peak, J.G., Pilas, B., Dudek, E.J. & Peak, M.J. (199lb) DNA breaks caused by monochromatic 365 nm ultraviolet-A radiation or hydrogen peroxide and their repair in human epithelioid and xeroderma pigmentosum cells. *Photochem. Photobiol.,* **54**, 197-203

Pearse, A.D., Gaskell, S.A. & Marks, R. (1987) Epidermal changes in human skin following irradiation with either UVB or UVA. *J. invest. Dermatol*., **88**, 83-87

Penn, I. (1980) Immunosuppression and skin cancer. *Clin. plast. Surg*., **7**, 361-368

Pepino, P., Hardy, M.A., Chabot, J.A., Berger, C., Marboe, C. & Wasfie, T. (1989) UVB irradiated allogeneic bone marrow transplantation in rats: prevention of graft *versus* host disease without immunosuppression. *Transpl. Proc*., **21**, 2995-2996

Perna, J.J., Mannix, M.L., Rooney, J.F., Notkins, A.L. & Straus, S.E. (1987) Reactivation of latent herpes simplex virus infection by ultraviolet light: a human model. *J. Am. Acad. Dermatol*, 17, 473-478

Perry, L.L. & Greene, M.I. (1982) Antigen presentation by epidermal Langerhans cells: loss of function following ultraviolet (UV) irradiation *in vivo. Clin. Immunol. Immunopathol*, **24**, 204-219

Perticone, P. Hellgren, D. & Lambert, B. (1986) Effects of UV-irradiation on the SCE frequency in human lymphocyte cultures. *Mutat. Res*., **175**, 83-89

Peto, R., Pike, M.C., Day, N.E., Gray, R.G., Lee, P.N., Parish, S., Peto, J., Richards, S. & Wahrendorf, J. (1980) Guidelines for simple sensitive significance tests for carcinogenic effects in long-term animal experiments. In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans,* Suppl. 2, *Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal,* Lyon, pp. 311-26

Phelps, R.G., Bernstein, L.E., Harpaz, N., Gordon, R.E., Cruickshank, F.A. & Schwartz, E. (1989) Characterization of a dermal derived malignant mesenchymal tumor arising in ultraviolet irradiated mice. *Am. J. Pathol.,* **135**, 149-159

Phillips, R. (1983) *Sources and Applications of Ultraviolet Radiation,* London, Academic Press

Pierceall, W.E. & Ananthaswamy, H.N. (1991) Transformation of NIH 3T3 cells by transfection with UV-irradiated human c-Ha-*ras*-1 proto-oncogene DNA. *Oncogene,* **6**, 2085-2091

Pierceall, W.E., Mukhopadhyay, I, Goldberg, L.H. & Ananthaswamy, H.N. (1991) Mutations in the p53 tumor suppressor gene in human cutaneous squamous cell carcinomas. *Mol. Carcinog*., **4**, 445-449

Pitcher, H.M. & Longstreth, J.D. (1991) Melanoma mortality and exposure to ultraviolet radiation: an empirical relationship. *Environ. ins*., **17**, 7-21

Pitts, D.G., Cullen, A.P. & Hacker, P.D. (1977) Ocular effects of ultraviolet radiation from 295 to 365 nm. *Invest. Ophthalmol. visual Sci.,* **16**, 932-939

Plummer, N.A., Greaves, M.W., Hensby, C.N. & Black, A.K. (1977) Inflammation in human skin induced by ultraviolet radiation. *Postgrad. med. J*., **53**, 656-657

Poulsen, J.T , Staberg, B., Wulf, H. C. & Brodthagen, H. (1984) Dermal elastosis in hairless mice after UV-B and UV-A applied simultaneously, separately or sequentially. *Br. J*. ***Dermatol.,*** **110,** 531-538

Pound, A.W. (1970) Induced cell proliferation and the initiation of skin tumour formation in mice by ultraviolet light. *Pathology*, **2**, 269-275

Putschar, W. & Holtz, F. (1930) Production of skin tumours in rats by long duration UV irradiation (Ger.). *Z. Krebsforsch.,* **33**, 219-260

Putvinsky, A.V., Sokolov, A.I., Roshchupkin, D.I. & Vladimirov, Y.A. (1979) Electric breakdown of bilayer phospholipid membranes under ultraviolet irradiation-induced lipid peroxidation. *FEBS Lett.,* **106**, 53-55

Räsänen, L., Reunala, T., Lehto, M., Jansen, C., Rantala, I. & Leinikki, P. (1989) Immediate decrease in antigen-presenting function and delayed enhancement of interleukin-I production in human epidermal cells after in vivo UVB irradiation. *Br. J. Dermatol*, **120**, 589-596

Rasmussen, R.E., Hammer-Wilson, M. & Berns, M.W. (1989) Mutation and sister chromatic exchange induction in Chinese hamster ovary (CHO) cells by pulsed excimer laser radiation at 193 nm and 308 nm and continuous UV radiation at 254 nm. *Photochem. Photobiol*, **49**, 413-418

Ray-Keil, L. & Chandler, J.W. (1986) Reduction in the incidence of rejection of heterotopic murine corneal transplants by pretreatment with ultraviolet radiation. *Transplantation*, **42**, 403-406

Reddy, A.L., Fialkow, P.J. & Salo, A. (1978) Ultraviolet radiation-induced chromosomal abnormalities in fetal fibroblasts from New Zealand black mice. *Science*, **201**, 920-922

Reeve, V.E., Greenoak, G.E., Gallagher, C.H., Canfield, P.J. & Wilkinson, F.J. (1985) Effect of immunosuppressive agents and sunscreens on UV carcinogenesis in the hairless mouse. *Aust. J. exp. Biol. med. Sci.,* **63**, 655-665

Resnick, M.A., Westmoreland, J., Amaya, E. & Bloom, K (1987) UV-Induced damage and repair in centromere DNA of yeast. *Mol. gen. Gener.,* **210**, 16-22

Rigel, D.S., Friedman, R.J., Levenstein. M.J. & Greenwald, D.I. (1983) Relationship of fluorescent lights to malignant melanoma: another view. *J. Dermatol. surg. Oncol*., **9**, 836-838

Ringvold, A. (1980) Cornea and ultraviolet radiation. *Acta ophthalmol.,* **58**, 63-68

Rivers, J.K., Norris, P.G., Murphy, G.M., Chu, A.C., Midgley, G., Morris. J., Morris, R.W., Young, A.R. & Hawk, J.L.M. (1989) UVA sunbeds: tanning, photoprotection, acute adverse effects and immunological changes. *Br. J. Dermatol.,* 120, 767-777

Roberts, L.K. & Daynes, R.A. (1980) Modification of the immunogenic properties of chemically induced tumors arising in hosts treated concomitantly with ultraviolet light. *J. Immunol.,* **125**, 438-447

Roberts, L.K., Samlowski, W.E. & Daynes, R.A. (1986) Immunological consequences of ultraviolet radiation exposure. *Photodermatology,* **3**, 284-298

Robertson, D.F. (1972) *Solar Ultraviolet Radiation in Relation to Human Sunburn and Skin Cancer,* PhD Thesis, University of Queensland, Australia

Robertson, B., Gahring, L., Newton, R. & Daynes, R. (1987) In vivo administration of interleukin 1 to normal mice depresses their capacity to elicit contact hypersensitivity responses: prostaglandins are involved in this modification of immune function. *J. invest. Dermatol,* **88**, 380-387

Robinson, J.K. (1987) Risk of developing another basal cell carcinoma. A 5-year prospective study. *Cancer,* **60**, 118-120

Roffo, A.H. (1934) Cancer and the sun: carcinomas and sarcomas caused by the action of the sun in toto (Fr.). *Bull. Assoc. fr. Étude Cancer,* **23**, 590-616

Roffo, A.H. (1939) Physico-chemical etiology of cancer (with special emphasis on the association with solar radiation) (Ger.). *Strahlentherapie,* **66**, 328-350

Ronai, Z.A. & Weinstein, I.B. (1988) Identification of a UV-induced trans-acting protein that stimulates polyomavirus DNA replication. *J. Virol.,* **62**, 1057-1060

Ronai, Z.A., Lambert, M.E., Johnson, M.D., Okin, E. & Weinstein, I.B. (1987) Induction of asynchronous replication of polyoma DNA in rat cells by ultraviolet irradiation and the effects of various inhibitors. Cancer Res., **47**, 4565-4570

Ronai, Z.A., Lambert, M.E. & Weinstein, I.B. (1990) Inducible cellular responses to ultraviolet light irradiation and other mediators of DNA damage in mammalian cells. *Cell Biol. Toxicol.,* **6**, 105-126

Rooney, J.F., Bryson, Y., Mannix, M.L., Dillon, M., Wohlenberg, C.R., Banks, S., Wallington, C.J., Notkins, A. L. & Straus, S.E. (1991) Prevention of ultraviolet-light-induced herpes labialis by sunscreen. *Lancet,* **338**, 1419-1422

Rosario, R., Mark, G.J., Parrish, J.A. & Mihm, M.C., Jr (1979) Histological changes produced in skin by equally erythemogenic doses of UVA, UVB, UVC with psoralens. *Br. J. Dermatol.,* **101**, 299-308

Rosdahl, I.K (1979) Local and systemic effects on the epidermal melanocyte population in UV-irradiated mouse skin. *J. invest. Dermatol*., **73**, 306-309

Rosenstein, B.S. (1988) The induction of DNA strand breaks in normal human skin fibroblasts exposed to solar ultraviolet radiation. *Radiat. Res.,* **116**, 313-319

Rosenstein, B.S. & Ducore, J.M. (1983) Induction of DNA strand breaks in normal human fibroblasts exposed to monochromatic ultraviolet and visible wavelengths in the 240-546 nm range. *Photochem. Photobiol*., **38**, 51-55

Rosenstein, B.S. & Mitchell, D.L. (1987) Action spectra for the induction of pyrimidine (6-4)pyrimidone photoproducts and cyclobutane pyrimidine dimers in normal human skin fibroblasts. *Photochem. Photobiol,* **45**, 775-780

Rosenstein, B.S. & Mitchell, D.L. (1991) The repair of DNA damages induced in normal human skin fibroblasts exposed to simulated sunlight. *Rudiat. Res.,* **126**, 338-342

Rosenstein, B.S. & Rosenstein, R.B. (1985) Induction of chromosome aberrations in ICR 2A frog cells exposed to 265-313 nm monochromatic ultraviolet wavelengths and photoreactivating light. *Photochem. Photobiol*., **41**, 57-61

Rosenstein, B.S., Murphy, J.T. & Ducore, J.M. (1985) Use of a highly sensitive assay to analyze the excision repair of dimer and non-dimer DNA damages induced in human skin fibroblasts by 254 nm and solar ultraviolet radiation. *Cancer Res.,* **45**, 5526-5531

Rosenstein, B.S., Lai, L.-W., Ducore, J.M. & Rosenstein, R.B. (1989) DNA-protein crosslinking with normal and solar UV-sensitive ICR 2A frog cell lines exposed to solar UV-radiation. *Mutat. Res.,* **217**, 219-226

Rosenthal, F.S., Phoon, C., Bakalian, A.E. & Taylor, H.R. (1988) The ocular dose of ultraviolet radiation to outdoor workers. *Invest. Ophthalmol. visual Sci.,* **29**, 649-656

Rosenthal, F.S., Lew, R.A., Rouleau, L.J. & Thomson, M. (1990) Ultraviolet exposure to children from sunlight: a study using personal dosimetry. *Photodermatol. Photoimmunol. Photomed.,* **7**, 77-81

Rosenthal, F.S., West, S.K., Munoz, B., Emmett, E.A., Strickland, R.T. & Taylor, H.R. (1991) Ocular and facial skin exposure to ultraviolet radiation in sunlight: a personal exposure model with application to a worker population. *Health Phys*., **61**, 77-86

Roser, M., Böhm, A., Oldigs, M., Weichenthal, M., Reimers, U., Schmidt-Preuss, U., Breitbart, E.W. & Rüdiger, H.W. (1989) Ultraviolet-induced formation of micronuclei and sister chromatic exchange in cultured fibroblasts of patients with cutaneous malignant melanoma. *Cancer Genet. Cytogenet.,* **41**, 129-137

Roshchupkin, D.I., Pelenitsyn, A.B., Potapenko, A.Y., Talitsky, V.V. & Vladimirov, Y.A. (1975) Study of the effects of ultraviolet light on biomembranes—IV. The effect of oxygen on UV-induced hemolysis and lipid photoperoxidation in rat erythrocytes and liposomes. *Photochem. Photobiol*., **21**, 63-69

Ross, J.A., Howie, S.E.M., Norval, M., Maingay, J. & Simpson, T.J. (1986) Ultraviolet-irradiated urocanic acid suppresses delayed-type hypersensitivity to herpes simplex virus in mice. *J. invest. Dermatol.,* 87, 630-633

Ross, J.A., Howie, S.E.M., Norval, M. & Maingay, J. (1987) Two phenotypically distinct T cells are involved in ultraviolet-irradiated urocanic acid-induced suppression of the efferent delayed-type hypersensitivity response to herpes simplex virus, type 1 in vivo. *J. invest Dermatol*., **89**, 230-233

Roth, D.E., Hodge, S.J. & Callen, J.P. (1989) Possible ultraviolet A-induced lentigines: a side effect of chronic tanning salon usage. *J. Am. Acad. Dermatol*., 20, 950-954

Roza, L., van der Wulp, K.J.M., MacFarlane, S.J., Lohman, P.H.M. & Baan, R.A. (1988) Detection of cyclobutane thymine dimers in DNA of human cells with monoclonal antibodies raised against a thymine dimer-containing tetranucleotide. *Photocherm. Photobiol*, **48**, 627-633

Ruiz-Rubio, M., Woodgate, R., Bridges, B.A., Herrera, G. & Blanco, M. (1986) New role for photoreversible pyrimidine dimers in induction of prototrophic mutations in excision-deficient *Escherichia coli* by ultraviolet light. *J. Bactenol*., **166**, 1141-1143

Rusch, H.P., Kline, B.E. & Baumann, C.A. (1941) Carcinogenesis by ultraviolet rays with reference to wavelength and energy. *Arch. Pathol*., **31**, 135-146

Russell, W.O., Wynne, E.S., Loquvam, G.S. & Mehl, D.A. (1956) Studies on bovine ocular squamous carcinoma ('cancer eye'). I. Pathological anatomy and historical review. *Cancer,* **9**, 1-52

Saftlas, A.F., Blair, A., Cantor, K.P., Hanrahan, L. & Anderson, H.A. (1987) Cancer and other causes of death among Wisconsin farmers. *Am. J. ind. Med.,* **11**, 119-129

Sagher, D. & Strauss, B. (1983) Insertion of nucleotides opposite apurinic/apyrimidinic sites in deoxyribonucleic acid during in vitro synthesis: uniqueness of adenine nucleotides. *Biochemistry,* **22**, 4518-4526

Sammartano, L.J. & Tuveson, R.W. (1985) Hydrogen peroxide induced resistance to broad-spectrum near-ultraviolet light (300 400 nm) inactivation in *Escherichia coli. Photochem. Photobiol*., **41**, 367-370

Sammartano, L.J. & Tuveson, R.W. (1987) Escherichia cold strains carrying the cloned cytochrome d terminal oxidase complex are sensitive to near-UV inactivation. *J. Bactenol*., 169, 5304-5307

Sancar, A. & Rupp, W.D. (1983) A novel repair enzyme: UVRABC excision nuclease of Escherichia coli cuts a DNA strand on both sides of the damaged region. *Cell*, **33**, 249-260

Sanderson, B.J.S., Dempsey, J.L. & Morley, A.A. (1984) Mutations in human lymphocytes: effects of x- and UV-irradiation. *Mutat. Res.,* **140**, 223-227

Sanford, K.K., Parshad, R., Jones, G., Handleman, S., Garrison, C. & Price, F. (1979) Role of photosensitization and oxygen in chromosome stability and 'spontaneous' malignant transformation in culture. *J. natl Cancer Inst*., **63**, 1245-1255

Santamaria, L., Giordono, G.G., Alfisi, M. & Cascione, F. (19GG) Effects of light on 3,4-benzpyrene carcinogenesis. *Nature,* **210**, 824-825

Santamaria, L., Bianch, A., Arnaboldi, A., Daffara, P. & Andreoni, L. (1985) Photocarcinogenesis by methoxypsoralen, neutral red, proflavine, and long UV radiation. *CancerDetect. Prev*., 8, 447-454

Sauder, D.N., Tamaki, K., Moshell, A.N., Fujiwara, H. & Katz, S.I. (1981) Induction of tolerance to topically applied TNCB using TNP-conjugated ultraviolet light-irradiated epidermal cells. *J. Immunol.,* **127**, 261-265

Sauder, D.N., Noonan, F.P., DeFabo, E.C. & Katz, S.I. (1983) Ultraviolet radiation inhibits alloantigen presentation by epidermal cells: partial reversal by the soluble epidermal cell product, epidermal cell-derived thymocyte-activating factor (ETAF). *J. invest. Dermatol.,* 80, 485-489

Sayre, R.M. & Kligman, L.H. (1992) Discrepancies in the measurement of spectral sources. *Photochem. Photobiol*., **55**, 141-143

Schaaper, R.M., Kunkel, T.A. & Loeb, L.A. (1983) Infidelity of DNA synthesis associated with bypass of apurinic sites. *Proc. natl Acad. Sci. USA,* **80**, 487-491

Schaaper, R. M., Dunn, R. L. & Glickman, B.W. (1987) Mechanisms of ultraviolet-induced mutation. Mutational spectra in the *Escherichia coli* lacI gene for a wild-type and an excision-repair deficient strain. *J. mol. Biol.,* **198**, 187-202

Schacter, B., Lederman, M.M., LeVine, M.J. & Ellner, J.J. (1983) Ultraviolet radiation inhibits human natural killer activity and lymphocyte proliferation. *J. Immunol.,* **130**, 2484-2487

Scheibner, A., McCarthy, W.H., Milton, G.W. & Nordlund, J.J. (1983) Langerhans cell and melanocyte distribution in 'normal' human epidermis. *Aust. J. Dermatol*., 24, 9-16

Scheibner, A., Hollis, D.E., McCarthy, W.H. & Milton, G.W. (1986a) Effects of exposure to ultraviolet light in a commercial solarium on Langerhans cells and melanocytes in human epidennis. *Aust. J. Dermatol*., **27**, 35-41

Scheibner, A., Hollis, D.E., McCarthy, W.H. & Milton, G.W. (1986b) Effects of sunlight exposure on Langerhans cells and melanocytes in human epidermis. *Photodermatology,* **3**, 15-25

Schothorst, A.A., Slaper, H., Telgt, D., Alhadi, B. & Suurmond, D. (1987a) Amounts of ultraviolet B (UVB) received from sunlight or artificial UV sources by various population groups in the Netherlands. In: Passchier, W.F. & Bosnjakovic, B.F.M., eds, *Human Exposure to Ultraviolet Radiation: Risks and Regulations,* Amsterdam, Elsevier, pp. 269-273

Schothorst, A.A., Enninga, E.C. & Simons, J.W.I.M. (1987b) Mutagenic effects per erythemal dose of artificial and natural sources of ultraviolet light. In: Passchier. W.F. & Bosnjakovic, B.E.M., eds, *Human Exposure to Ultraviolet Radiation: Risks and Regulutions,* Amsterdam, Elsevier, pp. 103-107

Schothorst, A.A., Evers, L.M., Noz, K.C., Filon, R. & van Zeeland, A.A. (19'31) Pyrimidine dimer induction and repair in cultured human skin keratinocytes or melanocytes after irradiation with monochromatic ultraviolet radiation. *J. invest. Dermatol*., **96**, 916-920

van der Schroeff, J.G., Evers, L.M., Boot, A.J.M. & Bos, J.L. (1990) *ras* Oncogene mutations in basal cell carcinomas and squamous cell carcinomas of human skin. *J. invest. Dermatol*., **94**, 423-425

Schulze, R. (1962) On the climate of the Earth (Ger.). *Strahlentherapie,* **ll9**, 321-348

Schulze, R. (1970) Global radiation climate (Ger.). *Wiss. Forschungsber*, **72**, 1-220

Schulze, R. & Grafe, K. (1969) Consideration of sky ultraviolet radiation in the measurement of solar ultraviolet radiation. In: Urbach, F., ed., *The Biological Effects of Ultraviolet Radiation* (Proceedings of the First International Conference), Oxford, Pergamon Press, pp. 359-373

Schwartz, S.M. & Weiss, N.S. (1988) Place of birth and incidence of ocular melanoma in the United States. *Int. J. C.ancer*, **41**, 174-177

Schwarz, T., Urbanska, A., Gschnait, E & Luger, T.A. (1986) Inhibition of the induction of contact hypersensitivity by a UV-mediated epidermal cytokine. *J. invest. Dermatol*., **87**, 289-291

Schwarz, T., Urbanski, A., Kirnbauer, R., Kock, A., Gschnait, F. & Luger, TA. (1988) Detection of a specific inhibitor of interleukin 1 in sera of UVB-treated mice. *J. invest. Dermatol*., **91**, 536-540

Scotto, J. & Fears, TR. (1987) The association of solar ultraviolet and skin melanoma incidence among Caucasians in the United States. *Cancer Invest*., **5**, 275-283

Scotto, J., Kopf, A.W. & Urbach, F. (1974) Non-melanoma skin cancer among Caucasians in four areas of the United States. *Cancer*, **34**, 1333-1338

Scotto, J., Fears, T. & Gori, G. (1976) *Measurements of Ultraviolet Radiations in the United States and Comparisons with Skin Cancer Data* (NIH Publ. No. 76-1029). Washington DC, US Department of Health, Education, and Welfare

Scotto, J., Fears, T.R. & Fraumeni, J.F., Jr (1982) Solar radiation. In: Schottenfeld, D. & Fraumeni, J.F., Jr, eds, *Cancer Epidemiology and Prevention,* Philadelphia, W.B. Saunders, pp. 254-276

Scotto, J., Fears, T.R. & Fraumeni, J.F., Jr (1983) *Incidence of Nonmelanoma Skin Cancer in the United States* (NIH Publ. No. 83-2433), Bethesda, MD, National Cancer Institute

Seddon, J.M., Gragoudas, E.S., Glynn, R.J., Egan, K.M., Albert, D.M. & Blitzer, P.H. (1990) Host factors, UV radiation and risk of uveal melanoma. A case-control study. *Arch. Ophthalmol.,* **108**, 1274-1280

Seetharam, S., Protić-Sabljić. M., Seidman, M.M. & Kraemer, K.H. (1987) Abnormal ultraviolet mutagenic spectrum in plasmid DNA replicated in cultured fibroblasts from a patient with the skin cancer-prone disease, xeroderma pigmentosum. *J. clin. Invest.,* **80**, 1613-1617

Seguin, L.R., Tarone, R.E., Liao, K. & Robbins, J.H. (1988) Ultraviolet light-induced chromosomal aberrations in cultured cells from Cockayne syndrome and complementation group C xeroderma pigmentosum patients: lack of correlation with cancer susceptibility. *Am. J. hum. Genet.,* **42**, 468-475

Sekiya, T., Fushimi, M., Hori, H., Hirohashi, S., Nishimura, S. & Sugimura, T. (1984) Molecular cloning and the total nucleotide sequence of the human c-Ha-ras-1 gene activated in a melanoma from a Japanese patient. *Proc. natl Acad. Sci. USA,* **81**, 4771-4775

Servilla, K.S., Burnham, D.K. & Daynes, R.A. (1987) Ability of cyclosporine to promote the growth of transplanted ultraviolet radiation-induced tumors in mice. *Transplantation,* **44**, 291-295

Setlow, R.B. (1968) Photoproducts in DNA irradiated *in vivo. Photochem. Photobiol.,* **7**, 643-649

Setlow, R.B. (1975) The relevance of photobiological repair. *An. Acad. Bras. Cienc.,* 45 (Suppl. 215), 215-220

Setlow, R.B. & Carrier, W.L. (1966) Pyrimidine dimers in ultraviolet-irradiated DNA's. *J. mol. Biol.,* **17**, 237-254

Setlow, R.B., Swenson, P.A. & Carrier, W.L. (1963) Thymine dimers and inhibition of DNA synthesis by ultraviolet irradiation of cells. *Science,* **142**, 1464-1466

Setlow, R.B., Woodhead, A.D. & Grist, E. (1989) Animal model for ultraviolet radiation-induced melanoma: platyfish-swordtail hybrid. *Proc. natl Acad. Sci.* USA, **86**, 8922-8926

Shabad. L.M. & Litvinova, S.N. (1972) The combined effect of UV irradiation and 7,12-DMBA on the skin of hairless mice (Russ.). *Biull. eksp. Biol. Med*., **73**, 84-85

Shanmugaratnam, K., Lee, H.R & Day, N.E., eds (1983) *Cancer Incidence in Singapore 1968-1977* (IARC Scientific Publications No. 47), Lyon, IARC, p. 73

Shetlar, M.D. (1980) Cross-linking of proteins to nucleic acids by ultraviolet light. *Photochem. Photobiol. Rev.,* **5**, 105-197

Shukla, V.K., Hughes, D.C., Hughes, L.E., McCormick, F. & Padua, R.A. (1989) *ras* Mutations in human melanotic lesions: *K-ras* activation is a frequent and early event in melanoma development. *Oncogene Res.,* **5**, 121-127

Siede, W. & Eckardt, F. (1986) Analysis of mutagenic DNA repair in a thermoconditional mutant of *Saccharomyces cerevisiae.* III. Dose-response pattern of mutation induction in UV-irradiated *rev2*^{ts} cells. *Mol. gen. Genet.,* **202**, 68-74

Siemiatycki, J. (1991) *Risk Factors for Cancer in the Workplace,* Boca Raton, FL, CRC Press

Silverstone, H. & Gordon, D. (1966) Regional studies in skin cancer. Second report: wet tropical and subtropical coasts of Queensland. *Med.* J. *Aust.,* **2**, 733-740

Silverstone, H. & Searle, J.H.A. (1970) The epidemiology of skin cancer in Queensland: the influence of phenotype and environment. *Br. J. Cancer,* **24**, 235-252

Singh, B. & Gupta, R.S. (1982) Mutagenic response to ultraviolet light and X-rays at five independent genetic loci in Chinese hamster ovary cells. *Environ. Mutag.,* **4**, 543-551

Sisson, T.R.C. & Vogl, T.P. (1982) Phototherapy of hyperbilirubinemia. In: Regan, J.D. & Parrish, J.A., eds, *The Science of Photomedicine,* New York, Plenum, pp. 477-509

Sjövall, P. & Christensen, O.B. (1986) Local and systemic effect of ultraviolet irradiation (UVB and UVA) on human allergic contact dermatitis. *Acta dermatol. venereol.,* **66**, 290-294

Slaga, T.J., Klein-Szanto, A.J.P., Triplett, L.L., Yotti, L.P. & Trosko, J.E. (1981) Skin tumor-promoting activity of benzoyl peroxide, a widely used free radical-generating compound. *Science*, **213**, 1023-1025

Slaper, H. (1987) *Skin Cancer and UV Exposure: Investigations on the Estimation of Risks,* PhD Thesis, University of Utrecht

Sliney, D.H. (1986) Physical factors in cataractogenesis: ambient ultraviolet radiation and temperature. *Invest. Ophthalmol. visual Sci.,* **27**, 781-790

Sliney, D.H. (1990) The IRPA/INIRC guidelines or limits of exposure to laser radiation. In: Grandolfo, M., Rindi, S. & Sliney, D.H., eds, *Light, Lasers, and Synchrotron Radiation. A Health Risk Assessment,* New York, Plenum, pp. 341-346

Sliney, D.H. & Wolbarsht, M. (1980) *Safety with Lasers and Other Optical Sources: A Comprehensive Handbook,* New York, Plenum

Sliney, D., Wood, R.L., Jr, Moscato, P.M., Marshall, W.J. & Eriksen, P. (1990) Ultraviolet exposure in the outdoor environment: measurement of ambient ultraviolet exposure levels at large zenith angles. In: Grandolfo, M., Rindi, S. & Sliney, D.H., eds, *Light, Lasers, and Synchrotron Radiation. A Health Risk Assessment,* New York, Plenum, pp. 169-180

Smith, K.C. (1964) The photochemistry of thymine and bromouracil *in vivo. Photochem. Photobiol*., **3**, 1-10

Smith, K.C. (1976) The radiation-induced addition of proteins and other molecules to nucleic acids. In: Wang, S.Y., ed., *Photochemistry and Photobiology of Nucleic Acids,* Vol. 2, New York, Academic Press, pp. 187-218

Smith, K.C., ed. (1989) *The Science of Photobiology,* 2nd ed., New York, Plenum, pp. 47-53

Sorahan, T. & Grimley, R.P (1985) The aetiological significance of sunlight and fluorescent lighting in malignant melanoma: a case-control study. *Br. J. Cancer,* **52**, 765-769

Spangrude, G.J., Bernhard, E.J., Ajioka, R.S. & Daynes, R.A. (1983) Alterations in lymphocyte homing patterns within mice exposed to ultraviolet radiation. *J. immunol.,* **130**, 2974-2981

Spellman, C.W. & Daynes, R.A. (1978) Properties of ultraviolet light-induced suppressor lymphocytes within a syngeneic tumor system. *Cell. Immunol.,* **36**, 383-387

Spellman, C.W., Woodward, J.G. & Daynes, R.A. (1977) Modification of immunological potential by ultraviolet radiation. I. Immune status of short-term UV-irradiated mice. *Transplantation,* **24**, 112-119

Spikes, J.D., Kripke, M.L., Connor, R.J. & Eichwald, E.J. (1977) Time of appearance and histology of tumors induced in the dorsal skin of C3Hf mice by ultraviolet radiation from a mercury arc lamp. *J. natl Cancer Inst*., **59**, 1637-1643

Spitzer, W.O., Hill, G.B., Chambers, L.W., Helliwell, B.E. & Murphy H.B (1975) The occupation of fishing as a risk factor in cancer of the lip. *New Engl. J. Med.,* **293**, 419-424

Spruance, S.L. (1985) Pathogenesis of herpes simplex labialis: experimental induction of lesions with UV light. *J. clin. Microbiol.,* **22**, 366-368

Staberg, B., Wulf, H.C., Poulsen, T., Klemp, P. & Brodthagen, H. (1983a) Carcinogenic effect of sequential artificial sunlight and UVA irradiation in hairless mice. Consequences for solarium 'therapy'. *Arch. Dermatol.,* **119**, 641-643

Staberg, B., Wulf, H.C., Klemp, P. Poulsen, T. & Brodthagen, H. (1983b) The carcinogenic effect of UVA radiation. *J. invest. Dermatol*., **31**, 517-519

Stanley, S.K, Folks, T.M. & Fauci, A.S. (1989) Induction of expression of human immunodeficiency virus in a chronically infected promonocytic cell line by ultraviolet irradiation. *AIDS Res. hum. Retroviruses*, **5**, 375-384

Stefanini, M., Lagomarsini, P., Arlett, C.F., Marinoni, S., Borrone, C., Crovato, F., Trevisan, G. Cordone, G. & Nuzo, F. (1986) Xeroderma pigmentosum (complementation group D) mutation is present in patients affected by trichothiodystrophy with photosensitivity. *Hum. Genet.,* **74**, 107-112

Stein, B., Rahmsdorf, H.J., Steffen, A., Litfin, M. & Herrlich, P. (1989) UV-Induced DNA damage is an intermediate step in UV-induced expression of human immunodeficiency virus type 1, collagenase, *c-fos,* and metallothionein. *Mol. cell. Biol*., **9**, 5169-5181

Steinitz, R., Parkin, D.M., Young, J.L., Bieber, C.A. & Katz, L., eds (1989) *Cancer lncidence in Jewish Migrants to Israel, 1961-1981* (IARC Scientific Publications No. 98), Lyon, IARC, pp. 114-115, 134-135

Stenbäck, F. (1975a) Species-specific neoplastic progression by ultraviolet light on the skin of rats**,** guinea pigs, hamsters and mice. *Oncology,* **31**, 209-225

Stenbäck, F. (1975b) Studies on the modifying effect of ultraviolet radiation on chemical skin carcinogenesis. *J. invest. Dermatol*., **64**, 253-257

Stenbäck, F. (1975c) Ultraviolet light irradiation as initiating agent in skin tumor formation by the two-stage method. *Eur. J. Cancer,* **11**, 241-246

Stenbäck, F. (1978) Life history and histopathology of ultraviolet light-induced skin tumors. *Natl Cancer Inst. Monogr*., **50**, 57-70

Stenbäck, F. & Shubik, P. (1973) Carcinogen-induced skin tumorigenesis in mice: enhancement and inhibition by ultraviolet light. *Z. Krebsforsch*., **79**, 234-240

Sterenborg, H.J.C.M. & van der Leun, J.C. (1987) Action spectra for tumorigenesis by ultraviolet radiation. In: Passchier, W.E. & Bosnjakovic, B.F.M., eds, *Human Exposure to Ultraviolet Radiation: Risks and Regulations,* Amsterdam, Elsevier, pp. 173-191

Sterenborg, H.J.C.M. & van der Leun, J.C. (1988) Change in epidermal transmission due to UV-induced hyperplasia in hairless mice: a first approximation of the action spectrum. *Photo-dermatology*, **5**, 71-82

Sterenborg, H.J.C.M. & van der Leun, J.C. (1990) Tumorigenesis by a long wavelength UVA source. *Photochem. Photobiol*., **51**, 325-330

Sterenborg, H.J.C.M., de Gruijl, F.R. & van der Leun, J.C. (1986) UVA induced epidermal hyperplasia in hairless mice. *Photodermatology*, **3**, 206-214

Sterenborg, H.J.C.M., van der Putte, S.C.J. & van der Leun, J.C. (1988) The dose-response relation-ship of tumorigenesis by ultraviolet radiation of 254 nm. *Photochem. Photobiol*., **47**, 245-253

Sterenborg, H.J.C.M., de Gruijl, F.R., Kelfkens, G. & van der Leun, J.C. (1991) Evaluation of skin cancer risk resulting from long term occupational exposure to radiation from ultraviolet lasers in the range from 190 to 400 nm. *Photochem. Photobiol.,* **54**, 775-780

Stierner, U., Rosdahl, I., Augustsson, A. & Kågedal, B. (1989) UVB irradiation induces melanocyte increase in both exposed and shielded human skin. *J. invest. Dermatol*., **92**, 561-564

Stingl, L.A., Sauder, D.N., Iijima, M., Wolff, K., Pehamberger, H. & Stingl, G. (1983) Mechanism of UVB induced impairment of the antigen-presenting capacity of murine epidermal cells. *J. Immunol.,* **130**, 1586-1591

Streeter, P.R. & Fortner, G.W. (1988a) Immune response to ultraviolet-induced tumors. II. Effector cells in tumor immunity. *Transplantation,* **46**, 250-255

Streeter, P.R. & Fortner, G.W. (1988b) Immune response to ultraviolet induced tumors. III. Analysis of cloned lymphocyte populations exhibiting antitumor activity. *Transplantation*, **46**, 256-260

Streilein, J.W. & Bergstresser, PR. (1981) Langerhans cell function dictates induction of contact hypersensitivity or unresponsiveness to DNFB in Syrian hamsters. *J. invest* ***Dermatol.,*** **77,** 272-277

Streilein, J.W., Toews, G.T., Gilliam, J.N. & Bergstresser, P.R. (1980) Tolerance or hypersensitivity to 2,4-dinitro-1-fluorobenzene: the role of Langerhans cell density within epidermis. *J. invest. Dermatol.,* **74**, 319-322

Strickland, P.T. (1982) Tumor induction in Sencar mice in response to ultraviolet radiation. *Carcinogenesis*, **3**, 1487-1489

Strickland, P.T. (1986) Photocarcinogenesis by near-ultraviolet (UVA) radiation in Sencar mice. *J. invest. Dermatol.,* **87**, 272-275

Strickland, P.T., Burns, F.J. & Albert, R.E. (1979) Induction of skin tumors in the rat by single exposure to ultraviolet radiation. *Photochem. Photobiol*., **30**, 683-688

Strickland, P.T., Creasia, D. & Kripke, M.L. (1985) Enhancement of two-stage skin carcinogenesis by exposure of distant skin to UV radiation. *J. natl Cancer Inst.,* **74**, 1129-1134

Strickland, P.T., Bruze, M. & Creasey, J. (1988) Cyclobuta-dithymidine induction by solar-simulating UV radiation in human skin. I. Protection by constitutive pigmentation. *Photodermatology*, **5**, 166-169

Sundararaman, N., St John, D.E. & Venkateswaran, S.V. (1975) *Solar Ultraviolet Radiation Received at the Earth's Surface Under Clear and Cloudless Conditions,* Springfield, VA, National Technical Information Service

Sutherland, B.M., Harber, L.C. & Kochevar, I.E. (1980) Pyrimidine dimer formation and repair in human skin. *Cancer Res.,* **40**, 3181-3185

Sutherland, B.M., Delihas, N.C., Oliver, R.P. & Sutherland, J.C. (1981) Action spectra for ultraviolet light-induced transformation of human cells to anchorage-independent growth. *Cancer Res.,* **41**, 2211-2214

Sutherland, B.M., Freeman, A.G. & Bennett, P.V. (1988) Human cell transformation in the study of sunlight-induced cancers in the skin of man. *Mutat. Res*., **199**, 425-436

Suzuki, H., Fukuyama, K. & Epstein, W.L. (1977) Changes in nuclear DNA and RNA during epidermal keratinization. *Cell Tissue Res*., **184**, 155-167

Suzuki, F., Han, A., Lankas, G.R., Utsumi, H. & Elkind, M.M. (1981) Spectral dependencies of killing, mutation, and transformation in mammalian cells and their relevance to hazards caused by solar ultraviolet radiation. *Cancer Res.,* **41**, 4916-4924

Swerdlow, A.J. (1979) Incidence of malignant melanoma of the skin in England and Wales and its relationship to sunshine. *Br. med. J*., **ii**, 1324-1327

Swerdlow, A.J. (1983a) Epidemiology of melanoma of the eye in the Oxford region. 1952-78. *Br J. Cancer,* **47**, 311-313

Swerdlow, A.J. (1983b) Epidemiology of eye cancer in adults in England and Wales, 1962-77. *Am. J. Epidemiol.,* **118**, 294-300

Swerdlow, A.J. (1985) Seasonality of presentation of cutaneous melanoma, squamous cell cancer and basal cell cancer in the Oxford region. *Br J. Cancer,* **52**, 893-900

Swerdlow, A.J., English, J.S.C., MacKie, R.M., O'Doherty, C.J., Hunter, J.A.A., Clark, J. & Hole, D.J. (1988) Fluorescent lights, ultraviolet lamps, and risk of cutaneous melanoma. *Br. med. J*., **297**, 647-650

Sylvania (undated) *Germicidal and Short-wave Ultraviolet Radiation,* Danvers, MA, GTE Products Corporation

Szabó, G., Gerald, A.B., Pathak, M.A. & Fitzpatrick, TB. (1972) The ultrastructure of racial color differences in man. In: Riley, V., ed., *Pigmentation. Its Genesis and Biologic Control,* New York, Appleton-Century-Crofts, pp. 23-41

Szebeni, J. & Tollin, G. (1988) Some relationships between ultraviolet light and heme-protein-indueed peroxidative lipid breakdown in liposomes, as reflected by fluorescence changes: the effect of negative surface charge. *Photochem. Photobiol.,* **47**, 475-479

Takebe, H., Nishigori, C. & Satoh, Y. (1987) Genetics and skin cancer of xeroderma pigmentosum in Japan. *Jpn. J. Cancer Res. (Gann),* **78**, 1135-1143

Talve, L., Stenbäck, F. & Jansén, C.T. (1990) UVA irradiation increases the incidence of epithelial tumors in UVB-irradiated hairless mice. *Photodermatol. Photoimmunol Photomed.,* **7**, 109-115

Tamaki, K. & Iijima, M. (1989) The effect of ultraviolet B irradiation on delayed-type hypersensitivity, cytotoxic T Iymphocyte activity, and skin graft rejection. *Transplantation,* **47**, 372-376

Tan, E.M. & Stoughton, R.B. (1969) Ultraviolet light induced damage to deoxyribonucleic acid in human skin. *J. invest. Dermatol.,* **52**, 537-542

Taylor, H.R., West, S.K., Rosenthal, F.S., Muñoz, B., Newland, H.S., Abbey, H. & Emmett, E.A. (1988) Effect of ultraviolet radiation on cataract formation. *New Engl. J. Med*., **319**, 1429-1433

Taylor, H.R., West, S.K., Rosenthal, F.S., Muñoz, B., Newland, H.S. & Emmett, E.A. (1989) Corneal changes associated with chronic UV irradiation. *Arch. Ophthalmol.,* **107**, 1481-1484

Teppo, L., Pakkanen, M. & Hakulinen, T. (1978) Sunlight as a risk factor of malignant melanoma of the skin. *Cancer,* **41**, 2018-2027

Teppo, L., Pukkala, E., Hakama, M., Hakulinen, T. Herva, A. & Saxen, E. (1980) Way of life and cancer incidence in Finland. A municipality-based ecological analysis. *Scand. J. soc. Med.,* **Suppl. 19,** 5-84

Tessman, I. & Kennedy, M.A. (1991) The two-step model of UV mutagenesis reassessed: deamination of cytosine in cyclobutane dimers as the likely source of the mutations associated with photoreactivation. *Mol. gen. Genet.,* **227**, 144-148

Thiers, B.H., Maize, J.C., Spicer, S.S. & Cantor, A.B. (1984) The effect of aging and chronic sun exposure on human Langerhans cell population. J. *invest. Dermutol.,* **82**, 223-226

Tjernlund, U. & Juhlin, L. (1982) Effect of UV radiation on immunological and histochemical markers of Langerhans cells in normal appearing skin of psoriatic patients. *Acta dermatol.,* **272**, 171-176

Tlsty, T.D., Brown, P.C. & Schimke, R.T. (1984) UV radiation facilitates methotrexate resistance and amplification of the dihydrofolate reductase gene in cultured 3T6 mouse cells. *Mol. cell. Biol.,* **4**, 1050-1056

Toda, K.-I., Miyachi, Y., Nesumi, N., Konishi, J. & Imamura, S. (1986) UVB/PUVA-induced suppression of human natural killer activity is reduced by superoxide dismutase and/or interleukin 2 *in vitro. J. invest. Dermatol*., **86**, 519-522

Toews, G.B., Bergstresser, P.R. & Streilein, J.W. (1980) Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. *J. Immunol.,* **124**, 445-453

Tominaga, A., Lefort, S., Mizel, S.B., Dambrauskas, J.T, Granstein, R., Lowy, A., Benacerraf, B. & Greene, M.I. (1983) Molecular signals in antigen presentation. I. Effects of interleukin 1 and on radiation-treated antigen-presenting cells *in vivo* and *in vitro. Clin. Immunol. Immunopathol,* 29, 282-293

Trosko, J.E. & Brewen, J.G. (1967) Inhibition of ultraviolet-induced chromosome breaks by cysteamine in 5-bromouracil-substituted mammalian cells. *Radiat. Res.,* **32**, 200-213

Tucker, M.A., Boice, J.D., Jr & Hoffman, D.A. (1985a) Second cancer following cutaneous melanoma and cancers of the brain, thyroid, connective tissue, bone and eye in Connecticut, 1935-82. *Natl Cancer Inst. Monogr*., **68**, 161-189

Tucker, M.A., Shields, J.A., Hartge, P., Augsberger, J., Hoover, R.N. & Fraumeni, J.F., Jr (1985b) Sunlight exposure as risk factor for intraocular malignant melanoma. *New Engl. J. Med.,* **313**, 789-792

Turner, B.J., Siatkowski, R.M., Augsburger, J.J., Shields, J.A., Lustbader, E. & Mastrangelo, M.J. (1989) Other cancers in uveal melanoma patients and their families. *Am. J. Ophthalmol.,* **107**, 601-608

Tuveson, R.W. & Sammartano, L.J. (1986) Sensitivity of *HemA* mutant *Escherichia coli* cells to inactivation by near-UV light depends on the level of supplementation with 8-aminolevulinic acid. *Photochem. Photobiol.,* **43**, 621-626

Tyrrell, R.M. (1973) Induction of pyrimidine dimers in bacterial DNA by 365 nm radiation. *Photochem. Photobiol.,* **17**, 69-73

Tyrrell, R.M. (1982) Cell inactivation and mutagenesis by solar ultraviolet radiation. In: Helene, C., Charlier, M., Montenay-Garestier, T. & Laustriat, O., eds, *Trends in Photobiology,* New York, Plenum, pp. 155-172

Tyrrell, R.M. (1984) Mutagenic action of monochromatic UV radiation in the solar range on human cells. *Mutat. Res.,* **129**, 103-110

Tyrrell, R.M. (1985) A common pathway for protection of bacteria against damage by solar UVA (334 nm, 365 nm) and an oxidising agent (H_2O_2). *Mutat. Res.,* **145**, 129-136

Tyrrell, R.M. (1991) UVA (320-280 nm) radiation as an oxidative stress. In: Sir, H., ed., *Oxidative Stress: Oxidants and Antioxidants,* London, Academic Press, pp. 57-83

Tyrrell, R.M. & Pidoux, M. (1986) Endogenous glutathione protects human skin fibroblasts against the cytotoxic action of UVB, UVA and near-visible radiations. *Photochem. Photobiol.,* **44**, 561-564

Tyrrell, R.M. & Pidoux, M. (1988) Correlation between endogenous glutathione content and sensitivity of cultured human skin cells to radiation at defined wavelengths in the solar ultraviolet range. *Photochem. Photobiol.,* **47**, 405-412

Tyrrell, R.M. & Pidoux, M. (1989) Singlet oxygen involvement in the inactivation of cultured human fibroblasts by UVA (334 nm, 365 nm) and near visible (405 nm) radiations. *Photochem. Photobiol.,* **49**, 407-412

Tyrrell, R.M., Ley, R.D. & Webb, R.B. (1974) Induction of single-strand breaks (alkali-labile bonds) in bacterial and phage DNA by near UV (365 nm) radiation. *Photochem. Photobiol.,* **20**, 395-398

Ullrich, S.E. (1985) Suppression of lymphoproliferation by hapten-specific suppressor T lymphocytes from mice exposed to ultraviolet radiation. *Immunology,* **54**, 343-352

Ullrich, S.E. (1986) Suppression of the immune response to allogeneic histocompatibility antigens by a single exposure to ultraviolet radiation. *Transplantation,* **42**, 287-291

Ullrich, S.E. (1987) The effect of ultraviolet radiation-induced suppressor cells on T-cell activity. *Immunology*, **60**, 353-360

Ullrich, S.E. & Kripke, M.L. (1984) Mechanisms in the suppression of tumor rejection produced in mice by repeated UV radiation. *J. Immunol.,* **133**, 2786-2790

Ullrich, S.E., Yee, G.K. & Kripke, M.L. (1986a) Suppressor lymphocytes induced by epicutaneous sensitization of UV-irradiated mice control multiple immunological pathways. *Immunology*, **58**, 185-190

Ullrich, S.E., Azizi, E. & Kripke, M.L. (1986b) Suppression of the induction of delayed-type hypersensitivity reactions in mice by a single exposure to ultraviolet radiation. *Photochem. Photobiol.,* **43**, 633-638

Ultra-Violet Products, Inc. (1977) *Laboratory Applications for Ultraviolet Equipment,* San Gabriel, CA

United Kingdom Stratospheric Ozone Review Group (1991) *Stratospheric Ozone 1991,* London, Her Majesty's Stationery Office

United Nations Environment Programme (1989) *Environmental Effects Panel Report,* Geneva

Unrau, P., Wheatcroft, R., Cox, B. & Olive, T. (1973) The formation of pyrimidine dimers in the DNA of fungi and bacteria. *Biochim. biophys. Acta,* **312**, 626-632

Urbach, F., Davies, R.E. & Forbes, P.D. (1966) Ultraviolet radiation and skin cancer in man. In: Montagna, W. & Dobson, R.L., eds, *Advances in Biology of Skin,* Vol. VII, *Carcinogenesis,* Oxford, Pergamon Press, pp. 195-214

Urbach, F., Epstein, J.H. & Forbes, P.D. (1974) Ultraviolet carcinogenesis: experimental, global and genetic aspects. In: Pathak, M.A., Harber, L.C., Seiji, M. & Kukita, A., eds, *Sunlight and Man. Normal and Abnormal Photobiologic Responses,* Tokyo, University of Tokyo Press, pp. 259-283

Vågerö, D., Ringbäck, G. & Kiviranta, H. (1986) Melanoma and other tumours of the skin among office, other indoor and outdoor workers in Sweden 1961-1979. *Br J. Cancer*, **53**, 507-512

Vågerö, D., Swerdlow, A.J. & Beral, V. (1990) Occupation and malignant melanoma: a study based on cancer registration data in England and Wales and in Sweden. *Br. J. inc. Med*., **47**, 317-324

Valerie, K. & Rosenberg, M. (1990) Chromatin structure implicated in activation of HIV-1 gene expression by ultraviolet light. *New Biol*., **2**, 712-718

Valerie, K., Delers, A., Bruck, C., Thiriart, C., Rosenberg, H., Debouck, C. & Rosenberg, M. (1988) Activation of human immunodeficiency virus type 1 by DNA damage in human cells. *Nature*, **333**, 78-81

Varghese, A.J. & Patrick, M.H. (1969) Cytosine derived heteroadduct formation in ultraviolet-irradiated DNA. *Nature,* **223**, 299-300

Varghese, A.J. & Wang, S.Y. (1967) Ultraviolet irradiation of DNA *in vitro* and *in vivo* produces a third thymine-derived product. *Science*, **156**, 955-957

van't Veer, L.J., Burgering, B.M.T., Versteeg, R., Boot, A.J..M., Ruiter, D.J., Osanto, S., Schrier, P.I. & Bos, J.L. (1989) N-*ras* Mutations in human cutaneous melanoma from sun-exposed body sites. *Mol. cell. Biol*., **9**, 3114-3116

Verma, A.K., Lowe, N.J. & Boutwell, R.K. (1979) Induction of mouse epidermal ornithine decarboxylase activity and DNA synthesis by ultraviolet light. *Cancer Res*., **39**, 1035-1040

Vermeer, M., Schmieder, G.J., Yoshikawa, T., van den Berg, J.-W., Metzman, M.S., Taylor, J.R. & Streilein, J.W. (1991) Effects of ultraviolet B light on cutaneous immune responses of humans with deeply pigmented skin. *J. invest. Dermatol*., **97**, 729-734

Vitaliano, PR (1978) The use of logistic regression for modelling risk factors: with application to nonmelanoma skin cancer. *Am. J. Epidemiol.,* 108, 402-414

Vitasa, B.C., Taylor, H.R., Strickland, P.T., Rosenthal, F.S., West, S., Abbey, H., Ng, S.K, Munoz, B. & Emmett, E.A. (1990) Association of nonmelanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Maryland watermen. *Cancer,* **65**, 2811-2817

Vlček, D., Podstavkova, S., Miadokova, E., Adams, G.M.W. & Small, G.D. (1987) General characteristics, molecular and genetic analysis of two new UV-sensitive mutants of *Chlamydomonas reinhardtii. Mutat. Res.,* **183**, 169-175

Vogel, J., Cepeda, M., Tschachler, E., Napolitano, L.A. & Jay, G. (1992) UV activation of human immunodeficiency virus gene expression in transgenic mice. *J. Virol.,* **66**, 1-5

Vuillaume, M., Daya-Grosjean, L., Vincens, P. Pennetier, J.L., Tarroux, P. Baret, A., Calvayrac, R., Taieb, A. & Sarasin, A. (1992) Striking differences in cellular catalase activity between two DNA repair-deficient diseases: xeroderma pigmentosum and trichothiodystrophy. *Carcinogenesis,* **13**, 321-328

Walker, G.C. (1984) Mutagenesis and inducible responses to deoxyribonucleic acid damage in *Escherichia coli. Microbiol. Rev*., **48**, 60-93

Walter, S.D., Marrett, L.D., From, L., Hertzman, C., Shannon, H.S. & Roy, P. (1990) The association of cutaneous malignant melanoma with the use of sunbeds and sunlamps. *Am. J. Epidemiol,* **131**, 232-243

Walter, S.D., Marrett, L.D., Shannon, H.S., From, L. & Hertzman, C. (1992) The association of cutaneous malignant melanoma and fluorescent light exposure. *Am. J. Epidemiol.,* **135**, 749-762

Wang, S.-Y. & Varghese, A.J. (1967) Cytosine-thymine addition product from DNA irradiated with ultraviolet light. *Biochem. biophys. Res. Commun.,* **29**, 543-549

Waterhouse, J., Muir, C., Correa, P. & Powell, J., eds (1976) *Cancer Incidence in Five Continents, Vol.* III (IARC Scientific Publications No. 15). Lyon, IARC

Waterhouse, J., Muir, C., Shanmugaratnam, K. & Powell, J., eds (1982) *Cancer Incidence in Five Continents, Vol. IV* (IARC Scientific Publications No. 42), Lyon. IARC

Weast, R.C., ed. (1989) *CRC Handbook of Chemistry and Physics,* 70th ed., Boca Raton, FL, CRC Press, p. E-209

Webb, R.B. (1977) Lethal and mutagenic effects of near-ultraviolet radiation. *Photochem. Photobiol. Rev.,* **2**, 169-261

Webb, R.B. & Malina, M.M. (1970) Mutagenic effects of near ultraviolet and visible radiant energy on continuous cultures of *Escherichia coli. Photochem. Photobiol*., **12**, 457-468

van Weelden, H. & van der Leun, J.C. (1986) Photorecovery by UVA. In: Urbach. F. & Gange. R.W., eds, *The Biological Effects of UVA Radiation,* New York, Praeger, pp. 147-155

van Weelden, H., de Gruijl, F.R. & van der Leun, J.C. (1986) Carcinogenesis by UVA, with an attempt to assess the carcinogenic risks of tanning with UVA and UVB. In: Urbach, F. & Gange, R.W., eds, *The Biological Effects of WA Radiation,* New York, Praeger, pp. 137-146

van Weelden, H., de Gruijl, F.R., van der Putte, S.C.J., Toonstra, J. & van der Leun, J.C. (1988) The carcinogenic risks of modern tanning equipment: is UVA safer than UVB? *Arch. dermatol. Res.,* 280, 300-307

van Weelden, H., van der Putte, S.C.J., Toonstra, J. & van der Leun, J.C. (1990a) UVA-lnduced tumours in pigmented hairless mice and the carcinogenic risks of tanning with UVA. *Arch. dermatol. Res.,* **282**, 289-294

van Weelden, H., van der Putte, S.C.J., Toonstra, J. & van der Leun, J.C. (1990b) Ultraviolet B-induced tumors in pigmented hairless mice, with an unsuccessful attempt to induce cutaneous melanoma. *Photodermatol. Photoimmunol. Photomed*., **7**, 68-72

Weinstock, M.A., Colditz, G.A., Willett, W.C., Stampfer, M..J., Bronstein, B.R., Mihm, M.C., Jr & Speizer, F.E. (1989) Nonfamilial cutaneous melanoma incidence in women associated with sun exposure before 20 years of age. *Pediatrics,* **84**, 199-204

Weinstock, M.A., Colditz, G.A., Willett, W.C., Stampfer, M.J., Bronstein, B.R., Mihm, M.C., Jr & Speizer, F.E. (1991a) Melanoma and the sun: the effect of swimsuits and a 'healthy' ten on the risk of nonfamilial malignant melanoma in women. *Am. J. Epidemiol.,* **134**, 462-470

Weinstock, M.A., Stryker, W.S., Stampfer, M.J., Lew, R.A., Willett, W.C. & Sober, A.J. (1991b) Sunlight and dysplastic nevus risk. Results of a clinic-based case-control study. *Cancer*, **67,** 1701-1706

Weiss, J., Garbe, C., Bertz, J., Biltz, H., Burg, G., Hennes, B., Jung, E.G., Kreysel, H.-W., Orfanos, C.E., Petzold, D., Schwermann, M., Stadler, R., Tilgen, W., Tronnier, H. & Volkers, W. (1990) Risk factors for the development of malignant melanoma in Germany (Ger.). *Hautartz,* **41**, 309-313

Wells, R.L. & Han, A. (1984) Action spectra for killing and mutation of Chinese hamster cells exposed to mid- and near-ultraviolet monochromatic light. *Mutat. Res.,* **129**, 251-258

Welsh, E.A. & Kripke, M.L. (1990) Murine Thy-1^+ dendritic epidermal cells induce immunologic tolerance *in vivo. J. Immunol.,* **144**, 883-891

West, S.K., Rosenthal, F.S., Bressler, N.M., Bressler, S.B., Munoz, B., Fine, S.L. & Taylor, H.R. (1989) Exposure to sunlight and other risk factors for age-related macular degeneration. *Arch. ophthalmol,* **107**, 875-879

Wheatcroft, R., Cox, B.S. & Haynes, R.H. (1975) Repair of UV-induced damage and survival in yeast. 1.Dimer excision. *Mutat. Res.,* 30, 209-218

Wheeler, C.E., Jr (1975) Pathogenesis of recurrent herpes simplex infections. *J. invest. Dermatol.,* **65**, 341-346

Whelan, S.L., Parkin, D.M. & Masuyer, E., eds (1990) *Patterns of Cancer in Five Continents* (IARC Scientific Publications No. 102), Lyon, IARC, p. 29

Whitaker, C.J., Lee, W.R. & Downes, J.E. (1979) Squamous cell skin cancer in the north-west of England, 1967-69, and its relation to occupation. *Br. J. ind. Med.,* **36**, 43-51

WHO (1977) *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. International Classification of Diseases,* 1975 rev., Vol. 1, Geneva, p. 102

WHO (1979) *Ultraviolet Radiation* (Environmental Health Criteria 14), Geneva

Willis, I., Menter, J.M. & Whyte, H.J. (1981) The rapid induction of cancers in the hairless mouse utilizing the principle of photoaugmentation. J. *invest. Dermatol.,* **76**, 404-408

Willis, I., Menter, J.M., de Fabo, E., Margolin, R. & Fisher, M. (1986) Photoaugmentation of UVB effects by UVA. In: Urbach, F. & Gange, R.W., eds, *The Biological Effects of UVA Radiation,* New York, Praeger, pp. 187-201

Winkelmann, R.K., Baldes, E.J. & Zollman, P.K. (1960) Squamous cell tumors induced in hairless mice with ultraviolet light. *J. invest. Dermatol.,* **34**, 131-138

Winkelmann, R.K., Zollman, P.E. & Baldes, E.J. (1963) Squamous cell carcinoma produced by ultraviolet light in hairless mice. *J. invest. Dermatol.,* **40**, 217-224

Wiskemann, A., Sturm, E. & Klehr, N.W. (1986) Fluorescent lighting enhances chemically induced papilloma formation and increases susceptibility to tumor challenge in mice. *J. Cancer Res. clin. Oncol.,* **112**, 141-143

Withrow, T.J., Lugo, M.H. & Dempsey, M.J. (1980) Transformation of Balb 3T3 cells exposed to a germicidal UV lamp and a sunlamp. *Photochem. Photobiol.,* **31**, 135-141

Witkin, E.M. (1976) Ultraviolet mutagenesis and inducible DNA repair in *Escherichia coli. Bactenol. Rev.,* **40**, 869-907

Wittenberg, S. (1986) Solar radiation and the eye: a review of knowledge relevant to eye care. *Am. J. Optom. physiol. Opt.,* **63**, 676-689

Wolf, C., Steiner, A. & Hönigsmann, H. (1988) Do oral carotenoids protect human skin against ultraviolet erythema, psoralen phototoxicity, and ultraviolet-induced DNA damage? J. *invest. Dermatol.,* **90**, 55-57

Wood, R.D., Skopek, TR. & Hutchinson, F. (1984) Changes in DNA base sequence induced by targeted mutagenesis of lambda phage by ultraviolet light. *J. mol. Biol.,* **173**, 273-291

Wulff, D.L. & Fraenkel, G. (1961) On the nature of thymine photoproduct. *Biochim. biophys. Acta,* **51***,* 332-339

Yang, X.-Y., Ronai, Z.A., Santella, R.M. & Weinstein, I.B. (1988) Effect of 8-methoxypsoralen and ultraviolet light A on EGF receptor (HER-1) expression. *Biochem. biophys. Res.* ***Commun.,*** **157,** 590-596

Yasumoto, S., Hayashi, Y. & Aurelian, L. (1987) Immunity to herpes simplex virus type 2. Suppression of virus-induced immune responses in ultraviolet B -irradiated mice. *J. Immunol.,* **139**, 2788-2793

Yoshikawa, J., Rae, V, Bruins-Slot, W., Van den Berg, J.-W., Taylor, J.R. & Streilein, J.W. (1990) Susceptibility to effects of UVB radiation on induction of contact hypersensitivity as a risk factor for skin cancer in humans. *J. invest. Dermatol.,* **95**, 530-536

Young, R.W. (1988) Solar radiation and age-related macular degeneration. *Surv. Ophthalmol.,* **32**, 252-269

Young, M. & Russell, W.T (1926) *An Investigation into the Statistics of Cancer in Different Trades and Professions* (Medical Research Council Special Report No. 99), London, Her Majesty's Stationery Office

Young, A.R., Walker, S.L., Kinley, J.S., Plastow, S.R., Averbeck, D., Morliere, P. & Dubertret, L. (1990) Phototumorigenesis studies of 5-methoxypsoralen in bergamot oil: evaluation and modification of risk of human use in an albino mouse skin model. *J. Photochem. Photobiol. B. Biol.,* **7**, 231-250

Zanetti, R., Rosso, S., Faggiano, F., Roffino, R., Colonna, S. & Martina, G. (1988) A case-control study on cutaneous malignant melanoma in the province of Torino, Italy (Fr.). *Rev. Epidemiol Sante publ,* **36**, 309-317

Zelle, B., Reynolds, R.J., Kottenhagen, M.J., Schuite, A. & Lohman, PH.M. (1980)The influence of the wavelength of ultraviolet radiation on survival, mutation induction and DNA repair in irradiated Chinese hamster cells. *Mutat. Res.,* **72**, 491-509

Zigman, S. & Vaughan, T. (1974) Near-ultraviolet light effects on the lenses and retinas of mice. *Invest. Ophthalmol*., **13**, 462-465

Zigman, S., Yulo, T. & Schultz, J. (1974) Cataract induction in mice exposed to near UV light. *Ophthal. Res.,* **6**, 259-270

Zigman, S., Fowler, E. & Kraus, A.L. (1976) Black light induction of skin tumors in mice. *J. invest. Dermatol.,* **67**, 723-725

Zmudzka, B.Z. & Beer, J.Z. (1990) Activation of human immunodeficiency virus by ultraviolet radiation. *Photochem. Photobiol.,* **52**, 1153-1162

Zölzer, F. & Kiefer, J. (1983) Wavelength dependence of inactivation and mutagenesis in haploid yeast cells of diffcrcnt sensitivities. *Photochem. Photobiol.,* **37**, 39-48

Zölzer, F. & Kiefer, J. (1984) Wavelength dependence of inactivation and mutation induction to 6-thioguanine-resistance in V79 Chinese hamster fibroblasts. *Photochem. Photobiol.,* **40**, 49-53

Zölzer, F., Kiefer, J. & Rase, S. (1988) Inactivation and mutation induction to 6-thioguanine resistance in V79 hamster fibroblasts by simulated sunlight. *Photochem. Photobiol.,* **47**, 399-404

Appendix B: Profile for Solar Radiation and Exposure to Sunlamps and Sunbeds. Report on Carcinogens, Ninth Edition (2000)

SOLAR RADIATION AND EXPOSURE TO SUNLAMPS OR SUNBEDS
First listed in the *Ninth Report on Carcinogens

CARCINOGENICITY

Solar radiation is *known to be a human carcinogen*, based on sufficient evidence of carcinogenicity from studies in humans, which indicate a causal relationship between exposure to solar radiation and cutaneous malignant melanoma and non-melanocytic skin cancer. Some studies suggest that solar radiation may also be associated with melanoma of the eye and non-Hodgkin's lymphoma (reviewed in IARC V.55, 1992).

Exposure to sunlamps or sunbeds is *known to be a human carcinogen*, based on sufficient evidence of carcinogenicity from studies in humans, which indicate a causal relationship between exposure to sunlamps or sunbeds and human cancer. Epidemiological studies have shown that exposure to sunlamps or sunbeds is associated with cutaneous malignant melanoma (Swerdlow et al., 1988; Walter et al., 1990; Autier et al., 1994; Westerdahl et al., 1994). Exposure-response relationships were observed for increasing duration of exposure, and effects were especially pronounced in individuals under 30 and those who experienced sunburn. Malignant melanoma of the eye is also associated with use of sunlamps. In contrast, there is little support for an association of exposure to sunlamps or sunbeds with non-melanocytic skin cancer (IARC V.55, 1992).

The evidence that solar radiation and exposure to sunlamps or sunbeds are human carcinogens is supported by experimental studies in laboratory animals, and studies demonstrating UV-induced DNA damage in human and animal cells. Sunlamps and sunbeds emit radiation primarily in the ultraviolet A (UVA) and ultraviolet B (UVB) portion of the spectrum. Numerous studies have shown that simulated solar radiation, broad spectrum UV radiation, UVA radiation, UVB radiation, and UVC radiation are carcinogenic in experimental animals. There is evidence for benign and malignant skin tumors and for tumors of the cornea and conjunctiva in mice, rats, and hamsters. UV radiation also causes a wide spectrum of DNA damage resulting in mutations and other genetic alterations in a variety of *in vitro* and *in vivo* assays for genotoxicity, including assays using human skin cells (IARC V.55, 1992).

PROPERTIES

Solar radiation from the sun includes most of the electromagnetic spectrum (IARC V.55, 1992). Of the bands within the optical radiation spectrum, UV light is the most energetic and biologically damaging. UV light is divided into UVA, UVB, and UVC. UVA is the most abundant of the three, representing 95% of the solar UV energy to hit the equator, and UVB represents the other 5%. The short wavelength UVC rays are

* there is no separate CAS registry number assigned to solar radiation and exposure to sunlamps or sunbeds.

absorbed by ozone, molecular oxygen, and water vapor in the upper atmosphere so that measurable amounts from solar radiation do not reach the earth's surface (Farmer and Naylor, 1996).

Molecules that absorb UV and visible light contain moieties called chromophoric groups in which electrons are excited from the ground state to higher energy states. In returning to lower energy or ground states, the molecules generally re-emit light (Dyer, 1965). Molecules sensitive to UV light absorb and emit UV light at characteristic maximum wavelengths (λ), often expressed as λ_{max}.

> Photochemical and photobiological interactions occur when photons of optical radiation react with a photoreactive molecule, resulting in either a photochemically altered molecule or two dissociated molecules (Phillips, 1983; Smith, 1989; both cited by IARC V.55, 1992). To alter molecules, a sufficient amount of energy is required to alter a photoreactive chemical bond (breaking the original bond and/or forming new bonds).

UVB is considered to be the major cause of skin cancer despite its not penetrating the skin as deeply as UVA or reacting with the epidermis as vigorously as UVC. UVB's reactivity with macromolecules combined with depth of penetration make it the biologically most potent portion of the UV spectrum, with respect to short-term and long-term effects. UVA, while possibly not as dangerous, also induces biological damage (Farmer and Naylor, 1996).

> Photobiological reactions of concern for skin cancer risk due to UV light exposure are the reactions with the main chromophores of the epidermis—urocanic acid, DNA, tryptophan, tyrosine and the melanins. DNA photoproducts include pyrimidine dimers, pyrimidine-pyrimidone (6-4) photoproducts, thymine glycols, and DNA exhibiting cytosine and purine damage and other damage such as DNA strand breaks and cross-links and DNA-protein cross-links. The different DNA photoproducts have varying mutagenic potential (IARC V.55, 1992).
>
> UV-induced DNA photoproducts produce a variety of cellular responses that contribute to skin cancer. Unrepaired DNA photoproducts may result in the release of cytokines that contribute to tumor promotion, tumor progression, immunosuppression, and the induction of latent viruses (Yarosh and Kripke, 1996; IARC V.55, 1992).

USE

Aside from the many benefits of sunlight/solar radiation, artificial sources of UVR are used for cosmetic tanning, promotion of polymerization reactions, laboratory and medical diagnostic practices and phototherapy, and numerous other applications (IARC V.55, 1992).

SOURCES

Ultraviolet light is naturally emitted by the sun and artificially from lamps such as tungsten-halogen lamps, gas discharge, arc, fluorescent, metal halide, and electrodeless lamps (IARC V.55, 1992) and lasers such as the 308-nm XeCl (xenon chloride) excimer and the 193-nm ArF (argon fluoride) excimer (Sterenborg et al., 1991).

The use of sunlamps and tanning beds is as a cosmetic source. The latter chiefly emit UVA (315-400 nm) although certain lamps that emitted considerable UVB and UVC radiation were more common before the mid-1970s (IARC V.55, 1992). However, UVB produces a better tan than UVA and recently, at least in the United States and United Kingdom, use of sunlamps with more UVB radiation has become widespread (Wright et al., 1997; cited by Swerdlow and Weinstock, 1998). Low-pressure mercury vapor lamps, sunlamps, and black-light lamps are considered to be low-intensity UV sources. High-intensity UV sources include high-pressure mercury vapor lamps, high-pressure xenon arcs, xenon-mercury arcs, plasma torches, and welding arcs. Three different UVA phosphors have been used in sunlamps sold in the United States over the past 20 years, producing emission spectra that peak at 340 nm, 350 nm, or 366 nm. Two modern U.S. sunlamps evaluated by the FDA emitted 99.0% and 95.7% UVA and the rest UVB radiation (<320 nm). A new high-pressure UVA sunbed with eighteen 1600-W filtered arc lamps emitted 99.9% UVA. An older-type sunlamp used more than 20 years ago (UVB/FS type) emitted 48.7% UVA (Miller et al., 1998).

EXPOSURE

The greatest source of human exposure to UVR is solar radiation; however, the exposure varies with the geographical location. With decreasing latitude or increasing altitude, there is greater exposure; for every 1000 feet above sea level, a 4% compounded increase in UVR exists. Decreases in the stratospheric ozone caused by chemicals generating free radicals increase UVR exposure. Heat, wind, humidity, pollutants, cloud cover, snow, season, and the time of day also affect UVR exposure (Consensus Development Panel, 1991).

Although use of sunscreen is known to protect from skin damage induced by UVR, sunscreen use has not become habitual by a large fraction of the U.S. population. For example, Newman et al. (1996) surveyed a random sample of persons in San Diego, a location with one of the highest incidences of skin cancer in the United States. Sunscreen was used only about 50% of the time on both face and body by tanners, about 40% of the time on the face, and 30% of the time on the body.

Most bulbs sold in the United States for use in sunbeds emit “substantial doses of both UVB and UVA” (Swerdlow and Weinstock, 1998, citing “personal communication from industry sources”). Many of the home and salon devices in the 1980s emitted both

UVA and UVB radiation, but current devices emit predominantly UVA (FTC, 1997; Sikes, 1998).

FDA scientists calculated that commonly used fluorescent sunlamps would deliver 0.3 to 1.2 times the annual UVA dose from the sun to a typical tanner requiring 20 sessions at 2 minimal erythemal doses (MED) per session. The common sunlamps would deliver to a frequent tanner (100 sessions at 4 MED/session) 1.2 to 4.7 times the UVA received annually from solar radiation. The frequent tanner would receive 12 times the annual UVA from solar radiation from the recently available high-pressure sunlamps (Miller et al., 1998).

> In 1987, an American Academy of Dermatology (AAD) survey found that, although 96% of the U.S. population surveyed knew that sun exposure causes cancer, one-third of the adults responding develop tans. By 1987, the indoor tanning industry was one of the fastest growing in the United States (Sikes, 1998). Surveys of U.S. telephone book Yellow Pages found 11,000 indoor tanning facilities in 1986 and more than 18,000 facilities in 1988. About 11% of women and 6% of men were frequent patrons (Research Studies-SIS, 1989). New York State alone was estimated to have 1300 commercial tanning facilities in 1993 (Lillquist et al., 1994). By 1995, indoor tanning facilities were a $1 billion industry serving 1 million patrons a day (Guttman, 1995). About 1 to 2 million patrons visit tanning facilities as often as 100 times per year (Sikes, 1998).

A 1990 survey of 1,564 holders of drivers' licenses residing in New York State outside of the New York City area, who were aged 17 to 74 years, were white, and had never had skin cancer, found that 21.5% of the respondents had ever used sun lamps (28.1% among those 16 to 24 years old) but that only 2.3% used sun lamps at least once a month. Ever users were more likely to be women, younger, and never married or divorced or separated (Lillquist et al., 1994). Surveys in the early 1990s of adolescents who had ever used tanning devices have found about twice as many girls as boys among the users (33% vs. 16% and 18.5% vs. 7.4%) (Banks et al., 1992; Mermelstein and Riesenberg, 1992; both cited by Lillquist et al., 1994).

Up to 25 million persons per year in North America are currently estimated to use sunbeds. Teenagers and young adults are prominent among users. A study of high school students in St. Paul, Minnesota, found that 34% had used commercial sunbeds at least 4 times in the past year. Fifty-nine percent of the users reported some skin injury. A 1995 U.S. survey found that commercial tanning salon patrons included 8% aged 16 to 19 years and 42% aged 20 to 29 years; 71% were female (Hurt and Freeman, undated; cited by Swerdlow and Weinstock, 1998).

Wisconsin dermatologists, ophthalmologists, and emergency room personnel reported treating 372 patients with ocular and/or dermal injuries from artificial tanning devices in a 12-month survey ca. 1990. Of these patients, 53% to 65% were exposed to tanning beds or booths and 17 to 35% were exposed to reflector bulb lamps. In the group of 155 emergency room patients with first or second degree skin burns from artificial

tanning, 58% were burned at tanning salons and 37% were burned at home (Garrett, 1990). Although FDA has mandated rules that require that tanning equipment labeling warn about overexposure, skin cancer, possible premature skin aging, and photosensitivity with certain cosmetics and medications, a Public Interest Research Group survey of 100 tanning salons in 8 states and the District of Columbia found 183 tanning devices without the required warnings (Cosmetic Insiders' Report, 1991). Sikes (1998) stated, without attribution, that tanning devices caused 1,800 reported injuries in 1991, mostly in persons aged 15 to 24 years old. A survey of 31 tanning salons in 1989 in the greater Lansing, Michigan, area, population 450,000, found that 87% of the facilities offered their clients "tanning accelerators." Respondents of five establishments stated that their tanning accelerators contained psoralens, but this could not be confirmed (Beyth et al., 1991).

> Workers in many occupations, e.g., agricultural, construction, and road work laborers, spend a large component of their work day outdoors. Outdoor workers, therefore, are the largest occupational group exposed to solar UVR. Occupational exposure to artificial UVR occurs in industrial photo processes, principally UV curing of polymer inks, coatings, and circuit board photoresists; sterilization and disinfection; quality assurance in the food industry; medical and dental practices; and welding. Welders are the largest occupational group with artificial UVR exposure. However, only arc welding processes produce significant levels of UVR. UVR from welding operations is produced in broad bands whose intensities depend on factors such as electrode material, discharge current, and gases surrounding the arc (NIOSHa, 1972). [OSHA regulations require many protective measures to reduce UVR exposure of workers engaged in or working in the vicinity of arc welding operations.]

A study conducted on laboratory UV lasers such as those used in cornea shaping and coronary angioplasty showed that the relative risk may increase to a level comparable to that of individuals with an outdoor profession (Sterenborg et al., 1991).

Applying a mathematical power model based on human data, Lytle et al. (1992) suggested that there is an increased risk of squamous cell carcinoma (SCC) from exposure to UV-emitting fluorescent lamps. The estimates of annual incidence of new SCC, for indoor workers exposed to UV light, indicated that an exposure to typical fluorescent lighting (unfiltered by a clear acrylic prismatic diffuser) may add 3.9% (1.6%-12%) to the potential risk from solar UVR, thus resulting in an induction of an additional 1500 (600-4500) SCC per year in the United States. There is a small increased risk of SCC from exposure to UV-emitting fluorescent lamps, when compared to 110,000 SCC caused by solar exposure.

NIOSHa (1972) estimated that 211,000 workers in the manufacturing industries (Standard Industrial Codes [SICs] 19-39) were exposed to UVR; 49,000, in the transportation and communication industries (SICs 40-49); 17,000, in the wholesale, miscellaneous retail, and service stations categories (SICs 50, 59, 55); and 41,000, in the

services industries (SICs 70-89). The sources considered were arc welding, air purifiers, and sanitizers.

REGULATIONS

The U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) have promulgated regulations concerning sunlamp products and UV lamps intended for use in sunlamp products. Manufacturers must notify CDRH of product defects and repair and replacement of defects. CDRH issues written notices and warnings in cases of noncompliance. Several performance requirements must be met by sunlamp products (21 CFR 1040.20), including irradiance ratio limits, a timer system, protective eyewear to be worn during product use, compatibility of lamps, and specific labels. The label should include the statement "DANGER—Ultraviolet radiation" and warn of the dangers of exposure and overexposure.

OSHA requires extensive UVR protective measures of employees engaged in or working adjacent to arc welding processes. Arc welding emits broad spectrum UVR. Workers should be protected from the UVR by screening, shields, or goggles. Employees in the vicinity of arc welding and cutting operations should be separated from them by shields, screens, curtains, or goggles. If possible, welders should be enclosed in individual booths. In inert-gas metal-arc welding UVR production is 5 to 30 times more intense than that produced by shielded metal-arc welding. OSHA-required protective measures in shipyard employment and marine terminals include filter lens goggles worn under welding helmets or hand shields and protective clothing that completely covers the skin to prevent UVR burns and other damage (OSHA, 1998a, 1998b, 1998c).

ACGIH (1996) has set various Threshold Limit Values (TLVs) for skin and ocular exposures. TLVs for occupational exposure are determined by these parameters:

1. "For the near UV spectral region (320 to 400 nm), total irradiance incident upon the unprotected eye should not exceed 1.0 mW/cm^2 for periods greater than 10^3 seconds (approximately 16 minutes) and for exposure times less than 10^3 seconds should not exceed 1.0 J/cm^2."
2. Unprotected eye or skin exposure to UVR should not exceed 250 mJ/cm^2 (180 nm) to $1.0x10^5$ mJ/cm^2 (400nm) for an 8-hour period. The TLVs in the wavelength range 235 to 300 nm are 3.0 (at 270 nm) to 10 mJ/cm^2.
3. Effective irradiance for broad band sources must be determined by using a weighting formula.
4. "For most white-light sources and all open arcs, the weighting of spectral irradiance between 200 and 315 nm should suffice to determine the effective irradiance. Only specialized UV sources designed to emit UV-A radiation would normally require spectral weighting from 315 to 400 nm."
5. The permissible ultraviolet radiation exposure for unprotected eye and skin exposure may range from 0.1 $\mu W/cm^2$ (8 hours/day) to 30000 $\mu W/cm^2$ (0.1 sec/day).

6. "All of the preceding TLVs for UV energy apply to sources which subtend an angle less than 80°. Sources which subtend a greater angle need to be measured only over an angle of 80°."

ACGIH (1996) added that even though conditioned (tanned) individuals may not be any more protected from skin cancer, they can tolerate skin exposure in excess of the TLV without erythemal effects. NIOSH criteria for a recommended standard for occupational exposure to UVR are practically identical to those given in ACGIH items 1 and 2 above (NIOSHa, 1972).

The Federal Trade Commission (FTC) investigates false, misleading, and deceptive advertising claims about sunlamps and tanning devices (FTC, 1997).

The American Medical Association passed a resolution in December 1994 that called for a ban of the use of suntan parlor equipment for nonmedical purposes. Dermatologists have urged the FDA to take action to discourage use of suntan parlors and suntan beds (Blalock, 1995). Currently, the FDA Center for Devices and Radiological Health and the Centers for Disease Control and Prevention (CDC) encourage avoidance of sunlamps and sunbeds (AAD, 1997). Although 27 states and municipalities had promulgated some regulations on indoor tanning facilities by late 1995, they are seldom enforced (Blalock, 1995). The American Academy of Dermatology's Tanning Parlor Initiative provides a manual giving instructions on petitioning state, regional, and local governments on this issue and examples of regulatory legislation (Dermatology Times, 1990). Regulations are summarized in Volume II, Table A-35.