INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

ENVIRONMENTAL HEALTH CRITERIA 160

ULTRAVIOLET RADIATION

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organisation, or the World Health Organization.

An Authoritative Scientific Review of Environmental and Health Effects of UV, with Reference to Global Ozone Layer Depletion

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization

World Health Orgnization
Geneva, 1994

The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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     PREFACE

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PREFACE

        The World Health Organization (WHO), in collaboration with the
United Nations Environment Programme (UNEP) and the International
Non-Ionizing Radiation Committee (INIRC) of the International
Radiation Protection Association (IRPA), published the first
Environmental Health Criteria (EHC) monograph on Ultraviolet
Radiation in 1979. At the United Nations Conference on the
Environment and Development (UNCED) in 1992 it was declared under
Agenda 21 that there should be activities on the effects of
ultraviolet radiation. Specifically:

"(i) Undertake, as a matter of urgency, research on the effects on
human health of the increasing ultraviolet radiation reaching the
earth's surface as a consequence of depletion of the stratospheric
ozone layer;

(ii) On the basis of the outcome of this research, consider taking
appropriate remedial measures to mitigate the above-mentioned
effects on human beings".

        Within the United Nations mandate, and that of the 1993 WHO
Global Strategy for Health and Environment, this monograph has been
drafted to provide the essential authoritative review on which
future research programmes in UV can progress.

        IRPA initiated activities in NIR by forming a Working Group on
Non-Ionizing Radiation in 1974. This Working Group later became the
INIRC at the IRPA meeting held in Paris in 1977. In May 1992 the
INIRC was chartered as an independent scientific commission called
the International Commission on Non-Ionizing Radiation Protection
(ICNIRP). ICNIRP continues the work of the IRPA/INIRC by reviewing
the scientific literature on NIR and making assessments of health
risks of human exposure to such radiation. Using the Environmental
Health Criteria monographs, developed in conjunction with WHO,
ICNIRP recommends guidelines on exposure limits, drafts codes of
practice, and works in conjunction with other international
organizations to promote safety and standardization in the
non-ionizing radiation fields.

        A UNEP/WHO/ICNIRP Task Group to review the final draft of the
updated Environmental Health Criteria on Ultraviolet (UV) Radiation
met in Geneva from 8-11 December, 1993. Dr W. Kreisel, Executive
Director, World Health Organization opened the meeting on behalf of
WHO. Dr H. Gopalan and Mr R. Matthes welcomed the participants on
behalf of UNEP and ICNIRP respectively.

        The first revision of this publication was compiled by members
of the IRPA/INIRC and more recently by members of ICNIRP. Chapters
were prepared by Drs B. Armstrong, J-P. Cesarini, L. Court, P.
Dolan, G. Johnson, A. Kricker, A. McKinlay, M. Repacholi, M.

Selgrade, D. Sliney and R. Tyrrell. These chapters together with the
report of an informal consultation held in Geneva, in August 1993 on
"The Effects of Solar UV Radiation on the Eye", the International
Agency for Research on Cancer (IARC) report of the meeting on
"Health, Solar UV Radiation and Environmental Change " held in Lyon
in October 1992, and the meeting on Immunotoxicology held in

Bilthoven in July 1993, were used by Drs M. Repacholi and D. Sliney
to compile the review draft in September 1993. Comments were
received from a broad cross-section of specialists in the UV fields
and their reviews were gratefully received. These comments were then
incorporated for Task Group review. Final scientific editing of the
text was completed by Drs J-P. Cesarini, A. McKinlay, M. Repacholi
and D. Sliney. Sincere thanks to Christine Cornish and Nancy Smith
for their assistance in the preparation of this text. An editorial
group consisting of Drs M. Repacholi, H. Gopalan and T. Kjellström
coordinated the preparation of this monograph.

     This monograph comprises a review of the data on the effects of
exposure on biological systems pertinent to the evaluation of human
health risks. Its purpose is to give an overview of the known
biological effects of UV, identify gaps in knowledge and provide
direction for further research. This monograph will assist health
authorities, regulatory and similar agencies to provide guidance on
health risks from exposure to UV and limits for occupational and
general public exposure.

     Earlier reports were not necessarily included, as they were
reviewed in the 1979 monograph. Every effort has been made to
distinguish clearly between established biological effects and those
that have been reported as preliminary or isolated results, or as
hypotheses proposed to explain observed results. The conclusions are
based on established knowledge of interactions of UV with biological
systems.

     Subjects reviewed include: the physical characteristics of UV;
measurement techniques; applications and sources of exposure;
mechanisms of interaction; biological effects; guidance on
protective measures; and recommendations on exposure limits.

     This monograph will also serve as a scientific database for the
planned WHO/UNEP/IARC/ICNIRP International Research Programme on
Health, Solar UV Radiation and Environmental Change (INTERSUN). The
general objectives of INTERSUN are to:

(i) evaluate the quantitative relationship between solar UV at the
surface of the earth and human health effects, develop reliable
predictions of the health consequences of changes in UV, provide
baseline estimates of the incidence of health effects of UV in
representative populations around the world, and develop practical
ways of monitoring change in these effects over time in relation to
environmental and behavioural change;

(ii) provide essential input into the development of environmental
and public health policies and actions in relation to depletion of
stratospheric ozone; and

(iii) provide a framework for monitoring the effects of solar UV and
the impact of prevention programmes.

     Health agencies and regulatory authorities are encouraged to
set up and develop programmes that ensure effective protection
against the health effects of UV. It is hoped that this criteria
monograph will provide useful information for such endeavours.

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NOTE TO READERS OF THE CRITERIA MONOGRAPH

Every effort has been made to present information in the
criteria monographs as accurately as possible without unduly
delaying their publication. In the interest of all users of the
Environmental Health Criteria monographs, readers are kindly
requested to communicate any errors that may have occurred to the
Director of the International Programme on Chemical Safety, World
Health Organization, Geneva, Switzerland, in order that they may be
included in corrigenda, which will appear in subsequent volumes.

1. SUMMARY AND CONCLUSIONS

This monograph is concerned with the effects of ultraviolet
(UV) radiation exposure on human health and the environment. Such a
review of the scientific literature is considered timely in view of
the consequences of increased levels of UV at the surface of the
earth resulting from depletion of stratospheric ozone.

1.1 Physical Characteristics

Exposure to UV occurs from both natural and artificial sources.
The sun is the principal source of exposure for most people. Solar
UV undergoes significant absorption by the atmosphere. With
depletion of the stratospheric ozone people and the environment will
be exposed to higher intensities of UV. The consequences of this
added UV exposure are considered so serious that it was a major
topic for discussion at the World Environment Conference, held in
Rio de Janeiro in 1992. In Agenda 21, adopted by the Conference, it
was specifically recommended to "undertake, as a matter of urgency,
research on the effects on human health of the increasing
ultraviolet radiation reaching the earth's surface as the
consequence of depletion of the stratospheric ozone layer." It is
this issue that underscores the current need to better understand
the potential health and environmental risks of UV exposure.

UV is one of the non-ionizing radiations in the electromagnetic
spectrum and lies within the range of wavelengths 100 nm (which
corresponds to a photon energy of approximately 12 eV) to 400 nm.
The short wavelength limit of the UV region is often taken as the
boundary between the ionizing radiation spectrum (wavelengths < 100
nm) and the non-ionizing radiation spectrum. UV can be classified
into UVA (315 - 400 nm), UVB (280 - 315 nm) and UVC (100 - 280 nm)
regions, although other conventions for UVA, UVB and UVC wavelengths
bands are in use.

Most artificial sources of UV, except for lasers, emit a
spectral continuum of UV containing characteristic peaks, troughs
and lines. These sources include various lamps used in medicine,
industry, commerce, research and the home.

UV-induced biological effects depend on the wavelengths of the
radiation. It is necessary for a proper determination of hazard to
have spectral emission data. These consist of spectral irradiance (W

m^{-2} nm^{-1}) measurements or calculations of emissions from the source. The total irradiance (W m^{-2}) is obtained by summing over all wavelengths emitted. The biological or hazard weighted irradiance (W m^{-2} effective) is determined by multiplying the spectral irradiance at each wavelength by the biological or hazard weighting factor (which quantifies the relative efficacy at each wavelength for causing the effect) and summing over all wavelengths. Such factors are obtained from action spectra.

1.2 Action Spectrum and Minimum Erythemal Dose

An action spectrum is a graph of the reciprocal of the radiant exposure required to produce the given effect at each wavelength. All the data in such curves are normalized to the datum at the most efficacious wavelength(s). By summing the biologically effective irradiance over the exposure period, the biologically effective radiant exposure (J m^{-2} effective) can be calculated. For UV induced erythema, the action spectrum adopted by the International Commission on Non-Ionizing Radiation Protection (ICNIRP), International Commission on Illumination (CIE), the International Electrotechnical Commission (IEC) and various national bodies, is a composite curve obtained by statistical analysis of many research results on the minimum radiant exposure of UV at different wavelengths necessary to just cause erythema.

The most commonly used quantity for describing the erythemal potential of an exposure to UV is the number of minimum erythemal doses (MEDs) represented by the exposure. An MED is the radiant exposure of UV that produces a just noticeable erythema on a previously unexposed skin. It corresponds to a radiant exposure of monochromatic radiation at the maximum spectral efficacy for erythema (around 300 nm) of approximately 150 to 2000 J m^{-2} effective, depending on skin type. In this text 200 - 300 J m^{-2} effective is used as the value of 1 MED for comparative safety purposes for white skin.

1.3 Cellular and Molecular Studies

To produce any change, UV must be absorbed by the biomolecule. This involves absorption of a single photon by the molecule and the production of an excited state in which one electron of the absorbing molecule is raised to a higher energy level. The primary products caused by UV exposure are generally reactive species or free radicals which form extremely quickly but which can produce effects that can last for hours, days or even years. DNA is the most critical target for damage by UVB and UVC radiations. While a considerable amount of knowledge is available concerning the interaction of UV with nucleic acids, controversy exists as to which lesion constitutes the most important type of pre-mutagenic damage.

Cell death, chromosome changes, mutation and morphological transformations are observed after UV exposure of procaryotic and eucaryotic cells. Many different genes and several viruses (including HIV) are activated by UV exposure. The genes activated by UVB and UVC are different from those activated by UVA. Studies of DNA repair defective disorders have clearly established a link between UV induced DNA damage in skin and various types of cancer.

1.4 Animal Studies

Solar UV has been shown to produce cancers in domestic and food animals. In experimental animals UV causes predominantly squamous cell carcinomas. UVB is most effective at producing SCCs, although they are produced by UVA but at much higher intensities, similar to the levels needed for erythema and tanning. The effectiveness of UVC is unknown except at one wavelength (254 nm). At this wavelength the effectiveness is less than UVB.

Melanomas are much less common and only two animal models have been found for induction of melanoma by UV alone. An initial action spectrum determined for a type of hybrid fish indicates a peak in the UVB range but also shows a high level of effectiveness in the UVA. Basal cell carcinomas are rare in animals.

Exposure to suberythemal doses of UV have been shown to exacerbate a variety of infections in rodent models. UV affects infections both at the site of exposure and at distant sites. Recent work indicates that systemic infections without skin involvement may be affected. Enhanced susceptibility appears to result from T-helper cell activity. The mechanisms associated with this suppression appear to be the same as those identified with suppression to contact and delayed type hypersensitivity responses. Suppression of these immune responses appears to be mediated by release of soluble mediators from UVB exposed skin which alters the antigen presentation by Langerhans and other cells so that they fail to activate TH 1 cells. The resulting immune suppression is antigen specific, can occur regardless of whether or not antigen is applied at the site of exposure, and is relatively long lasting. UV exposure also prevents the development of protection immunity to a variety of infections in mice and rats.

Many studies in experimental animals have demonstrated that UV exposure can cause both acute and delayed effects such as cataract, photokeratitis, damage to the corneal epithelium and various retinal effects. Studies of photochemical retinal injury in aphakic monkeys have shown that the retina is six times more vulnerable to photochemical damage from UV than the visible wavelengths.

1.5 Health Effects on Humans

1.5.1 Skin

Acute effects on the skin consist of solar erythema, "sunburn", which, if severe enough, may result in blistering and destruction of the surface of the skin with secondary infection and systemic effects, similar to those resulting from a first or second degree heat burn. Although UVC is very efficiently absorbed by nucleic acids, the overlying dead layers of skin absorb the radiation to such a degree that there is only mild erythema and, usually, no late

sequelae, even after repeated exposures. Much less is known about the biological effects of UVA. However, doses of UVA, which alone may not show any biological effect, can, in the presence of certain environmental, consumer and medicinal chemical agents, result in injury to tissues (phototoxicity, photoallergy, enhancement of photocarcinogenesis).

Chronic skin changes due to UV consist of skin cancer (both melanoma and non-melanocytic), benign abnormalities of melanocytes (freckles, melanocytic naevi and solar or senile lentigines), and a range of other chronic injuries resulting from UV exposure to keratinocytes, blood vessels and fibrous tissue, often described as "photoaging" (solar elastosis). The much increased rates of skin cancer in patients with xeroderma pigmentosum, who have a deficiency in the capacity to repair UV-induced DNA damage, suggest that direct UV damage of the DNA may be a step in the cause of these cancers. This suggestion has also been supported by the observation of UV specific mutations of the p53 tumour suppressor gene in a proportion of patients with non-melanocytic skin cancer. Oxidative and immune suppressant effects may also contribute to the capacity of UV to cause skin cancers.

Cancer of the lip is much more common in fair than dark skin populations and is associated with outdoor work. However possible confounding with tobacco and alcohol use has not been adequately controlled in any study.

The worldwide incidence of malignant melanoma has continued to increase. Strong epidemiological evidence exists that sun exposure causes cutaneous melanoma and non-melanocytic skin cancer. Their incidence is less in darker than light skin groups living in the same geographical area. Risk of skin cancer decreases with increasing pigmentation. The anatomical site most seen for squamous cell carcinoma (SCC) is the head and neck, areas most exposed to the sun. Incidence of both melanoma and non-melanocytic skin cancer are increased in areas of high ambient solar UV radiation. Melanoma is strongly related to frequency of recreational exposure to the sun and to history of sunburns.

There is suggestive evidence that exposure to sunlamps may increase the risk of melanoma, but the studies conducted so far have not consistently controlled confounding factors.

1.5.2 Immune system

A number of studies suggest that UV exposures at environmental levels suppress immune responses in both rodents and man. In rodents this immune suppression results in enhanced susceptibility to certain infectious diseases with skin involvement and some systemic infections. Mechanisms associated with UV-induced immunosuppression and host defence mechanisms which provide for protection against

infectious agents, are similar in rodents and man. It is therefore reasonable to assume that exposure to UV may enhance the risk of infection and decrease the effectiveness of vaccines in humans. However additional research is necessary to substantiate this.

1.5.3 Eye

The acute effects of UV on the eyes consist of the development of photokeratitis and photoconjunctivitis, which are unpleasant but usually reversible and easily prevented by appropriate eyewear. Chronic effects on the eye consist of the development of pterygium and squamous cell cancer of the conjunctiva and cataracts. A review of the studies suggests that there is sufficient evidence to link acute ocular exposure to photokeratitis but our knowledge of the effects of chronic exposure is less certain. While there is sufficient evidence that cortical and posterior subcapsular cataracts (PSC) can be caused by UVB in laboratory animals, there is limited evidence to link cortical and PSC cataracts in humans to chronic ocular exposure to UVB. Insufficient information is available to separate out the other factors contributing to cataract formation, or to state the proportion of cataracts which can be attributed to UVB exposure. There is also limited evidence to link the development of climatic droplet keratopathy and pterygium, but insufficient evidence to link uveal melanoma with UV exposure.

1.6 Environment

Increased levels of UV due to ozone layer depletion may have serious consequences for living organisms. A 10% reduction in ozone could lead to as much as a 15-20% increase in UV exposure depending on the biological process being considered. While the impact on human health, crop production, fisheries etc. is largely unknown, adverse effects of increased exposure to UVB have been reported on plant growth, photosynthesis and disease resistance. Further, the impact of increased UV levels on aquatic ecosystems (the major contributor to the earth's biomass) may be substantial.

Phytoplankton, at the base of the aquatic food chain, serves as food for larvae of fish and shrimp. These in turn are consumed by fish, which subsequently provide an essential food source for many human beings and other animals. A significant reduction in phytoplankton from increased UVB exposure will directly affect the human and animal marine food source.

1.7 Guidelines on Exposure Limits and Protective Measures

Guidance on exposure limits for UV are described in chapter 13. International guidelines define exposure limits (ELs) below which it is expected that nearly all people may be repeatedly exposed without adverse effects. The ELs are intended to be used to evaluate potentially hazardous exposures from, for example, solar radiation, arcs, gas and vapour discharges, fluorescent lamps and incandescent

sources. The ELs are generally below levels which are often used for the UV exposure of patients required as part of medical treatment and below levels associated with sunbed exposure. ELs are not intended to apply to exposure of pathologically photosensitive individuals, to people concomitantly exposed to photosensitising agents or to neonates.

Finally this monograph describes protection and control measures such as the containment of UV sources, and methods for personal protection including the use of sunscreen preparations, clothing, eye and skin protection, and behavioural modifications.

While topical application of sunscreen is a preferred method of absorbing UVB, some preparations do not absorb the longer wavelength UVA effectively. Moreover, some have been found to contain ingredients that are mutagenic in sunlight. There is still much research necessary before the impact on health of increased levels of UVA will be known. In the meantime people using sunscreens should use only those with the highest sun protection factor (SPF) and be aware that they are for their protection from the sun and not for tanning purposes. Use of wide brimmed hats, protective clothing and UV absorbing eye glasses is still the best personal protection against the adverse effects of UV exposure.

With increasing levels of solar UV resulting from depletion of the ozone layer, and the continuing rise in the level of melanoma worldwide, people should become more aware of their UV exposure and take appropriate precautions. These precautions include staying out of the sun during the period around noon (the period when the UV levels are highest), or wearing UV protective clothing, hats and sun glasses. Broad spectrum (UVB and UVA protective) sunscreens should be used when other means of protection are not feasible. These sunscreens should be used to reduce exposure rather than lengthen the period of exposure to the sun. Protection of young children is particularly important for the prevention of long-term consequences of UV exposure. In general behavioural patterns must change to protect against increasing solar UV levels.

2. PHYSICAL CHARACTERISTICS

2.1 Electromagnetic Spectrum

Oscillations of electromagnetic fields can cause energy to be transported in the form of electromagnetic radiation. Examples of this type of radiative transport of energy include radiofrequency waves, light and x rays. Ultraviolet (UV) radiation is one form of electromagnetic energy in the optical region of the electromagnetic spectrum. All electromagnetic radiation is characterized by frequency f and wavelength lambda. These two quantities are linked through the relationship:

$$f = c/lamda$$

where c is the speed of light (3×10^8 m s^{-1}). The energy of a single photon is determined by the wavelength of the photon as described by the relationship

(photon energy) = hf = hc/lamda   where h = 1.24 eV nm

Non-ionizing radiation (NIR) is the term generally applied to all forms of electromagnetic radiation whose primary mode of interaction with matter is other than by producing ionization. NIR refers to electromagnetic fields and radiation with wavelengths exceeding 100 nm, which is equivalent to quantum (photon) energies below 12.4 eV, the minimum energy needed to break the weakest macromolecular bonds. The non-ionizing spectrum encompasses all fields of radiation from UV to DC fields.

For purposes of health protection, the optical portion of NIR can be subdivided into several wavelength ranges, as shown in table 2.1. The nomenclature was standardized by the International Commission on Illumination (CIE) however, some scientists use a modification of this system by shifting the 315 nm break point between UVA and UVB to 320 nm; the reader should always check the definition given in each publication. For the purposes of this document, the CIE convention is followed.

Table 2.1 Optical Radiation Spectral Bands

Ultraviolet radiation	100 - 400 nm
UVA	315 - 400 nm
UVB	280 - 315 nm

```
        UVC                           100 - 280 nm
        Visible radiation (light)     400 - 760 nm
        Infrared radiation (IR)       760 - 10⁶ nm = 1 mm
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UV of wavelengths less than 180 nm has no direct biological effect on humans since it is effectively absorbed in a few

centimetres of air. For this reason, the spectral region below 180 nm is frequently referred to as the *vacuum ultraviolet region*.

2.2 Radiometric Quantities and Units

Radiometric quantities are absolute physical quantities used to describe the characteristics of a source or radiation field. For UV, ten generic radiometric terms are summarized in table 2.2. Each of these quantities can be defined for a certain wavelength or frequency range, or can be integrated over the whole spectrum of a given source. Since UV is normally absorbed over a surface, with very limited penetration depth, the most common quantities used to describe exposure dose and dose rate to UV are: radiant exposure (incident energy divided by the receptor surface area) and irradiance (incident power divided by the receptor surface area) respectively. Radiant exitance is the power per area of the emitted radiation *at the emitting surface*. The receptor surface is most often considered as a flat plane. However, for some biological and chemical purposes, the radiation incident on a cylindrical or spherical surface may also be considered.

For the purpose of radiation protection, physical quantities are needed to describe sources and fields of radiation as well as the interaction of this optical radiation with matter. These are described in IRPA/INIRC(1985).

2.3 UV Production

Sources of electromagnetic radiation can be categorized in several different ways; for example they can be grouped according to the type of material or the type of equipment that produces the radiation. At the submicroscopic level, the manner in which the radiation originates can be described in terms of nuclear, electronic or molecular transitions between energy states or by the acceleration of charged particles. Common sources of UV emission involve energy transitions between electronic states of molecules in materials.

2.3.1 Thermal emitters

When the temperature of a material increases, electrons in the molecules are raised to higher energy states, a variety of energy transitions take place and photons are emitted. The higher the temperature the greater is the fraction of these photons at higher energies. Matter at temperatures above 2500 K emits a significant number of photons in the UV spectral range. The emission spectra of such incandescent sources are characteristically smooth - so-called "continuum", possibly with superimposed spectral emission lines.

Table 2.2 Radiometric terminology for UV:
       Useful radiometric quantities and units

Quantity	Symbol	Defining equation	Unit and abbreviation
Radiant energy	Q_e	$Q_e = \int \Phi_e \, dt$	joule (J) = 1 watt second
Radiant energy density	W_e	$W_e = \dfrac{dQ_e}{dV}$	joule per cubic metre ($J\ m^{-3}$)
Radiant flux (radiant power)	Φ_e , P	$\Phi_e = \dfrac{dQ_e}{dt}$	watt (W)
Radiant exitance	M_e	$M_e = \dfrac{d\Phi_e}{dA}$ $= \int L_e \cos\Theta \, d\Omega$	watt per square metre ($W\ m^{-2}$)
Irradiance or Radiant Flux Density	E_e	$E_e = \dfrac{d\Phi_e}{dA}$	watt per square metre ($W\ m^{-2}$)
Radiant intensity	I_e	$I_e = \dfrac{d\Phi_e}{d\Omega}$	watt per steradian ($W\ sr^{-1}$)
Radiance[1]	L_e	$L_e = \dfrac{d^2\Phi_e}{d\Omega\, dA\, \cos\Theta}$	watt per steradian per square metre ($W\ sr^{-1}\ m^{-2}$)

Table 2.2 (contd).

Quantity	Symbol	Defining equation	Unit and abbreviation

Radiant exposure (dose in photobiology)	H_e	$H_e = \dfrac{dQ_e}{dA}$	joule per square metre ($J\ m^{-2}$)
Radiant efficiency[2] (of a source)	n_e	$n_e = \dfrac{P}{P_i}$	unitless
Optical density[3]	D_e	$D_e = -\log_{10}(gamma_e)$	unitless

NOTE: All terms in this table are radiometric terms and should not be confused with photometric terms. The symbol A represents surface area, Omega is solid angle, Theta is the incident (zenith) angle, V represents volume, t is time. The units may also refer to narrow spectral bands in which the term is preceded by the word *spectral* and the unit is then per wavelength interval and the symbol has a subscript lamda. For example, spectral irradiance Egamma has units of $W\ m^{-2}\ nm^{-1}$ or $W\ cm^{-2}\ nm^{-1}$. While the metre is the preferred unit of length, the centimetre is still commonly used for many of the above terms and the nm or µm are most commonly used to express wavelength.

1. At the source $L = \dfrac{dI}{dA\ cosTheta}$ and at a receptor $L = \dfrac{dE}{dOmega\ cosTheta}$

2. P_i is electrical input power in watts

3. This formula applies only to situations where the radiation is not scattered, but only absorbed. In this case gamma represents the fraction of transmitted energy.

The spectral emission of a heated material is governed by basic physical laws. The Stefan-Boltzmann Law expresses the total radiation emitted by a heated material as a function of its temperature. The total radiant power emitted by a theoretically perfect radiator, a so-called black body, is proportional to the fourth power of its temperature (in kelvin, K). Any practical thermal emitter in equilibrium emits less radiant power than its equivalent black body at the same temperature and unlike a black body the amount depends on the nature of its surface. The spectral distribution of black body radiation is described by the Planck Radiation Law. Wien's Displacement Law is illustrated in figure 2.1, and describes mathematically the spectral distribution of emission from a black body and the wavelength of the maximum emission shift to shorter wavelengths as temperature increases. When a material is heated so that incandescence occurs, it first appears red and, with increasing temperature, progresses to white or blue.

2.3.2 Electrical gaseous discharges

Radiation may be produced when an electric current is passed through a gas or vapour. Atoms may be ionized if sufficient energy is transferred from a moving electron. Alternatively the moving electron may not impart sufficient energy for ionization, but instead may impart energy to raise the electrons of the gas to an excited (higher) energy level. When they return to a lower energy level, or their ground state, radiation of one or more characteristic wavelengths is emitted. The wavelengths of emission are determined by the type of gas or vapour present in the discharge and appear as spectral emission lines. The width of the lines and the amount of radiation in the interval between them depends on the pressure of the discharge. At low pressure, fine lines with little or no continuum are produced. As the pressure of the discharge is raised the lines broaden and their relative magnitudes alter. The magnitude of the continuum increases. The electrical gaseous discharge is the basis of operation of many UV emitting lamps.

2.3.3 Stimulated emission

Radiation can be produced by the specific electronic transition process of stimulated emission. This depends on the ability of the radiating medium to undergo "population inversion", i.e., achieving a condition where there are more atoms or molecules in a higher energy excited state than in a lower one. Once population inversion occurs an avalanche of photons can be generated by stimulated emission. Initially, spontaneously emitted photons stimulate other excited atoms to emit photons of the same energy in phase with one another. This is the basis of operation of the laser.

Figure 2.1   Black-body spectra.   Line AB shows Wien's Displacement Law for the shift of the peak wavelength with change in absolute temperature (in K) (from Sliney & Wolbarsht, 1980).
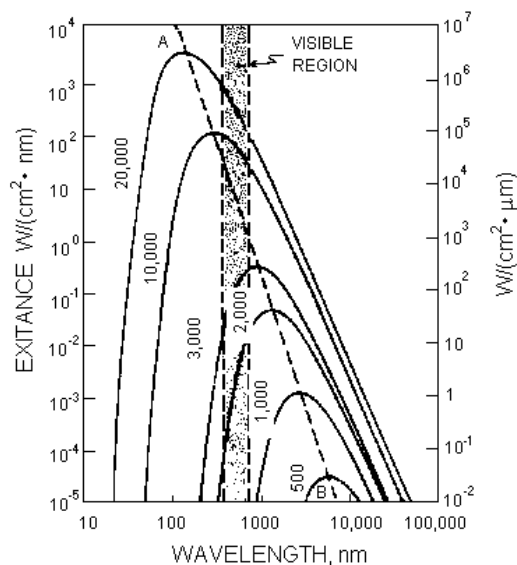
2.4 Summary

UV is a part of the non-ionizing region of the electromagnetic spectrum. Its position in the spectrum can be characterised by wavelength and it is quantified using radiometric quantities and units. Production of UV is possible by different mechanisms that are all based on atomic or molecular excitation. Excitation in a medium can be achieved by thermal, electrical or optical energy absorption. Emission of radiation is caused either by de-excitation or by stimulated synchronised processes.

3. UV SOURCES

3.1 The Sun

The sun is the main source of UV. The broad spectrum and intensity of UV from the sun are due to the high temperature at its surface and its size. The intensity of solar UV reaching the earth's atmosphere would probably be lethal to most living organisms on the earth's surface without the shielding afforded by the atmosphere. Solar UV undergoes absorption and scattering as it passes through the earth's atmosphere with absorption by molecular oxygen and ozone being the most important processes. The ozone layer prevents almost all UV of wavelengths lamda < 290 nm and a substantial fraction (in excess of 90% of the total energy) from 290 - 315 nm from reaching the earth's surface. Thus the terrestrial environment is exposed to UV between 290 nm and 400 nm. The spectrum, both before passage through the atmosphere and at sea level, is shown in figure 3.1

The solar radiation reaching the top of the earth's atmosphere is affected by the solar output and the earth-sun distance. Variations in solar output are much smaller than the variations caused by atmospheric attenuation factors. The irradiance incident on the top of the earth's atmosphere is summarised in table 3.1, but will vary with the exact distance of the earth from the sun at a particular time. The extreme values associated with this variation are approximately ± 3.3% above and below the annual mean and occur in January and July respectively.

Table 3.1 Spectral distribution of solar radiation prior to attenuation by the earth's atmosphere (Frederick et al., 1989).

Wavelength band	Irradiance (W m^{-2})	Percent of total
UVC	6.4	0.5
UVB	21.1	1.5
UVA	85.7	6.3

```
Total UV              113.2                     8.3
Visible and IR        1254                      91.7
```

The atmosphere has a profound effect on the irradiance which
reaches the surface of the earth. In January (in the northern
hemisphere) or July (in the southern hemisphere) when the solar
elevation is low, direct UV travels a longer path through the
atmosphere and a large amount of scattering occurs. In addition,
much of the resultant scattered UV propagates downwards to the
earth's surface at angles to the horizontal that are larger than the
solar elevation, hence travelling a shorter and less absorptive
path. This results in large ratios of scattered to direct UV. During
the summer the ratio of diffuse to direct UV is smaller.

Figure 3.1 Solar optical radiation attenuation by the earth's atmosphere.(from UNEP, 1987).
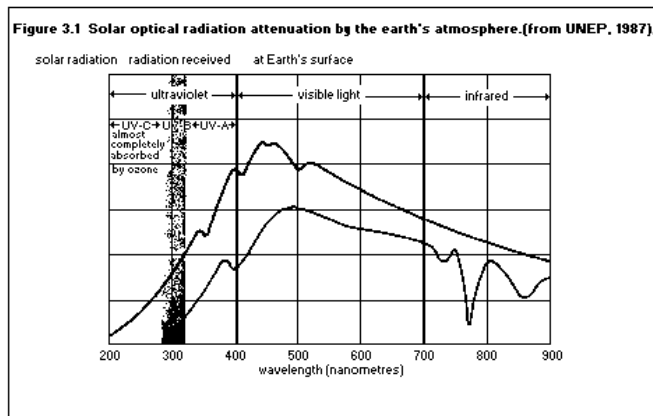
3.1.1 Factors affecting solar UV levels

     The total solar UV reaching the earth's surface, termed global
UV can be divided into two components: direct and diffuse. Global UV
reaching a horizontal surface is the quantity most often measured.
For biological entities such as people and trees, UV hitting
cylindrical or spherical surfaces may be more important.

     The amount and spectral distribution of solar UV irradiance
reaching the earth's surface depends on a number of factors,
including

(a) wavelength of the UV
(b) solar zenith angle, which depends on latitude, date of the year
     and time of day
(c) solar source spectrum incident at the top of the atmosphere (d)
     ozone column thickness and vertical distribution
(e) molecular absorption and scattering (including localized
     gaseous pollutants)
(f) aerosol absorption and scattering (including anthropogenic
(g) absorption, scattering and reflection by clouds
(h) reflectance characteristics (albedo) of the ground
(i) shadowing by surrounding objects
(j) altitude above sea level

     The presence of cloud cover, air pollution, haze, or even
scattered clouds, plays a significant role in attenuating UV. UVB
and UVA irradiances are reduced due to scattering by water droplets
and/or ice crystals in the clouds. Clouds can block a significant
portion of the UV which would have otherwise reached the surface.

     Cloud cover and type are highly variable. The transmission of
UV radiation through clouds depends on cloud height, type and
optical density. The resultant effect on UV transmission is
difficult to assess particularly in the case of partial cloudiness.
The effect of cloudiness on the solar irradiation of a horizontal
plane can be approximated by

          $F = 1 - 0.056\ C$

where C is the total cloud index in tenths of sky covered from 0 to
10, 10 being complete sky cover. Thus for complete cloud cover, the
transmitted UV irradiance would decrease by 72% and for half cloud
cover by 44%. In extreme cases cloud cover can decrease UV
irradiance by over 90%. Estimates of the average reduction of UVB
due to clouds (relative to cloudless skies) based on satellite
measurements of backscattered solar UV are 30% at 60 degrees
latitude, 10% at 20 degrees latitude and 20% at the equator.

3.1.2 Ozone depletion effects

     Over 90% of the total atmospheric ozone resides in the
stratosphere (the upper atmosphere). The total ozone column is
important for filtering solar UV. Only UVB is affected by changes in
the ozone column. UVC is almost completely absorbed by ozone and
oxygen in the atmosphere; even with severe ozone reduction UVC would
still be effectively absorbed by the remaining oxygen.

     As stratospheric ozone levels decrease, the resulting higher
levels of solar UVB could increase the production of reactive OH
radical molecules, potentially increasing the chemical reactivity of
the troposphere. In polluted areas with sufficient concentrations of
oxides of nitrogen (NO_x) (above 0.5 ppb by volume) and hydrocarbon

compounds this enhanced reactivity is calculated to result in
greater levels of tropospheric ozone and other potentially harmful
oxidized products, such as hydrogen peroxide and acids.

The amount of ozone in the free troposphere is increasing for
example over central europe and other parts of the globe. The effect
of these trends on UV radiation needs to be studied further (WMO,
1993). For high sun angles, tropospheric ozone is a more effective
absorber of UV radiation than stratospheric ozone because of the
increased path length of scattered radiation in the lower atmosphere
(Brühl & Crutzen, 1989).

The total ozone column is not uniform but varies with latitude
and time of year. At the same latitude, away from the equator and
tropics, the total ozone column tends to be greater in spring than
in autumn. Thus, even though the sun angles are the same on March 21
and September 21, the differences in total ozone column result in
more UVB in early autumn than in early spring. If cloud cover and
atmospheric pollution are not taken into account, in the tropics,
the relatively constant ozone column and the similar solar angles
throughout the year, result in little variation in solar UVB with
season.

Changes in total column ozone were observed by both ground
based and satellite based instruments from the WMO Global Ozone
Observing System. The measurements show pronounced ozone depletion
over Antarctica in months 9-12 (local early spring) (UNEP-WMO,
1989). Increases in biologically effective UVB were observed during
this same time period (NSF, 1993). Over representation of UVA in the
common broad band meter action spectrum, relative to most biological
action spectra, produces less pronounced relative and absolute
changes in assessed UVB. Therefore under cloud free conditions
common broad band meters are less sensitive in assessing the ground
level UVB effects of ozone depletion than detectors with a steeper
action spectrum response such as for DNA damage or for erythema.

3.1.3 Trends in UV

There have been no significant changes in ozone at the equator.
Total column ozone over the Northern mid-latitudes has decreased by
several percent over the past two decades. Efforts to detect changes
in UV over long time periods have failed due to changes in column
ozone.

Besides the problems indicated in the interpretation and
comparison of measurement data from different sites and sources,
there are also insufficient direct solar terrestrial UVB
measurements for constructing a global climatology or trend
assessment due to some of the following (Driscoll 1992):

(a) problems in establishing appropriate instrumentation: either
     highly sophisticated and reliable spectral instruments or broad
     band instruments which fairly represent the sensitivities of
     different biological and chemical targets (with different
     wavelength dependencies and sensitivity to different
     orientations),

(b) difficulty of maintaining accurate field instrument
     calibrations over many years, and

(c) practical limitations in establishing a global monitoring
     network especially with the potential for disturbance from
     locally polluted areas.

With insufficient spectral measurement data collected over long
periods, data from the more extensively used broad-band measurement
systems have been scrutinised. UV data from eight stations in the US
showed decreases in UVB between 0.5% and 1.1% per year during the
time period of 1974-1985 (Scotto et al., 1988). However, this
result does not agree with theoretical predictions and may be due to
problems in the long-term calibration of meters or local pollution
in mainly urban or semi-urban sites (Munkata, 1993; Smith & Ryan
1993). In Russia, a 12% decrease of UVB was observed in Moscow
between 1968 and 1983 with a concurrent 15% increase in turbidity
and a 13% increase in cloudiness. At the Jungfraujoch observing
station in the Swiss alps (3.6 km above sea level), increases of
0.7±0.2% per year in UVB were observed under clear sky conditions
between 1981 and 1989. A comparison of summer spectral data weighted
with the CIE erythemal action spectrum using the same
instrumentation at Lauder, New Zealand (45°S) and Neuherberg,
Germany (48°N) showed weighted UV irradiances were 1.6 times larger
in New Zealand due to decreased ozone column thickness (24% lower
than in Germany). Spectral filter measurements at 39o N between 1976
though 1990 showed large increases in monthly maximum values which
were not statistically significant (Correll et al., 1992).

3.1.4 Theoretical models

To overcome some of the deficiencies in interpreting the
results from solar UV measurements, theoretical models have been
used to predict UV levels. However, the theoretical determination of
the spectral distribution of global UV including the effects of
cloud cover and ground reflection is extremely complex. There are
three categories of models to predict UV transmission. Empirical and
semi-empirical models are useful for assessing daily or annual
erythemal doses as a function of latitude, solar zenith angle, cloud
cover and ground albedo. These models have been used for a long time
at a variety of locations. Two of the most common examples are the
models of Green et al. (1974) and Diffey (1977)

Two stream models simulate the radiative transfer through the atmosphere. They have been well verified with field data from Antarctica as well as mid-latitudes (e.g. Frederick *et al.,* 1989).

Multistream models allow for the angular distribution of UV transmission. This is useful for more detailed dosimetry (Stamnes *et al.,* 1988).

The maximum erythemally effective UVB irradiances, calculated by the Diffey model, are shown in table 3.2 for the Northern Hemisphere, as a function of latitude and time of year at sea level (Driscoll 1992). There are strong seasonal and latitudinal variations in UVB. Under cloudless skies, the UVB is more intense in summer and at all times of year is greater at lower latitudes. The solar elevation angle determines the length of the path of the sun's rays as they penetrate the atmosphere. When the sun is low in the sky, the path through the atmosphere is longer and the filtering action of the air is therefore increased. When the sun is directly overhead, the sun's rays have the shortest path through the atmosphere. Approximately 50% of the daily UV is received during the middle four hours around noon when the sun is high in the sky (Sliney, 1987).

The number of minimum erythemal doses (MEDs) in a 3 hour exposure period around noon for fair skin is shown as a function of latitude and time of year in table 3.3 for the Northern Hemisphere. For example, at 55°N (Newcastle), a calculated value of 6 MED would be received for a sensitive skin type in a 3 hour exposure around noon on a clear day in July (1 MED per half hour exposure).

Comparing the values in table 3.2 with the results of calculations using the model developed by Frederick *et al.* (1989) for clear sky conditions at noon, the latter are typically 50% higher. This may be due to differences in the biological action spectra used or in the spectral irradiance data calculated. The R-B meter response characteristic used by Frederick *et al.* (1989) does

not follow the CIE reference erythema action spectrum used in the model developed by Diffey (1977) at wavelengths greater than 300 nm.

3.1.5 UV monitoring

Recent public and scientific concern about ozone depletion and increased UV have lead to the establishment of many UV monitoring centres in the last few years. Five years ago less than fifty UV monitoring stations were operating around the world. Today more than 250 monitoring centres are underway for a variety of reasons. Governmental agencies, scientific institutions, universities and private groups have begun to monitor UV. The World Meteorological Organization (WMO) has established a global network called Global Atmosphere Watch (GAB). It presently has eight observatory stations that make continuous spectral and broad band UV measurements. The Global Environment Facility is supporting the creation of 10-15 additional stations in developing countries. Various national and multi-national agencies are also operating and establishing UV monitoring networks.

Table 3.2 Calculated clear sky noontime erythemally effective UVB irradiances (mW m-2 CIE erythemally weighted) on a horizontal surface as a function of latitude (°) and time of year for the sea level in the Northern Hemisphere using typical ozone values (Driscoll, 1992).

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
0	229	251	260	229	210	207	214	233	278	248	226	221
5	212	232	242	235	214	213	220	241	258	227	207	206
10	203	220	229	248	226	225	232	255	244	215	198	175
15	155	199	201	227	221	226	234	240	223	198	155	135
20	127	183	191	215	234	239	247	227	212	184	127	111
25	95	134	165	185	203	227	219	200	194	143	101	84
30	79	110	157	176	192	215	208	190	186	117	85	56
35	42	80	114	146	160	188	182	166	148	93	50	31
40	28	61	93	139	152	178	172	158	121	73	33	21
45	16	33	66	105	126	158	153	128	93	42	21	13
50	12	22	54	85	119	150	145	104	77	28	15	8
55	6	14	33	65	92	130	114	81	48	18	8	4
60	4	10	21	53	75	105	93	67	31	12	5	2
65	0	6	14	35	59	85	76	42	21	7	2	0
70	0	3	10	23	48	70	62	29	15	4	0	0
75	0	0	6	15	30	53	39	20	9	0	0	0
80	0	0	3	11	20	33	26	14	5	0	0	0
85	0	0	2	7	14	23	18	9	2	0	0	0
90	0	0	0	4	10	16	13	5	0	0	0	0

Table 3.3 Number of MEDs in a 3 h exposure period for a sensitive skin type (1 MED = 200 J m-2 effective) for the erythemally effective UVB irradiances given in table 3.2 as a function of latitude (°) and time of year for the Northern Hemisphere (Driscoll 1992).

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
0	12	14	14	12	11	11	12	13	15	13	12	12
5	11	13	13	13	12	12	12	13	14	12	11	11
10	11	12	12	13	12	12	13	14	13	12	11	9
15	8	11	11	12	12	12	13	13	12	11	8	7

```
20    7   10   10   12   13   13   13   12   11   10    7    6
25    5    7    9   10   11   12   12   11   10    8    5    5
30    4    6    8   10   10   12   11   10   10    6    5    3
35    2    4    6    8    9   10   10    9    8    5    3    2
40    2    3    5    8    8   10    9    9    7    4    2    1
45    1    2    4    6    7    9    8    7    5    2    1    1
50    1    1    3    5    6    8    8    6    4    2    1    0
55    0    1    2    4    5    7    6    4    3    1    0    0
60    0    1    1    3    4    6    5    4    2    1    0    0
65    0    0    1    2    3    5    4    2    1    0    0    0
70    0    0    1    1    3    4    3    2    1    0    0    0
75    0    0    0    1    2    3    2    1    0    0    0    0
80    0    0    0    1    1    2    1    1    0    0    0    0
85    0    0    0    0    1    1    1    0    0    0    0    0
90    0    0    0    0    1    1    1    0    0    0    0    0
```

The reasons for monitoring UV are generally divided into the following four areas:

   (i)   to provide information to the public on UV levels and
         variations,

   (ii) establishing a basic UV climatology,

   (iii) studying cause and effects of UV transmission, and

   (iv) detecting long term variability.

While these reasons are not mutually exclusive they can often dictate the type of care taken with instrument maintenance. The quality and care needed for trend detection requires a great deal more effort than for UV measurements to provide public information.

There are many difficulties in making accurate field measurements of ambient UV. Care must be taken that no part of the instrument is shaded from either direct or indirect sun; nearby surfaces must not change during the time period of monitoring; and

routine maintenance such as snow and debris removal must be conducted systematically to avoid trend bias. The value of the measurements for trend detection rely on diligent maintenance of the site including co-located measurements. The data must have spectral, temporal and angular resolution appropriate for validation of model calculations and for evaluation of biological effects (spectral resolution better than <1 nm). Broad band instruments are useful for establishing climatology and operations where spectral instruments are not practical.

Frequent and reliable calibration of the instrumentation is necessary. UV monitoring for the detection of trends is difficult and failure to detect a trend may be due to lack of awareness of changes in instrument behaviour and correction of it. Intercomparison of different types of UV monitoring instruments have shown that individual instrument characteristics can cause substantial differences in measurements. Further intercomparisons are necessary to understand and reduce the uncertainties of measurements.

3.1.6 Analysis of UV data

Atmospheric UV data are difficult to analyze. To date all UV data have been analyzed separately by each investigator and in a different manner. This variation in analysis makes the interpretation and comparison of results difficult. Unfortunately, the data are normally not easily obtained and re-analyzed for comparative studies.

UV data pose difficult problems because they are not generally independent and normally distributed, therefore robust time series techniques should be used to analyze the data correctly. Standard techniques, depending on how they are applied, can greatly over or under estimate the confidence in the observed trends, as well as supply spurious trends when used on UV data. Bishop (1992) has suggested that using proper statistical techniques, at least ten years of data will be necessary to correctly detect a trend of 5% per decade. This estimate was made based on analysis of a single station's data independently. However, analysing groups of data may allow trend detection in less time.

3.1.7 Conclusions

The earth's atmosphere has a profound effect on the UV irradiance reaching the earth's surface. It absorbs a large fraction of the incident UV and changes part to diffuse radiation. Variations in UV intensity depend on solar zenith angle, atmospheric ozone, cloudiness, aerosol load and other factors.

One of the most important tools to determine climatological values and long-term changes in solar UV radiation is the monitoring

of solar UV. Atmospheric parameters which modulate UV need to be observed in parallel to help explain the changes observed in the measurements. The existing data base is much too scarce to derive climatological values and trends on global or regional scales. Efforts are being made to establish national and international networks for measurements of solar UV radiation.

Models that simulate typical values and predictions of changes in UV radiation for different atmospheric conditions are also used.

The results from these models need to be compared with measurements.

3.2 Artificial Sources

Artificial sources of UV are commonplace. There are few artificial sources that result in human exposure to UV greater than that from the sun. However, exceptions are those used for medical therapy and diagnosis, cosmetic tanning. Industrial sources are generally effectively enclosed, but accidental exposure may occur. There are very few non-laser sources of optical radiation that emit UV solely.

Any unfiltered optical source, whose emissions are due to the heating of a material e.g. a filament lamp, that emits significant quantities of UV will also emit visible and infrared radiations. In the case of high temperature tungsten halogen lamps biologically significant amounts of shorter wavelength UVB are also emitted. Essentially the same holds true for high intensity (gaseous) discharge (HID) lamps. Some incandescent and HID lamps have sufficient intrinsic filtration in the glass envelope of the lamp. However, additional filtration, afforded by incorporation of the lamp in a suitably filtered luminaire, may be necessary.

Most man-made sources of UV can be grouped together in the categories shown below. The spectrum of the UV emitted varies from one source to another

Incandescent sources
    tungsten lamps

Gas discharges
    mercury lamps (low-, medium- and high-pressure)
    mercury lamps with metal halides
    xenon lamps
    hydrogen and deuterium lamps
    flash tubes

Electric discharges
    welding arcs
    carbon arcs

Fluorescent Lamps
    fluorescent lighting tubes
    fluorescent sunlamps (UVB emitters)
    fluorescent UVA tubes

Lasers
    excimer laser
    dye laser
    gas laser

3.2.1 Incandescent sources

When a material is heated a large number of energy transitions occur within its molecules and optical photons are emitted. An ideally efficient emitter (radiator) is termed a black body radiator. The total radiant power and its spectral distribution depend only on the temperature of the black body. The spectral emissions in terms of spectral radiant exitance of a black body radiator for different temperatures are illustrated in figure 3.2 and tabulated in table 3.4 (McKinlay *et al.,* 1988). The wavelength corresponding to the peak of the spectral emission of a black body radiator varies inversely as its temperature and as the temperature increases an increasing amount of UV is emitted. Incandescent sources whose temperatures are greater than about 2900 K emit significant amounts of UV with respect to possible effects on human health. The optical emission of the sun corresponds approximately to that of a black body radiator at a temperature of around 6000 K.
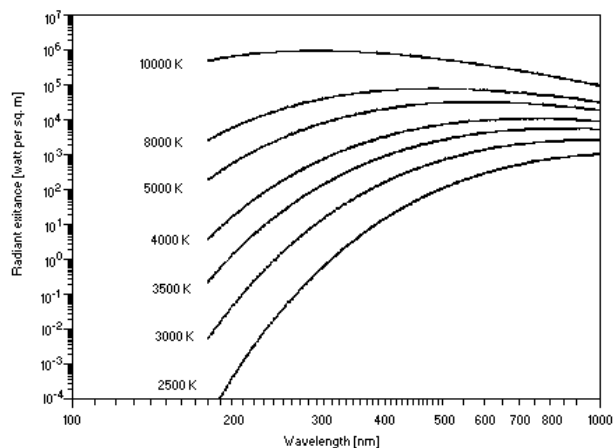

Figure 3.2 Spectral emissions of black body radiators at different temperatures (McKinlay et al., 1988)

By integrating over all wavelengths the area under an absolute plot of spectral radiant exitance against wavelength, the total radiant exitance M can be determined by the formula:

$$M = \text{sigma}\,T^4$$

where sigma = Stefan-Boltzmann constant (5.67×10^{-3} W m^{-2} K^{-4})
and   T = absolute temperature (K).

Table 3.4 Approximate radiant exitances of black body sources at different temperatures

Temperature K	UVB/C 200-315 nm [W m^{-2}]	UVA 315-340 nm [W m^{-2}]	UVA 340-400 nm [W m^{-2}]
1500	8.6×10^{-5}	5.6×10^{-4}	2.7×10^{-2}
2000	2.4×10^{-1}	7.9×10^{-1}	14.2
2500	29	62	634
3000	760	1147	8095
3500	8050	9220	5×10^4
4000	4.8×10^4	4.4×10^4	2×10^5
5000	6.3×10^5	4×10^5	1.4×10^6
6000	3.6×10^6	1.7×10^6	5×10^6
10000	1.4×10^8	3.2×10^7	6.9×10^7

In practice no material emits radiation with a black body spectrum. However, tungsten at high temperatures (such as used for the filaments of ordinary and tungsten halogen incandescent lamps) and molten metals approximate to theoretical black bodies. Such sources are termed grey bodies. The ratio of the actual spectral radiant exitance to the theoretical black body spectral radiant exitance is a measure of how closely the grey body approximates in its spectral emission at a particular wavelength to a black body and is termed the spectral emissivity (epsilon$_{lamda}$). Similarly, by summation over all wavelengths, the total radiant exitance M of a material is given by

$$M = \text{epsilon sigma }T^4$$

where epsilon is the emissivity.

The emissivity depends on the material and on its surface structure, and is a function of wavelength. For example, for tungsten at 3000 K (typical of a tungsten halogen lamp filament), the emissivity varies from an average of about 0.45 in the UVA region to about 0.2 in the IRB (1.4 - 3.0 µm) region.

The incandescent lamp is the oldest type of electric lamp still in common use. The optical radiation from incandescent lamps results from the heating of tungsten filaments which, with the exception of lamps for some photographic and graphic arts applications, are not heated to temperatures in excess of about 3000 K. Typical gas-filled incandescent filament lamps operate between 2700 and 3000 K with electrical input powers up to 500 W and the peaks of their spectral emissions are in the infra-red (IRA) region. The emissions of UV by tungsten filament lamps are generally negligible with respect to human health.

In applications where greater power (up to 5 kW) is required, tungsten-halogen (often called quartz-halogen) lamps are often used. These are quartz envelope tungsten filament lamps to which a halogen vapour (usually iodine) is added. The presence of the vapour enables operation at an increased gas pressure compared with conventional incandescent lamps, and evaporation from the filament is minimized. These features result in improved luminous efficacy and longer life. In order to operate efficiently, the temperature of the wall of the bulb must be maintained at not less than 260 ºC. The majority of the bulbs of tungsten-halogen lamps are made from silica (quartz) whose thermal properties are most suitable. The combination of filament temperatures which are likely to be in the range 2900 to 3450 K and quartz bulbs results in a significantly higher level of emission of potentially harmful UV compared with ordinary tungsten filament lamps. The incorporation of suitable secondary filtration to reduce UV emissions to an acceptable level is an important feature of the design of any illumination system using tungsten halogen lamps (McKinlay et al., 1989).

3.2.2 Gaseous discharge sources

The electrical excitation of a gas or vapour is a typical mechanism for generating optical radiation. An electric current is passed through a gas or a mixture of gases ionized to produce electrons and positive ions. Emissions are the result of electronic transitions in the atoms of a material from low to high energy states (absorption and excitation) followed by transitions from the high to low energy states (de-excitation and emission). This process is often combined with the process of luminescence, whereby the characteristic (line) photon emissions of the gas are absorbed by a luminescent material (luminophor or phosphor) which in turn emits optical radiation, typically as a continuum over a range of longer wavelengths. The 253.7 nm UV emission from a low pressure mercury vapour discharge is used as a source of excitation in low pressure

fluorescent lamps. By raising the pressure of the discharge to a few atmospheres the emission lines increasingly broaden effectively forming a continuum. In some cases the 253.7 nm line emission will be self-absorbed by the vapour of the discharge.

Low pressure discharge lamps

Germicidal lamps

The low pressure mercury-discharge lamp is often used for the purpose of germicide and disinfection. Such lamps are very efficient emitters of UV. Approximately 50% of the electrical power is converted to UV of which up to 95% is emitted at a wavelength of 253.7 nm (see figure 3.3). Germicidal type lamps are available in a range of sizes, shapes and powers. Small, low-wattage (5-10 W) germicidal lamps are often used as fluorescence-inducing lamps for the purposes of, for example, chromatographic analysis and the fluorescence identification and authentication of documents. The quartz envelopes of some lamps in this category transmit 185 nm wavelength radiation characteristic of mercury vapour.

Fluorescent lamps

The most common application of the low-pressure discharge is fluorescent lamps. These operate by means of a discharge between two electrodes through a mixture of mercury vapour and a rare gas, usually argon. Light is produced by conversion of 253.7 nm mercury emission to longer wavelength radiations by means of a phosphor coating on the inside of the glass envelope of the lamp. Lamps are available with many different phosphors and envelopes to produce a wide range of spectral emissions covering the visible (light), UVA and UVB regions. While the continuum emissions of fluorescent lamps are characteristic of the phosphors the narrow peak, spectral emissions are dominated by the characteristic line emission spectrum of the low-pressure mercury vapour discharge.

General lighting fluorescent lamps

These lamps are available in a range of physical sizes, powers and phosphors. The range of phosphors includes a large selection of "near white" and "special colour" lamps. In relation to other light sources the fluorescent lamp is particularly efficient, with about 20% of the input energy resulting in useful light. Detailed spectral analysis of the UV emissions of different general lighting fluorescent lamps have shown that in general UVB and UVC emissions are extremely low due to the marked attenuation of wavelengths < 320 nm afforded by the glass envelope.

Figure 3.3 Spectral emissions from a low pressure (germicidal) mercury discharge lamp.
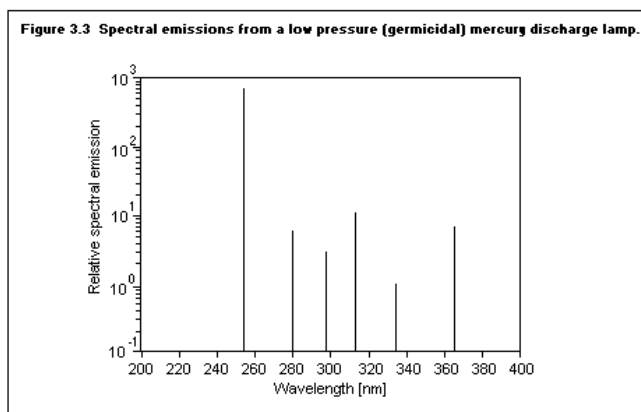
Frequently in office and industrial environments where fluorescent lamps are used, the luminaire assembly incorporates a diffuser or controller. Three materials are commonly used in the construction of diffusers; opal acrylic, opal styrene and opal polycarbonate. Controllers are luminaire covers that are configured with small prisms or lenses. Two commonly used materials are clear acrylic and clear styrene. Some luminaires incorporate opal (diffusing) sides and a clear figured [controller] base. The use of diffusers and controllers results in the absorption and reflection of the radiation emitted by the associated lamp. The UV-attenuating properties of different diffusers is demonstrated by the measurement data in table 3.5.

During the past few years the further development and improved design of general lighting fluorescent lamps have been evident in the production of compact fluorescent lamps. These lamps are essentially low power small diameter fluorescent tubes folded in a compact form. They are most readily available commercially with cool white phosphors but other phosphors are also available. For a given illuminance their spectral emissions of UV are essentially no different from those of full size tubular fluorescent lamps as shown in table 3.6.

Table 3.5 Measurements of UV irradiance from various diffusers/controllers with a white fluorescent lamp as the source. Irradiance totals in each waveband in mW m^{-2} (percentage in parentheses), (McKinlay et al., 1988).

Diffuser Type	UVA mW m^{-2}	UVB mW m^{-2}	UV$_{ACGIH}$** [mW m^{-2}]$_{effective}$
Bare lamp	22.32 (100d)	3.45 (100)	59 x 10^{-3} (100)
Clear acrylic[+]	16.35 (73)	2.91 (84)	48 x 10^{-3} (81)
Clear styrene[+]	2.87 (13)	0 (0)	0 (0)

Opal styrene*	0.92 (4)	3×10^{-3} (< 0.1)	0.02×10^{-3} (<0.1)
Opal polycarbonate*	0.20 (< 1)	12×10^{-3} (< 1)	0.09×10^{-3} (<1)

 + Surface figured with small prisms
 * Reeded surface
** ACGIH occupational hazard weighted irradiance: 1 maximum permissible
exposure for an 8 h working day is equivalent to 10^{-3} [W m^{-2}]$_{effective}$ ..

Table 3.6 Measurements of UV from compact fluorescent lamps,
normalised to an illuminance of 500 lux (Whillock et al., 1990)

Lamp type	UVA mW m^{-2}	UVB µW m^{-2}
Luma (7 W) LC7	47×10^3	0
Luma (7 W) LC7 with diffuser	197	0
Osram (11 W) Dulux EL	38×10^3	0.1
Philips (9 W) SL9	37×10^3	0
Sylvania (13 W) Lynx CFD	43×10^3	30.81
Thorn (16 W) 2D	54×10^3	2.48
Tungsram (16 W) Globulux	663	0

     "Special" applications fluorescent lamps

     Apart from a number of colour-rendering fluorescent lamps,
which are essentially variations of general lighting fluorescent
lamps, a number of special applications fluorescent lamps have been
developed.

     A common example of a UVB emitting fluorescent lamp is the FS
type lamp with spectral emission shown in figure 3.4. Such lamps
were previously used for cosmetic tanning and are now often used as
a source of UVB in biological experiments. The blacklight lamp uses
a nickel/cobalt-oxide (Woods glass) envelope that is almost entirely
opaque to light. The phosphor chosen for this type of lamp emits
around 370 nm in the UVA. Such lamps are used for a number of
commercial, scientific and industrial fluorescence purposes as well
as for display and entertainment. Three types of fluorescent lamps
that emit UVA in printing and copying merit mention viz; lamps
suitable for diazo printing with a principal emission around 360 nm;
those intended for modern fast diazo printing with a main emission
around 420 nm; and those used for photocopying with predominantly
green emissions.

     A medical treatment for hyperbilirubinaemia in neonates
(neonatal jaundice) consists of irradiating the newborn child with
phototherapy lamps emitting in the wavelength range approximately
400 to 470 nm. Some lamps used for this purpose have emission
spectra that extend into the UV region. Fluorescent lamps in
printing and copying include lamps for diazo printing with a
principal emission around 360 nm.

     The development of a range of phosphors with enhanced UVA
emissions has led to the widespread use of fluorescent lamps in
sunbeds, solaria and PUVA (Psoralen + UVA) treatment cabinets.

     High pressure discharge lamps

     The designation "high pressure discharge" lamps is taken in
this monograph to include the families of lamps often called high
intensity discharge (HID), such as mercury vapour or metal halide
lamps, where an electric arc is not created. At still higher
pressures, arcs may be produced, e.g., the xenon or mercury compact
(short-arc) lamps.

     Mercury and metal halide lamps

     High-pressure mercury vapour lamps are widely used for lighting
in commerce, streets, displays, floodlighting and a large number of
printing, curing and other industrial applications. The spectral
emissions of the discharge are in the blue, green and yellow regions
of the spectrum and a large amount of UV is also generated. The
general construction of high-pressure mercury lamps is a fused
silica (quartz) discharge tube containing the mercury/argon vapour
discharge mounted inside an outer envelope of soda-lime or
borosilicate glass.

     The outer glass envelope effectively absorbs most residual UV.
Consequently the quantity of potentially harmful UV emitted by such
lamps depends critically on the integrity of this envelope. In the
USA, but apparently not in Europe, it is a legally enforceable
manufacturing requirement that breakage of the outer envelope must
either cause the lamp to fail to operate, in which case the lamps
are described as "self-extinguishing" and are marked with the letter
"T", or if not "self-extinguishing" they should be marked with the
letter "R". In the latter case a warning notice must be included
with the packaging of the lamp (FDA., 1988). Data from measurements
made at 2 m from a mercury HID lamp with the outer envelope removed
illustrate the importance of this aspect of safety design, as shown
in table 3.7.

Figure 3.3 Spectral emissions of an FS type UVB fluorescent lamp.
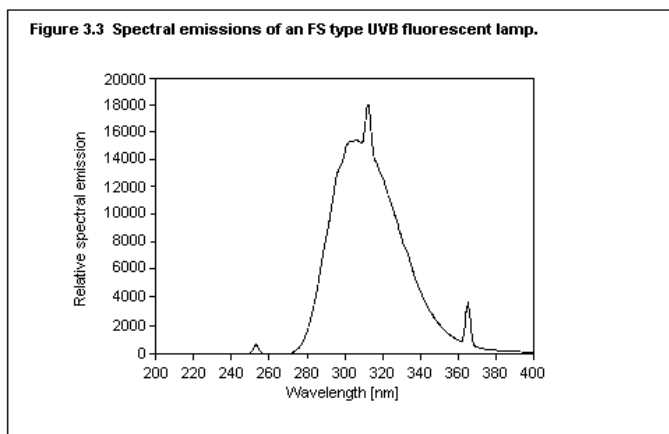
Table 3.7 UV emissions from HID mercury vapour general lighting (USA) lamps; effective irradiance in mW m$^{-2}_{effective}$, (ACGIH), (Piltingsrud et al., 1978).

Test condition	A		B		C		D	
Lamp type	With outer bulb	Without outer bulb	With outer bulb	Without outer bulb	With outer bulb	Without outer bulb	With outer bulb	Without outer bulb
General Electric H400 A33-1 Clear	2.5	110*	< 0.1	160	12.5	3640	0.2	0.2
Westinghouse H33 GL 400/DX White	< 0.1	1040	< 0.1	190	0.2	3680	< 0.1	0.3
General Electric H400D x 33-1 White	< 0.2	75*	< 0.1	180	0.5	3900*	< 0.1	< 0.1*
General Electric MV400/BUH [Metal halide]	< 0.3	122*	< 0.1	6*	1	510*	< 0.1	< 0.1*

Test Conditions:
A: Lamp mounted vertically - measurements at 2 m on mid-line axis of lamp.
B: Lamp mounted horizontally - measurements at 2 m on central axis of lamp.
C: Lamp mounted horizontally in reflector shield with no face plate - measurements at 2 m on central axis of lamp.
D: Lamp mounted horizontally in reflector shield with glass face fitted - measurements
   at 2 m on central axis of lamp.

* Lamps did not operate at normal intensity.

     The family of metal halide lamps encompasses a number of
different types of high pressure mercury lamps whose discharges all
contain additives. The additives are most typically metal halides
chosen to produce either a strongly coloured emission (usually a
single halide), to produce a more broadly spectrally uniform
emission (multi-halide) or to enhance the UV (most often UVA)
emission. Compared with ordinary high pressure mercury lamps the
luminous efficacies of metal halide lamps are high. They are used
for a range of industrial and commercial applications that include
photochemical processing, graphic and photographic illumination,
studio lighting, reprography and are also used for UVA cosmetic
tanning equipment, for some medical applications and for solar
radiation simulation. The UV irradiances of some metal halide lamps
used in filtered industrial applications requiring an activating
range of wavelengths between 320 and 440 nm, e.g. lithographic
platemaking and printed circuit photo-resist etching, are shown in
table 3.8 (McKinlay et al., 1988).

Table 3.8 UV irradiances measured at 1 m from typical graphics arts
metal halide mercury lamps (McKinlay et al., 1988)

Lamp type	Power [W]	UVC [W m^{-2}]	UVB [W m^{-2}]	UVA [W m^{-2}]
HPA 400	400	0.5	3.2	9.0
HPA 1000	930	2.3	9.0	23.0
HPA 2000	1750	4.5	19.0	48.0

     The emission of a device incorporating iron additive halide
lamps for phototherapy is illustrated in figure 3.5. The importance
of incorporating filtration in such devices in order to remove
unwanted components of the UV spectrum is illustrated.

Figure 3.5 Spectral emissions of a phototherapy system incorporating metal halide lamps. The system is fitted with 2 filters and the measurement data illustrated are for; none, one or both filters in place (McKinlay 1992, measurement data kindly provided by Diffey).
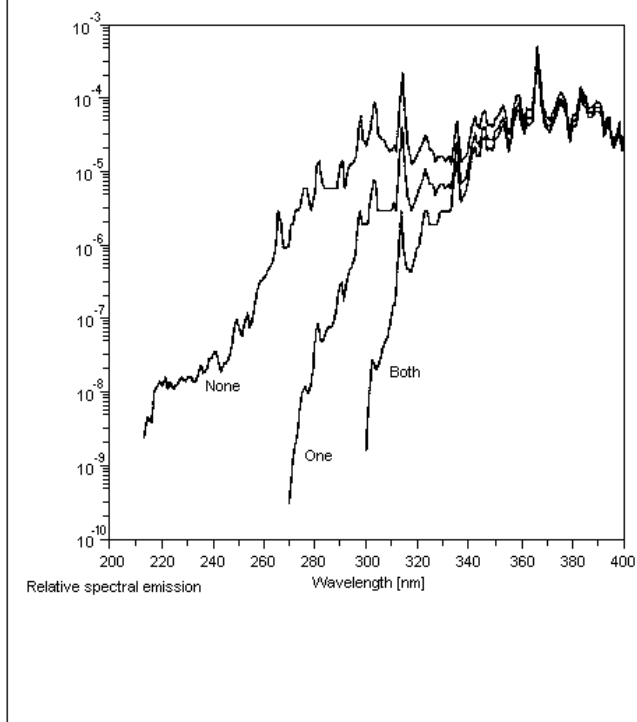
Xenon, compact and linear arcs

     Where an optical source of very high radiance is required and
of small size a very high pressure arc lamp may be used. These have
a filling gas of mercury vapour, mercury vapour plus xenon gas or
xenon gas. Metal halide types are also available. Two physical types
are commonly used; the compact (short) arc and the linear arc. The
spectral emission of xenon lamps, which at wavelengths shorter than
infra-red, closely matches that of a black-body radiator at about
6000 K. This enables their use in photography and as solar radiation
simulators.

     The spectral emission of xenon lamps, which at wavelengths
shorter than infrared closely matches that of a black body radiator
at about 6000 K, enables their use as solar radiation simulators.
Their emission spectrum is continuous from the UV through to the IR
regions. Large amounts of UVA, UVB and UVC are emitted by unfiltered
lamps to the extent that they can present a significant health
hazard if incorrectly used. The luminance of compact xenon arcs may
approach that of the sun and in some lamps with greater than 10 kW
rating the luminance may exceed that of the sun. They therefore
present a potentially severe retinal hazard if viewed.

3.2.3 Gas welding

     Oil, coal and gas flames normally operate at temperatures below
about 2000 K and consequently emit virtually no UV. Oxyacetylene and
oxyhydrogen flames burn at much higher temperatures and emit UV
mostly in the UVA region.

3.2.4 Arc welding

     By comparison with gas flame processes, the emissions of UV
from arc welding are very high (see figure 3.6) and many data on the
optical radiation emissions associated with a variety of electric
arc welding processes have been published (e.g., Sliney & Wolbarsht,
1980).

3.2.5 Lasers

     All lasers have three basic components (see figure 3.7): (a) a
laser (active) medium; (b) an energy source (pumping system) and;
(c) a resonant optical cavity. A pumping system is necessary to
provide energy to electrons to raise them to excited states and
achieve population inversion. Optical pumping, using an intense
source of light such as a xenon flashtube; electron-collision
pumping, using an electrical discharge and; chemical pumping, using
the energy released from making and breaking chemical bonds, are all
used for this purpose. A resonant optical cavity is formed by

mirrors placed at each end of the laser medium. The construction is
such that the beam passes through the laser medium several times and

the number of emitted photons is amplified during each transit. One
of the mirrors is chosen to be partially transmitting thus enabling
part of the beam to be emitted from the cavity (figure 3.7).
Examples of lasers that emit UV are presented in table 3.9.

Table 3.9 UV laser emissions and characteristics,
           (McKinlay, 1992)

Type	Name	Spectral emissions
Excimer	Argon fluoride [(ArF)	193 nm
	Krypton fluoride (KrF)	248 nm
	Xenon chloride (XeCl)	308 nm
	Xenon bromide (XeBr)	282 nm
	Xenon fluoride (XeF)	351 nm
	Krypton chloride (KrCl)	222 nm
Dye	Excimer-, Nitrogen-,	300 nm-
	Flash lamp pumped	340 nm-
Gas	Nitrogen (N_2)	337 nm
	Helium cadmium (He-Cd)	325 nm
Gas ion	Argon (Ar^+0	333 nm-
		357 nm
		363 nm
	Krypton (Kr^+)	337.5 nm
		350.7 nm
		356.4 nm

     A recent generation of UV lasers are the excimer lasers. The
active media used are rare gas halides such as ArF, KrCl, XeBr or
XeF. The molecules of those gases have only a short lifetime in the
ground state, however they are very stable in the excited state. As
a buffer medium, helium is often used. Population inversion is
easily achievable because the ground state is very unstable.

3.2.6 Sunbeds

     Sunbeds are broadly used for cosmetic tanning purposes. The
expression "sunbed" includes tanning equipment consisting of a UV
emitting lamp or a number of such lamps incorporated in a bed,
canopy or panel, or any combination thereof. There are four distinct
types of lamps in use, each with different UV emission
characteristics. Those are UVA, low-pressure fluorescent tubes; UVA,
filtered high-intensity discharge lamps; UVB, low-pressure
fluorescent tubes; UVB, filtered high-intensity discharge lamps.

**Figure 3.6 Emission spectrum from gas tungsten arc
welding. The spectral emissions of all kinds of arc
welding processes varies with the compositon of the
composition of the eletrodes and the metals being
joined, the plasma that is created and the shielding gas
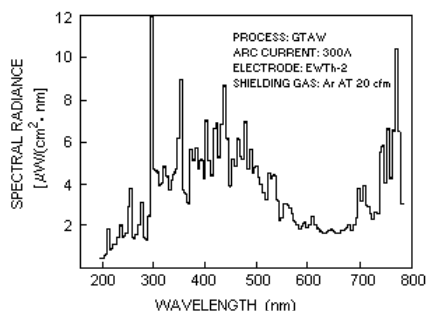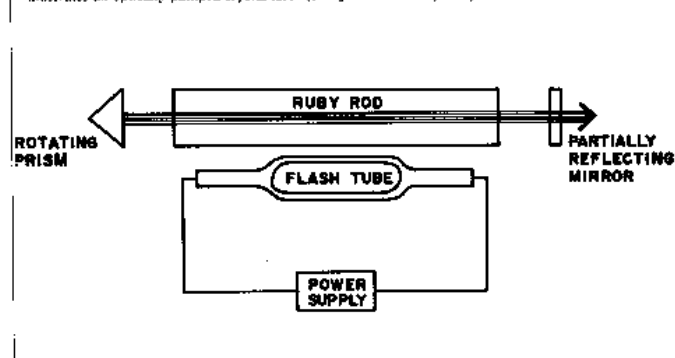used (Sliney & Wolbarsht, 1980).**

Figure 3.7 Simplified diagram of a laser. All lasers consist of a resonant cavity (generally two mirrors, one partially transmitting), an energy source and an active medium. The diagram here illustrates an optically pumped crystal laser (Sliney & Wolbarsht, 1980).

The emission characteristics and the health risks associated
with the use of each type of lamp are different. The last two lamp
types are associated with high levels of UVB and are now little
used. They have been almost universally replaced by the
predominantly UVA emitting lamp types.

4. HUMAN EXPOSURE

4.1 Sunlight

Outdoors, exposure to UV constantly changes during the day.
People are largely unaware of the degree of these changes. At noon,
when the sun is overhead, the level of UV at a wavelength of 300 nm
is ten times greater than at either three hours before (9 am) or
three hours after noon (3 pm). An untanned person with fair skin may
receive a mild sunburn in as little as 25 minutes at noon (depending
on the time of year and the latitude) but would have to lie in the
sun for at least two hours to receive the same dose after 3 pm. The
global biologically effective UV falling on a horizontal surface
occurs primarily during the midday hours, about 50% during the four
hours centred on noon-time zenith (Sliney, 1987).

Scattering of sunlight by air molecules (due to Raleigh
scattering) favours UV and blue light (hence the blue sky). For
longer pathlengths through the atmosphere when the sun is low in the
sky, more UV and sunlight is scattered. The sun which is white at
noonday becomes yellow and then orange as less UV and blue light are
present in the direct rays. When the sun is overhead staring at the
sun for 90 seconds would cause solar retinitis. A few hours later,
with the sun much lower in the sky, it would take many minutes to
reach a hazardous retinal dose, and it is virtually impossible to
cause any eye damage at sunset. Thus, the geometry of exposure as
well as the spectrum (hue) plays a major role in determining the
hazards from direct exposure from the sun (Sliney, 1983, 1986).

Estimation of an individual's lifetime UV exposure requires
knowledge of the ambient solar UV levels, history of outdoor
exposure and the relative exposures at the different anatomical
sites. Studies on the anatomical distribution of solar UV have been
reported (Diffey et al 1979; Rosenthal et al., 1985; Holman et
 al., 1983; Gies et al 1992a; Roy et al., 1988). The relative
doses at various body sites have been determined using UV sensitive
polysulphone film on rotating manikins and headforms. It was found
that even though the relative doses to the face and eyes are higher
in winter, due to the lower solar elevation, the absolute doses are
higher in summer. The presence of a brimmed hat reduced the face
exposure by a factor of at least two and the eye exposure was
reduced by a factor of 4 to 5 (Diffey et al., 1979, Roy et al
1988).

Polysulphone film badges have also been used to quantify the
solar UV exposure received by different subjects and results
compared to those calculated from personal diaries and measured
ambient solar UVB (Gies et al., 1992a). In general, when UV
exposure activities took place under close supervision, good
correlations were obtained between the polysulphone badges and the
ambient/diaries approach. Results from a recent study (Roy and Gies,

1993), of indoor, outdoor and retired workers indicated that
exposures to badge locations of up to 30% of ambient were recorded.
Through studies of this type, knowledge is gained on the amount and
pattern of exposure from routine activities and this can then be
applied in the design of educational campaigns to modify outdoor
behaviour and reduce UV exposure. The use of polysulphone or CR39
plastics (Wong et al., 1989; Sydenham et al., 1991) as
contact-lens dosimeters have been proposed, but lack of sensitivity
and personal comfort has discouraged their use in field studies.

4.2 Skin Exposure Geometry

UV incident on human skin can follow one of three courses, it
can undergo absorption, reflection, or scattering. Thus, the actual
radiant exposure received by the various layers of the skin will be
lower than the incident exposure. Reflection not only occurs at the
surface of the stratum corneum, but at all interfaces changing in
refractive index. Scattering occurs because of the different
structural elements, such as hair follicles and sebaceous glands,
and also by cellular components, such as mitochondria and ribosomes.
The remaining UV can penetrate into deeper skin layers.

UV penetrates into the dermis exposing a variety of cells and
structures, depending in part on the thickness of the human stratum
corneum and epidermis. The depth of penetration is wavelength
dependent the longer the wavelength the deeper the penetration
(Bruls et al., 1984). From figure 4.1 it is seen that the same
incident exposure of UVA or UVB radiation will result in a higher
actual exposure of UVA than UVB at a given depth. For example, if
the incident UV exposure was 100 kJ m^{-2} then 50 kJ m^{-2} of 365 nm
radiation would be present at a depth of 30 μm and only 19 kJ m^{-2}
at a depth of 70 μm. For 313 nm radiation only 33 kJ m^{-2} would be
present at 30 μm and 9.5 kJ m^{-2} at 70 μm. While less than 1% of
the UVC wavelengths can barely penetrate the epidermal layer (Bruls
 et al., 1984), about 1% of the incident UVA dose can penetrate
into the subcutaneous tissue (Parrish et al., 1978). The
distribution and size of melanin particles also plays an important
role in protecting epidermal cells. Melanin particles have a
distribution within the stratum corneum and epidermal cells
depending upon skin type. In dark skin types (5 and 6) these

particles are positioned within cells to provide optimum optical
protection for the cell nuclei and in adequate size in the stratum
corneum (Kollias *et al.,* 1991).

Figure 4.1 Schematic of human skin depicting the layers, cell types, structural components and percent transmittance of UVA, UVB and UVC radiation at different depths (Bruls et al., 1984).
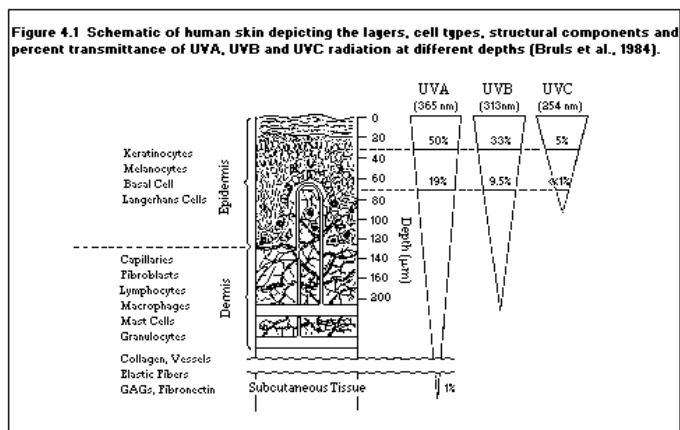
4.3 Ocular Exposure Geometry

     People seldom look directly at the sun when it is overhead and
very hazardous to view. It is not very hazardous to view when the
sun is low in the sky and falls within the normal field-of-view.
When the sun is more than 10° above the horizon, the natural
tendency is to partially close the eyelids or squint (called squint
reflex), thus shielding the retina from direct exposure. These
factors reduce the exposure to the cornea to a maximum of about 5%
of that falling upon the exposed top of head (Sliney, 1986). If the
squint and other behavioural factors are not considered, the dose to
the eyelid would be approximately 20% of the dose falling on a
horizontal surface.

     Although the cornea is more sensitive to UV injury than the
skin, people seldom experiences a corneal burn when in sunlight.
Using the action spectrum for human photokeratitis and
mathematically weighting this with the midday solar spectrum, the
time to achieve the threshold for photokeratitis is about 100
seconds (Sliney, 1987, Rosenthal *et al.,* 1988). Again, the
geometry of exposure precludes photokeratitis except when ground
reflectance exceeds approximately 10%. When the sun is overhead and
UV exposure is most severe, the brow ridge and upper lid shield the
cornea, and if the eye is turned away from the sun, the more intense
scattered UV from overhead strikes the cornea at a grazing angle of
incidence where most is reflected and little is absorbed (Sliney,
1983). Only when the incident UV rays are parallel to the pupillary
axis are most rays (approx. 98%) absorbed.

     When looking at snow, UV is reflected directly into the eye;
hence, the traditional eye protector of the Inuit or Eskimo, the
slit, in whalebone or in a seal-skin mask, provided geometrical
rather than spectral protection against UV exposure (Hedblom, 1961).
The lack of protection above and to the sides of sunglasses is a
serious shortcoming. However, to obtain a quantitative idea of this
component of exposure to the eye, measurements were made using a
simulated ocular geometry in sunlight (Sliney, 1986). The human eye
received 10 to 25 % of the UV dose when wearing glasses with lenses
opaque to UV compared to no lens in the glasses. Therefore, unless
goggles with side-shields are used, UV transmission factors in
lenses much less than 2-5 % do not provide the eye protection
suggested by the transmission factor (Sliney, 1986).

     The strong dependence of reflectance with angle of incidence is
termed Fresnel's Law of Reflection. This law not only explains the
survival of the cornea exposed overhead to UV, but also the glare
experienced over water. When the sun is overhead, water reflects
about 2% of the UV upward (Sliney, 1986). When low in the sky, much
of the sunlight is reflected while the UV and blue light are
filtered by the atmosphere. Nevertheless, the strong reflections

from water at these low sun angles create discomfort glare and UV
exposure of the cornea is further reduced because of the squint.

     If dark lenses are placed over the eyes, the natural aversion
to bright light, which leads to the squint reflex (that greatly
lowers retinal UV or exposure to the eye), would be disabled. This
may appear to be an unusual way to consider the comfort that shaded
lenses provide. However, poor sunglasses may actually lead to a
higher UV exposure (Sliney, 1983).

     However, quantifying the protective value of the upper and
lower eye lids when they close to squint is difficult. In terms of
UV exposure, at least a twenty-fold reduction is likely. For
shielding the retina from the direct image of the sun, the upper lid
probably provides a protection factor exceeding a thousand (Sliney -
personal communication). If a brimmed hat is worn, the direct image
of the sun on the retina is rare and overhead UV exposure is
virtually eliminated. However, while using a hat the lid opens
further and ground reflection of UV could become important.

     On an overcast day, the lids open wider, and although the UVB

irradiance is reduced by cloud cover, the actual UVB dose rate to
the eye from atmospheric scattering near the horizon may be reduced
by a factor of only two (Sliney, 1983). Hence, on a cloudy day the
eye may receive a greater UVB dose than on a bright sunny day.
However, a heavy overcast may attenuate the UVB sufficiently, that
this observation may not be true. As sunglasses are not typically
worn on an overcast day, one could argue that the concern over
sunglasses increasing total ocular exposure is unimportant. However,
sunglasses should have sufficient UV filtration so that ocular
exposure does not actually increase when they are worn on a sunny
day.

Eye and head movements can further reduce UV exposure. Most
humans in bright sunlight squint or avoid looking into the sun
sector of the sky. These behavioural and physiological factors are
not taken into account by simple UV measurements. There is an
obvious need to determine accurately the corneal and lenticular
exposure to ambient UV. Indeed, the results of previous
epidemiological studies of cataract may be questioned because of
inadequate dosimetry. Some epidemiological studies may have reached
incorrect conclusions regarding risk from UV or sunlight exposure by
assigning inaccurate exposure levels to population groups, because
they assumed that overhead UV exposure accurately predicts corneal
exposure.

4.4 Workplace

4.4.1 Outdoor work

Although humans have adapted and acclimatized to solar UV it
nevertheless represents the most hazardous source of optical
radiation likely to be encountered by the average person and with a
few exceptions by the worker. People who work outdoors will be
subjected to involuntary UV exposure. The highest exposure will
occur during the two hours period either side of noon. Workers must
be made aware of this and take appropriate precautions as discussed
in chapter 13.

In a study of various work and recreational situations
(Challoner *et al.,* 1976; Diffey *et al.,* 1982), it was found that
outdoor workers had the highest exposure, receiving approximately
10% of the ambient level, similar to that received during sailing
and sightseeing. Higher exposures were found for skiing (20%) and
the largest during sunbathing on a beach (80%). Office workers
received about 3% of the total ambient radiation with about half
that figure from weekend exposure (Leach *et al.,* 1978). The actual
exposures vary depending on the time of day and year, duration and
frequency of exposure.

4.4.2 Indoor work

Examples of indoor workplace exposures to UV are given below.

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 which emit significant amounts of UV (Diffey, 1990a).
The principal industrial applications of photopolymerisation include
the curing of protective coatings and inks and photoresists for
printed circuit boards. The curing of printing inks by exposure to
UV 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.

Sterilization

UV with wavelengths in the range 260-265 nm is the most
effective for sterilization and disinfection since it corresponds to
a maximum in the DNA absorption spectrum. Low-pressure mercury
discharge tubes are often used as the UV source as more than 90% of
the radiated energy lies in the 254 nm line, figure 3.2. 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 effluent,
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 UV and ozone has a very powerful
oxidizing action and can reduce the organic content of water to
extremely low levels (Phillips, 1983).

Welding

Welding equipment falls into two broad categories: gas welding
and electric arc welding. Only the latter process produces
significant levels of UV, the quality and quantity of which depend
primarily on the arc current, shielding gas and metals being welded
(Sliney & Wolbarsht, 1980). The levels of UV irradiance around
electric arc welding equipment are high; effective irradiance at 1 m
at 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 on
the type of welding and the metal being welded (Mariutti & Matzeu,

1987; Cox, 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).

4.4.3 Research

     Sources of UV are used by most experimental scientists engaged
in 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 (Diffey, 1990a).

4.4.4 Commerce

     Sunlamps emitting UV have been used for tanning, particularly
in northern Europe and North America. Prior to the mid-1970s, the
source of UV in sunlamps was usually an unfiltered mercury arc lamp
which emitted a broad spectrum of radiation, including large
quantities of UVB and UVC. There are four distinctly different types
of ultraviolet tanning lamps in use, each with different UV emission
characteristics viz.; low pressure UVA fluorescent lamps; filtered
high intensity discharge UVA lamps; low pressure UVB fluorescent
lamps and; filtered high intensity discharge UVB lamps (IRPA/INIRC

1991). The emission characteristics and the health risks associated
with each type of lamp are different (Diffey and McKinlay 1983, Gies
et al 1986, Diffey 1987). Tanning systems incorporating lamps that
emit predominantly UVB are now little used and have been almost
universally replaced by the low pressure UVA fluorescent and
filtered high intensity discharge UVA types. Tanning requires
deliberate exposure of the skin to UV; however, the eyes must be
protected. Similarly, staff working in tanning salons must ensure
their exposure is kept to a minimum.

     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.

     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).

     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).

     Signatures, banknotes and other documents can be authenticated
by exposing them to UVA, under which they fluoresce. UVA exposure of
the user is normally to hands and irradiance is low (< 10 W m^{-2})
(Diffey, 1990a).

4.4.5 Medicine and dentistry

     In both medical and dental applications of UV, the patient is
deliberately exposed to either treat or diagnose a disease or
disorder. While non-target areas of the patient must be covered,
care must also be taken to ensure staff are fully protected from UV
exposure (see chapter 13).

     The diagnostic uses of UV are confined largely to fluorescing
of the skin and teeth. UV exposure is limited to small areas (< 15
cm in diameter) and the UVA radiation dose per examination is
probably no more than 5×10^4J m^{-2}. Diagnostic techniques are
limited to the use of fluorescence to identify the presence of
various fungal and bacterial infectious agents on the skin or in
wounds. The source of UV most commonly used for this purpose is the

Woods lamp which emits predominantly UVA radiation (365 nm).
Exposure of the patient's skin to potentially
carcinogenically-effective UV is insignificant (Diffey, 1990a).

     UV phototherapy is a well established method for the treatment
of a number of skin conditions and in particular for psoriasis
(Green *et al.,* 1992). Two general types of UVB emitting lamps are
used in phototherapy, high intensity discharge (HID) mercury vapour
and mercury/metal halide vapour lamps and low pressure mercury
vapour fluorescent lamps. The spectral emissions of these different
types of lamps vary greatly and this, with other factors such as the
number and power of the lamps, the lamp to skin distance and the
individual sensitivity of the patient, determines the treatment
time. A treatment dose is chosen to cause erythema in a particular
patient. As treatment progresses and the skin becomes increasingly
acclimatised, individual treatment doses are increased accordingly.
Treatments may be given several times per week. Phototherapy has

also been used for the treatment of other skin conditions including
severe itching, acne, eczema, polymorphic light eruption (PLE),
pityriasis rosea and urticaria, and for renal failure (Green *et
al.,* 1992).

Seasonal affective disorder (SAD) is frequently treated by
exposure to sources of high illumination. Most treatment regimes
have employed sources incorporating so-called "full spectrum
lighting" whose emissions contain small amounts of UVA and UVB
radiations (Terman *et al.,* 1990).

PUVA

UV photochemotherapy is UV phototherapy used in conjunction
with the oral or topical application of a chemical
(photosensitising) agent to the patient. The most widely used
treatment is PUVA which involves the use of the photosensitising
agent 8-methoxypsoralen (8-MOP) in conjunction with UVA irradiation
for the treatment of psoriasis. The irradiation sources used for
such treatment incorporate either low pressure mercury vapour UVA
fluorescent lamps, or HID mercury vapour or mercury/metal halide
vapour lamps with an added filter to effectively attenuate the UVB.
The UVA irradiance on the skin from sources incorporating
fluorescent lamps is generally of the order of 60 W m^{-2} and for
the HID mercury systems, around 250 W m^{-2}. Treatments consist of a
starting dose of between 500 and 40,000 J m^{-2}, depending on skin
type, followed by further incremental doses two to three times
weekly. Total treatment radiant exposures of between 10^6 and 2.5
10^6 J m^{-2} have been reported for successful results. However,
studies have shown large uncertainties in the dosimetry associated
with PUVA treatment and point to equally large consequential
uncertainties about the actual treatment doses delivered (Diffey et
al 1980).

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. The lamps used for
phototherapy, although intended to emit only visible light, may also
have a UV component (Gies & Roy, 1990; Sliney & Wolbarsht, 1980).

Dentistry

Irradiation of the oral cavity with a Woods lamp can produce
fluorescence under certain conditions. This has been used in the
diagnosis of various dental disorders, such as early dental
cavities, the incorporation of tetracycline into bone and teeth,
dental plaque and calculus (Hefferren *et al.,* 1971).

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 hardened by exposure to UVA
radiation at a minimal irradiance of 100 W m^{-2} for about 30 s
(Eriksen, 1987; Diffey, 1990a).

4.5 Elective Exposure

By comparison to occupational exposure to UV, where control
measures are generally instituted to protect the eye and skin,
elective exposures can be much greater. Elective exposure results
from outdoor recreational activity, from intentional exposure to
sun-tanning equipment and to sunlight at the beach and elsewhere.
Actual dose estimates of elective exposure experienced by those who
attempt to maintain a tan may exceed 100 MED per year (Challoner *et
al.,* 1976; Diffey, 1993a; Diffey *et al.,* 1982).

5. DOSIMETRIC CONCEPTS

5.1 Interaction of UV with Matter

Attenuation of UV occurs due to absorption and scattering.
Reflection, refraction and diffraction are phenomena related to
boundaries between media. All of these interactions may change the
direction, intensity and the wavelength of UV. The quantities
describing interactions of UV with matter are dependent on the
wavelength.

The total energy absorbed in a material is influenced by
reflections from its surfaces. The attenuation coefficient describes
the attenuation of UV within tissue and is the sum of the absorption
and scattering coefficients. Penetration depth in a tissue is
inversely proportional to the exponential attenuation coefficient.

Absorption requires transfer of radiative energy to matter.
Apart from possible photomechanical effects, UV is absorbed as a
result of electron transitions at the atomic and molecular level.
Such molecular absorption can lead to photochemical reactions.

In most molecules the ground state or the singlet state (S_0)
consists of two paired electrons. On absorption of radiant energy
one of the electrons can make a transition to an excited state
(S_1), provided that the incident photon energy corresponds to an
existing level in the absorbing molecule. As shown in figure 5.1,
the molecule can release this absorbed energy from the excited state
by (a) transition directly back to the ground state, S_0, or (b)
transition to the generally long-lived excited triplet state, T_1,

and then discharging the remaining energy to return to S_0. In either case, transition back to S_0 may be radiative (a photon emitted) or non-radiative (energy dispersed by vibrational-rotational relaxation). The radiative $S_1 \rightarrow S_0$ transition is called "fluorescence" while radiative $T_1 \rightarrow S_0$ is called "phosphorescence". In addition, molecules in the S_1 or T_1 states can return to the ground state either by forming photoproducts or by transferring the energy to an acceptor molecule. The effectiveness of the photochemical process can be amplified by "photosensitizers" or impeded by "quenchers".

Figure 5.1 Three-level electronic energy level diagram. Dashed lines represent non-radiative transitions while solid lines correspond to radiative transitions
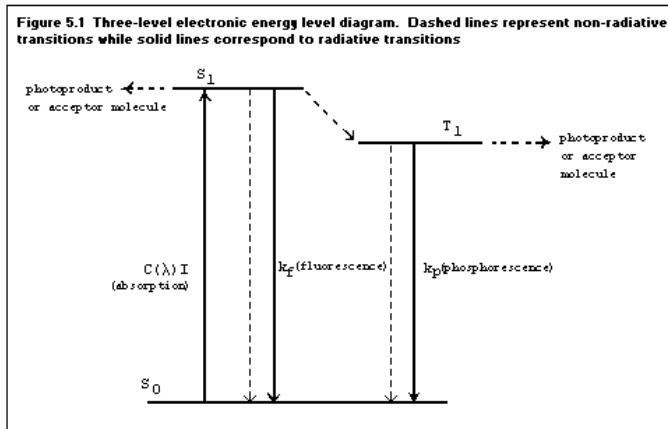
5.2 Biological Weighting Factors and Spectrally Weighted Quantities

Both radiant exposure H and irradiance E are quantities integrated over the total spectrum of interest. To describe the irradiance or radiant exposure in a very narrow spectral (wavelength) interval (Delta lambda), the quantities of *spectral irradiance* E_{lambda} and *spectral radiant exposure* H_{lambda} are employed. These have the units of: $W\ m^{-2}\ nm$ and $J\ m^{-2}\ nm$, respectively. If E_{lambda}Delta lambda is the irradiance in a narrow interval Delta lambda around the wavelength lambda, then the integrated irradiance E over the wavelength interval $lamda_1$ to $lambda_2$ can be written as:

$$E = \underset{lambda_1}{\overset{lambda_2}{Sigma}}\ E_{lambda}\ Delta\ lambda$$

E_{lambda} and H_{lambda} are spectral functions. Other spectroradiometric quantities exist with analogous definitions, e.g., spectral radiant power, spectral radiant energy, etc, as shown in table 2.2. The spectroradiometric quantities are important in photobiology, and are critical in any discussion of the biological effects of UV. The biological effects of UV are strongly wavelength dependent. As a measure of these effects, "effective" or "biologically active" quantities have been introduced (CIE, 1987). The effective irradiance E_{eff} is defined as:

$$E_{eff} = Sigma\ E_{lambda}\ S_{lambda}\ Delta\ lambda$$

and similarly, the effective radiant exposure is

$$H_{eff} = Sigma\ H_{lambda}\ S_{lambda}\ Delta\ lambda$$

where S_{lambda} is called the relative spectral effectiveness function or *action spectrum*.

The *action spectrum* gives the relative biological response of a tissue to irradiation at different wavelengths, and ideally will correspond to the absorption spectrum of critical absorbing molecules, or "chromophores." In biological systems, however, the action spectrum function is modulated by the shielding (i.e. thickness) of overlying tissue (e.g., stratum corneum of the skin), energy transfer, and the action of sensitizers and quenchers. The action spectrum is therefore specific for a certain effect arising in a certain tissue layer. For example, the action spectrum for erythema (skin) and photokeratitis (cornea) differ.

Based on a statistical analysis of the results of minimum erythema dose studies carried out over the past 20 years or so, and including data by Parrish *et al*. (1982) on the erythemal efficacy of UVA, the CIE has promulgated a reference action curve (McKinlay and Diffey, 1987), as shown in figure 5.2. This function consists of three straight lines when plotted on a semi-logarithmic scale, and although individual action spectra would not have the two inflection points, the function can be readily expressed by three mathematical functions. The function has been adopted internationally by the CIE and the IEC and is being used by national organizations and authorities for the determination of the erythemal potential of an exposure to a given source of UV. A slightly different action spectrum, which cannot be so readily expressed mathematically, has been recommended by IRPA (1991) for risk assessment in occupational

health (see figure 5.2).

The erythemal response of the skin to UV is usually inferred from the minimal erythema dose (MED). This value is determined by exposing adjacent areas of skin to increasing doses of UV, and recording the lowest dose to achieve erythema at a specified time, usually 24 h after irradiation.

The visual detection of erythema is subjective and is affected by unrelated factors such as viewing geometry, intensity and spectral composition of ambient illumination, colour of unexposed surrounding skin, (Chamberlain and Chamberlain 1980, Diffey and Robson, 1992), and the experience and visual acuity of the observer. The difficulty in judging accurately a minimal erythema response is reflected by the varying definitions proposed for this value: these range from the dose required to achieve a just perceptible erythema (Everett *et al.,* 1965, Kelfkens and van der Leun, 1989); to that dose which will just produce a uniform redness with sharp borders (Wucherpfenning, 1931).

The MED will vary according to the wavelength range over which the effective UV is summed and for radiation protection purposes is generally taken to lie in the range 200 to 300 J m^{-2} effective.

5.3 Measurement Techniques

There are three distinct types of measurement systems employed in the detection of UV: radiometers, spectroradiometers and dosimeters. Radiometers and spectroradiometers are direct-reading instruments that use electro-optical (physical) detectors to convert the incident radiation into an electrical signal. Radiometers measure all incident radiant power over a wide spectral range; whereas, spectroradiometers measure the radiant power distribution over a wide spectral range. Either by electronic means or by computer control, radiometers or spectroradiometers may be modified and calibrated to operate as "dosimeters" by time-integration of the output signal from the detector.

Figure 5.2 UV-induced action spectrum and the IRPA/INIRC relative spectral effectiveness factor (McKinlay & Diffey, 1987 and IRPA/INIRC, 1991).
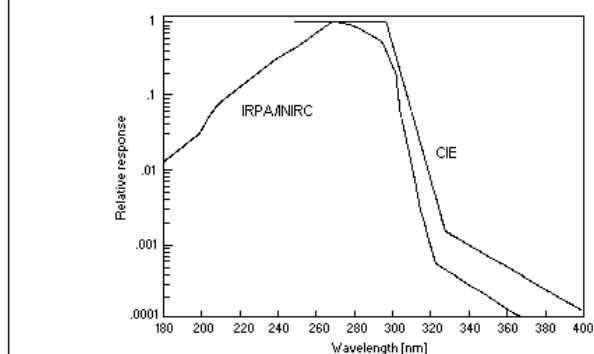
However, by dosimeters, one usually means devices that by nature respond directly to incident dose, i.e. radiant exposure. Dosimeters may be further optically modified and calibrated to respond according to an action spectrum, thereby serving as a direct-reading instrument for dose to a particular organ.

5.3.1 Detectors

The term detector normally refers to an electro-optical device which converts an optical signal (e.g UV or light) into an electronic signal which can be recorded. An important characteristic of any detector is the responsivity, defined as the quotient of the detector output (e.g amperes, A) and the radiant power incident upon the detector (e.g. watts, W). Thus units for responsivity may vary. The unit for irradiance-responsivity is often ampere-per-watt-per-square-metre (A W^{-1} m^{-2}). The spectral responsivity is the responsivity as a function of wavelength. The term detectivity is used to compare the detection capability (the smallest quantity of radiation that can be detected) of different types of detectors, the higher the detectivity the more sensitive the detector. Thermal detectors, such as thermopiles and pyroelectric detectors, have a much lower detectivity (less sensitive) than photodiodes, phototubes and photomultipliers.

The most common types of detectors for UV are semiconductor (junction) photodiodes, vacuum photodiodes (phototubes) and photomultipliers. Junction photodiodes are usually silicon (Si) photodiodes that may be enhanced to improve their UV responsivity and with a spectral responsivity between 190 and 1100 nm. Gallium-arsenide-phosphide (GaAsP) photodiodes have a spectral responsivity between 190 and 670 nm, and gallium-phosphide (GaP) photodiodes have a spectral responsivity between 190 and 520 nm.

Chemical detectors, such as photographic film emulsions or polymer films of polysulphone or CR-39 resins, respond to incident radiant exposure (J m^{-2}). Their responsivity is generally strongly wavelength dependant, and attempts are made to simulate a photobiological action spectrum directly.

The choice of an optimum detector for a specific instrument or measurement situation depends upon the requirements for ease of data collection, portability, electrical power requirements, size and accuracy. Each detector type has advantages and disadvantages. Important parameters to consider for instrument requirements are: spectral responsivity, noise-equivalent-power (NEP), linearity, time/frequency response, stability over time, environmental operating conditions, maintenance, ease of operation, the requirements upon additional electronics, and cost.

Biological detectors are also used. For example, biofilms using dried spores of *bacillus subtilis,* immobilized on transparent

polyester plastic sheets. After irradiation the biofilm is incubated in a growth medium and the proteins synthesized after spore germination, stained and evaluated by photometry. The biologically effective dose is calculated using a calibration curve. The UV response of this biofilm is additive and follows the reciprocity law in the normal range of fluence rates investigated. The response is independent of temperature (-20°C to 70°C) and humidity. The biofilm can be stored for up to 9 months at room temperature without significant influence on the viability of spores. These detectors have been used in Antarctica and in space to measure the biological consequences of ozone variations (Quintern *et al.,* 1992).

5.3.2 Radiometers

A radiometer is a detection system that measures incident radiation. A UV-radiometer usually measures irradiance in watts per square metre (W m^{-2}). The basic layout of a radiometer is shown in figure 5.3.

The diffuser shown in figure 5.3 may not always be present. When used, its purpose is to make the angular responsivity of the radiometer proportional to the cosine of the angle of incidence (measured from the normal to the diffuser surface). This arrangement is often called a *cosine-corrected* radiometer. The diffuser may be made from a flat or slightly curved piece of ground quartz or teflon, or it may be an integrating sphere. The purpose of the optical filter is to limit the spectral responsivity to a certain band, having a lower and upper wavelength cutoff. The band-width can vary upward from about 5 nm, but is often several tens or even hundreds of nanometres wide. Hence, radiometers are called broad-band meters as opposed to spectroradiometers. Ideally the spectral responsivity is constant within the band and zero outside, but in practice this is not possible. If the detector is sensitive to radiation outside the passband of the filter, which is normally the case, there will always be a non-zero responsivity outside the band. Signals which are produced by radiation from outside the band are called "out-of-band signals," "out-of-band leakage," or just "stray light." This limitation of radiometers can often be a serious problem, and is particularly troublesome in UV radiometers based on Si photodiode detectors, because the spectral responsivities of Si photodiodes extend to 1100 nm in the infrared. If one attempts to use such radiometers to measure small quantities of in-band radiation in the presence of large quantities of out-of-band radiation, the results will be prone to large errors. This is frequently encountered when attempting to measure the very small component of biologically active UV present in a light source spectrum.

Figure 5.3 General schematic of a radiometer system. Solid lines indicate the essential elements. Other features (dashed lines) are added to operate in certain environments or to provide spectroradiometric information (i.e., the monochromator). (From Sliney & Volbarscht, 1980)
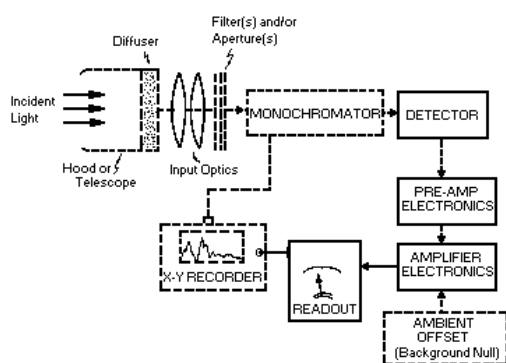
For many purposes it is desirable to have a UV radiometer which has a spectral responsivity equal to or closely resembling a certain action spectrum. If this is achieved, the radiometer signal is directly proportional to the "effective" or "biologically active" irradiance, because the radiometer will spectrally "weight" the different wavelengths according to the action spectrum S_{lambda}. A well known example of such a radiometer is a photometer (lux-meter or luminance-meter) which has a spectral responsiveness that closely matches the photopic (visual) response of the human eye. Radiometers are commercially available which have spectral responsivities that match, for example, the UV erythema action spectrum (McKinlay and Diffey, 1987) and UV hazard action spectrum adopted by the IRPA/INIRC (1991) and ACGIH.

5.3.3 Spectroradiometers

     A *spectroradiometer* is a radiometer that is capable of
measuring spectral radiometric quantities directly, such as spectral
irradiance or spectral radiance. The major difference between the
layout of a spectroradiometer and the layout of a radiometer is the
waveband selecting device which in a radiometer is usually a
broadband filter (see figure 5.3), whereas in a spectroradiometer it
is a monochromator or a spectrograph. Radiation entering a
monochromator or a spectrograph is dispersed by a grating or a prism
and only a small band of radiation is passed to the detector, the
so-called bandwidth. The spectroradiometer bandwidth can be selected
according to the application, but it is typically 1 - 5 nm. The
waveband passed to the detector can be changed manually or
automatically by rotating the grating or prism; the instrument is
scanned over the spectral range of interest. This type of instrument
is called a scanning spectroradiometer.

     In a spectrograph, a portion of the spectrum is incident upon a
photographic film, or a linear photodiode array which can be read
diode by diode. This can occur very rapidly and a spectrum displayed
almost instantly. This type of spectroradiometer is therefore useful
for studies where time resolution is important. Another advantage is
that there are no moving parts compared to a scanning
spectroradiometer. However, spectrographs have disadvantages over
scanning systems, such as spectral resolution and detectivity.

     Spectroradiometers are more complex to operate and maintain
than radiometers; they are considerably more expensive; and there
are many pitfalls for the inexperienced user. Spectroradiometers
generally employ the same kind of input optics as radiometers.

     In an ideal spectroradiometer, the monochromator passes a small
band of wavelengths to the detector, and passes no radiation outside
this band. In practice the out-of-band radiation (leakage or
stray-light) that is passed to the detector is of the order of 0.1
percent of the amount of in-band radiation depending upon the

quality and size of the monochromator. In certain measurement
situations this may give rise to errors (just as in radiometers):
the signal caused by out-of-band radiation may be of the same order
of magnitude as the signal caused by in-band radiation. For example,
if one attempts to measure the solar UV spectrum in the 290-310 nm
region, this error occurs because the solar spectrum decreases about
five orders of magnitude from 310 nm to 290 nm. To overcome this
error, a double monochromator may be used. A double monochromator is
essentially two identical monochromators coupled in tandem, the
output of the first becomes the input of the second monochromator.
The stray light of a double monochromator is typically 0.01 percent.

5.3.4 Personal dosimetry

     For personal monitoring of UV doses, radiometers are too bulky.
A thin-film polymer (eg polysulphone) dosimeter overcomes this
problem. It is a thin (0.04 mm) clear plastic film that may be worn
as a small badge comparable to those used to monitor ionizing
radiation. This allows monitoring of UVB doses on mobile subjects.
Polysulphone changes its absorbance (or transmittance) when
irradiated with UV (mainly by UVB). The received dose (radiant
exposure) is determined by measuring the change in absorbance of the
film before and after exposure (Diffey, 1989a). CR-39 plastic resins
have also been explored as UVB dosimeters; however, the low
sensitivity requires longer exposure periods (Wong *et al.,* 1989).

5.4 Calibration

     Improper or inadequate calibration of UV radiometers,
spectroradiometers and dosimeters is a serious and common source of
error. It is important to maintain a good calibration record for the
instruments, but only experience on instrument stability will
determine how often calibration is needed. The error caused by
calibration provides the minimum uncertainty that can be obtained in
measurement situations. Other sources of uncertainty include
geometry and spectrum of source emission, detector-source geometry
(angular errors), environmental influences and time factors.

     Radiometers can be calibrated by using a source of known
irradiance. This may either be a line source, such as a mercury lamp
or a laser, or by a broadband source, such as a tungsten halogen
lamp. It must be realized that the irradiance-responsivity will
depend upon the source used for calibration. For example, a
radiometer which has been calibrated against a line source will give
erratic readings if used to measure a broadband source. In practice
it is advisable to have radiometers calibrated against a source
which emits a spectrum similar to those of the sources to be
measured.

     Complete calibration of radiometers and spectral radiometers
include analysis of the cosine response of the instrument, the

azimuthal response and the temperature sensitivity of the
instrument. Recent work on instrument calibration and
intercomparison has shown that instruments can vary greatly in these
quantities even when the instruments agree on a simple spectral
calibration. In the field, instruments will measure different
quantities depending on the temperature and angle of incident
radiation.

     Spectroradiometers are calibrated against standard lamps of

known spectral irradiance (or radiance). Such lamps can be obtained
from the standards institutes in various countries. Intercomparison
of lamp calibration from institute to institute can vary by as much
as eight percent in the UV region, while better agreement is common
in the visible region of standard lamps. This discrepancy should be
noted when comparing results based on instruments calibrated from
different lamp standards.

       A tungsten halogen lamp is used as the standard lamp for
wavelengths between 250 and 2500 nm, whereas a deuterium lamp is
used in the region between 180 and 300-400 nm. It is good practice
to operate the standard lamp only when calibrating a
working-standard lamp and then use the working-standard for routine
calibration of a spectroradiometer. For very accurate work it is
recommended to maintain three calibrated lamps in order to find out
whether a change in response/calibration, at least of a
spectroradiometer, is caused by changes in the standard lamp used
for calibration or by changes in the spectroradiometer.

       Dosimeters are calibrated in the same way as radiometers except
that exposure time is an integral part of the calibration process.
To obtain a reliable calibration for radiometers and dosimeters, it
is advisable to calibrate them against a source which emits a
spectrum similar to the one that is to be measured.

6.   CELLULAR AND MOLECULAR STUDIES

6.1   Introduction

       This chapter provides an overview of the evidence for cellular
and molecular effects of UV exposure on biological systems. Since UV
exposure has been associated with skin and eye cancers in humans,
emphasis will be given to the process of carcinogenesis. It is known
that UV exposure results in photochemical modification of the
genetic material (DNA), but most of this damage is accurately and
efficiently repaired by the cell. However if the amount of damage is
too great some of the alterations to the DNA may remain as permanent
mutations. It has been proposed that if unrepaired damage occurs to
regulatory genes this may be involved in the process of
carcinogenesis. In this context mutations to and activation of genes
may be important.

       Other responses likely to result from UV exposure of cells
include increased cellular proliferation, which could have a tumour
promoting effect on genetically altered cells, as well as changes in
components of the immune system present in the skin. There is
evidence to suggest that UV exposure could elicit an
immunosuppressive effect which may compromise the body's ability to
identify and destroy tumour cells of the skin.

       This review includes summary descriptions of UV action and
repair of damage to biomolecules, particularly in DNA, cellular
chromophores and other target molecules, as well as damage to the
cell membrane and proteins. Consequences of damage to the cell, its
membranes and activation of genes are also reviewed.

6.2   Interactions with Biomolecules

       UV must be absorbed to produce a chemical change. At solar UV
intensities normally encountered, the first step in a photochemical
reaction is the absorption of a single photon by a molecule and the
production of an excited state in which one electron of the
absorbing molecule is raised to a higher energy level. Such
radiative transition can only occur efficiently when the photon
energy of the radiation is close to the energy difference of the
atom in the initial and final state (energy level). The
photochemistry that may then occur will therefore depend upon the
molecular structure and the wavelength of UV as well as the specific
reaction conditions. The primary products generated by UV absorption
are generally reactive species in a metastable excited state or free
radicals both of which form extremely fast. Dark chemical reactions
then occur often within microseconds but they may last for hours, as
is the case for the lipid peroxidation chain reaction. Finally these
relatively rapid processes are translated into photobiological
responses which may occur within seconds but can take years or even
decades to be manifested.

6.2.1 Cellular chromophores

       Since chromophores (see chapter 5 for definition) are
characterized by the wavelengths at which they absorb, the nature of
the critical chromophores will change as a function of wavelength
throughout the UV range. The peak absorption of DNA is dictated by
its component nucleic acids and occurs at around 260 nm. There is a
sharp drop in absorption through the UVB range and absorption is
undetectable by conventional means at wavelengths longer than 320
nm. Using special detectors Sutherland and Griffin, (1981) have
measured DNA absorption at wavelengths as long as 360 nm. Although
overall protein absorption peaks in the UVC range, the aromatic
amino acids such as tryptophan (lambda max = 280 nm at pH7) and
tyrosine (lambda max = 275 nm at pH7) exhibit absorptions that
extend into the UVA range so that direct damage to proteins can
occur at much longer wavelengths than direct damage to DNA.

       Several cellular components such as quinones, flavins, steroids
and porphyrins are important UVA chromophores. Porphyrins, which
exhibit an absorption with a peak around 405 nm, have been
implicated in the lethal action of UVA and near-visible light in
certain bacteria. Mutants in the bacterium *Escherichia coli* (E
coli) which are deficient in the synthesis of L-amino levulinic

acid, the first step in heme synthesis, are resistant to UVA radiation (Tuveson and Sammartano, 1986) strongly suggesting that porphyrin intermediates can be phototoxic. Porphyrin intermediates evidently also arise during heme synthesis in humans. Indeed, supplementation of human cells with amino levulinate (ALA) bypasses the synthase step and leads to accumulation of protoporphyrin IX (PPIX), the immediate precursor to heme and a strong photosensitiser. ALA appears to be preferentially taken up by skin cancer cells and the selective photosensitisation of such cells by PPIX is the basis of a new type of phototherapy based on endogenous sensitisers (Kennedy *et al.,* 1990). Iron chelators can enhance the sensitising effect by preventing the insertion of iron into the PPIX macrocycle thus preventing the formation of the relatively non-photoactive heme product. Accumulation of iron-free porphyrins is the basis of the acute photosensitivity of skin in patients with a variety of porphyrins. However, it is not clear to what extent PPIX, for example, leads to UVA-mediated cytoxicity in normal human skin cells.

Aside from DNA and proteins, the main chromophores in human skin are urocanic acid and melanins (for review see Anderson & Parrish, 1981). Trans-urocanic acid (4-amidazoleacrylic acid) is the deamination product of histidine generated by histidase and because of its broad absorption in the UV region has been considered as contributing to a modest extent to the natural sunscreen properties of skin. However, most notable is that the trans form can be photoisomerised to the cis form and it has been proposed that this conversion is a key factor in UV-induced immunosuppression (DeFabo

and Noonan, 1983). However, considerable controversy now surrounds this original suggestion (eg. see Gibbs 1993).

Melanins are the major UV absorbing chromophores in skin, exhibiting an extremely broad spectrum of absorption over the UVB, UVA and visible ranges. Melanins are complex polymeric proteins that are produced by melanocytes and transferred to keratinocytes. Although often considered to be neutral density filters, this is not strictly correct since melanins usually degrade upon UV exposure. There is some evidence that melanin may function as a photosensitizer of DNA damage.

In addition to iron-free porphyrins which generate singlet oxygen upon exposure to UVA radiation, other small molecules also have the potential to generate active oxygen intermediates upon UVA exposure (Tyrell, 1992). For example, the photochemical degradation of tryptophan by wavelengths which include the more energetic portion of the UVA spectrum is able to generate hydrogen peroxide and N-formyl kynurenin (McCormick *et al.,* 1976). Although the level of hydrogen peroxide generated *in vivo* by such a pathway would appear to be in the low micromolar range it could nevertheless be crucial to biological processes since iron complexes (such as citrate) that are present in the cytoplasm will react with hydrogen peroxide to generate the highly reactive hydroxyl radical in a superoxide driven Fenton reaction (see Gutteridge, 1985; Imlay *et al.,* 1988). Since the reaction is driven by the continual reduction of ferric iron to the ferrous state by superoxide anions, a cellular source of superoxide anions is also required. In this context it should be noted that both hydrogen peroxide and hydroxyl radical are generated by UVA irradiation of NADH and NADPH (Czochralska *et al.,* 1984; Cunningham *et al.,* 1985). However, it is not at all clear whether this is really the key source of superoxide anions or whether the main source is as a consequence of normal cellular metabolism.

6.2.2 Cellular targets

The chromophores for UV effects are not necessarily the critical targets which mediate the effects. The most important cellular target for UV is considered to be DNA since the crucial genetic material exists in unique and very low copy numbers in cells. Radiation in the UVB range is absorbed by DNA and leads to photochemical damage, so that DNA would certainly appear to be the primary chromophore and site of damage for most of the biological effects of short wavelength UV. DNA damage induced by UVB radiation is the key factor leading to sunlight-induced mutations in cancer-related genes and therefore in initiating the carcinogenic process. At longer wavelengths, targets may change. For example, the destruction of mitochondria may be a key factor in the breakdown of cellular integrity following certain types of photosensitisation. Membrane damage clearly takes on added significance when the UV

radiation employed (e.g.from sunlight) includes a strong component of longer wavelengths. Breakdown of membranes can lead to aberrant signal transduction as well as dramatic alterations in transport pathways. Leakage of essential components or an influx of extracellular molecules such as calcium can have severe cytostatic and even lethal consequences for the cell and will clearly have an influence on overall tissue/organ function.

6.3 Action Spectra

An action spectrum is a measure of the relative effectiveness of different wavelengths, within the spectral region of study, to produce a given response (see chapter 5 for definition). Clearly the number of photochemical and photobiological endpoints that can be measured is as large as the number of effects themselves and before undertaking action spectroscopy for a given end-point, there should exist a good *a priori* reason for the study. Numerous types of UV induced DNA damage have now been recognized that include stand breaks (single and double), cyclobutane-type pyrimidine dimers, 6-4

pyo photoproducts and the corresponding Dewar isomer, thymine
glycols, 8-hydroxy guanine, and many more. In addition, DNA-protein
cross-links are produced during UV exposure. Larger scale genetic
alterations include chromosome breakage, sister chromatid exchanges
and chromatid aberrations. Although partial UV action spectra are
now available for many of these lesions, the most studied have been
the different types of pyrimidine dimers. Since the indirect
oxidising component of radiation damage increases with increasing
wavelength, there is a dramatic shift in the type of lesion induced
as the wavelength increases. Pyrimidine dimers are characteristic of
the direct absorption that occurs at shorter UV wavelengths whereas
strand breaks and 8-hydroxy guanine type lesions become increasingly
important at longer wavelengths. At a higher level of complexity,
action spectra for cell death, mutation, *in vitro* transformation,
growth delays, cell permeability, etc, may also be measured.

One goal of determining action spectra has been to correlate
end-points with a specific type of initial damage. However, such
evaluations are complex partly because the absorbing chromophores
and crucial lesions will often change as a function of wavelength.
At the whole organism level, action spectra may be determined for
effects on entire organs, for example, various markers of leaf
damage in plants, erythema induction in skin and even tumour
induction.

Studies in cultured cells may be of value in predicting
responses in whole organs such as skin but various parameters must
be evaluated. In particular, the penetration of UV to the critical
chromophores as a function of wavelength must be taken into account
by considering the transmission through overlying tissue. As an
example, we may wish to calculate the relative cytotoxic action of
the different wavelengths in sunlight to cells at the basal layer of

the epidermis. In order to do this, an action spectrum must be
available for the cytotoxic action of individual wavelengths on
cultured epidermal keratinocytes. In addition, data is needed for
transmission through human skin to the target cells since this will
change as a function of wavelength. Finally if the effect of a
particular UV source is required (such as terrestrial sunlight under
defined conditions) then this must be determined by
spectroradiometry or from available data. The relative biological
effectiveness of individual wavelengths of sunlight in killing cells
at the basal level of the epidermis may then be predicted by
convoluting these three spectra. In practice, interactions
(synergistic, additive or antagonistic) exist between different UV
wavelength regions and these must also be taken into account in the
evaluation of the biological effects of broad spectrum sources.
Although action spectra may be of value for predictive evaluations,
the primary aim of studies with cultured cells is often to determine
chromophores. For this purpose, action spectra must be corrected in
order to express results as action per photon before comparison with
absorption spectra of critical biological molecules. Thus, DNA is
known to be an important chromophore in the UVB region. The results
are far more difficult to interpret in the longer wavelength UVA
region but at least for simpler organisms such as bacteria,
porphyrins have often been implicated. Action spectra, particularly
in plants, are often modified by protective absorbing molecules such
as carotenoids.

In response to questions posed by the threat to the ozone
layer, fairly detailed action spectra have now been determined for
squamous cell carcinoma in hairless mice and transmission
corrections made to estimate the spectrum in humans. DNA is clearly
the primary chromophore in the UVB region but a significant second
peak occurs in the long UVA wavelength region.

6.4 Biomolecular Damage

UV radiation can damage many cellular targets including the
nucleic acids, proteins and lipids. For the non-solar UVC
wavelengths, DNA is clearly the most important target and many
photochemical changes can occur as a result of direct absorption.
The genotoxic action of solar UVB radiation is also of critical
importance, although the spectrum of DNA damage begins to change as
oxidative events become more important. At longer UVA wavelengths,
indirect effects mediated by active oxygen intermediates are common
and except for events directly related to DNA modification (e.g.
mutation), it is difficult to discern the crucial targets.

6.4.1 Nucleic acids

Cyclobutane type pyrimidine dimers

Cyclobutane type pyrimidine dimers were the first type of
UV-induced base damage to be identified (Beukers & Berends, 1960)
and being the most frequent lesion induced by either UVC or UVB
radiation, they have been the most studied.

Cyclobutane-type pyrimidine dimer formation arises from the
production of reactive excited states (normally the forbidden but
long-lived triplet state) following absorption of UV radiation. The
action spectrum for dimer formation as shown in figure 6.1, closely
resembles that for the extinction coefficients of the appropriate
monomers, cytosine(C) or thymine(T) for wavelengths as long as 313
nm (Ellison & Childs, 1981) so that the mechanism of formation is
probably similar. Although pyrimidine dimer formation (e.g. thymine
lozenge thymine or T lozenge T) has been measured in the UVA range,
six orders of magnitude more energy is required at 365 nm as
compared to 254 nm (Tyrrell, 1973) and the mechanism of formation is
unclear. Most of the original observations concerning dimer

induction were made in isolated DNA, bacteriophage systems or in *E coli* but essential results have since been confirmed in mammalian cells including human skin fibroblasts. Action spectra determined in human and mouse skin are sharply attenuated at shorter wavelengths, but are otherwise basically similar to those obtained *in vitro*. The action spectra for cyclobutane pyrimidine dimer formation in naked DNA, cell cultures and epidermal DNA is given in figures 6.2 and 6.3. Based on studies with *E coli,* the ratio of T lozenge T, C lozenge T to C lozenge C changes appreciably with wavelength. For example, the ratio of T lozenge T to C lozenge T dimers is 0.63:1 at 313 nm (Ellison & Childs, 1981) but increases to 6:1 at 365 nm (Tyrrell, 1973).

Although repair of DNA damage is dealt with separately below, it is worth noting at this point that an extremely specific light-dependant repair process, photoreactivation, exists for repair of pyrimidine dimers in situ. Repair proceeds via photolyase which has been shown to be present almost ubiquitously throughout the animal world from *E coli* to non-placental mammals. Recent evidence suggests that photoreactivation may be less important in human cells (Li *et al.,* 1993). Nevertheless, the photoenzymatic splitting of pyrimidine dimers has provided a powerful technique since it has provided a way of linking a specific type of DNA damage (the pyrimidine dimer) with defined biological effects (e.g. cell death, tumour formation).

Figure 6.1 Formation of pyrimidine dimers within DNA (courtesy of National Radiological Protection Board, UK)
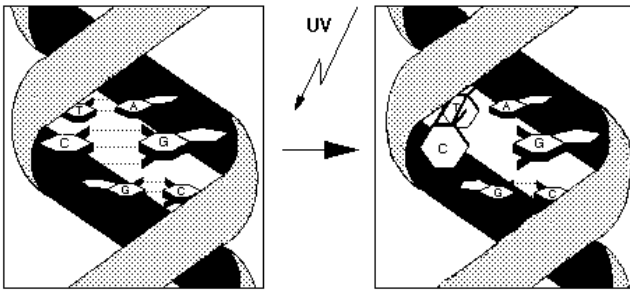
Figure 6.2 Action spectra for cyclobutane pyrimidine dimer formation in naked DNA and cultured cells. ■ Peak et al., 1984; ▲ Chan et al., 1986; ◆ Matsunaga et al., 1991; □ Enninga et al., 1986; ○ Doniger et al., 1981 (courtesy of National Radiological Protection Board, UK).
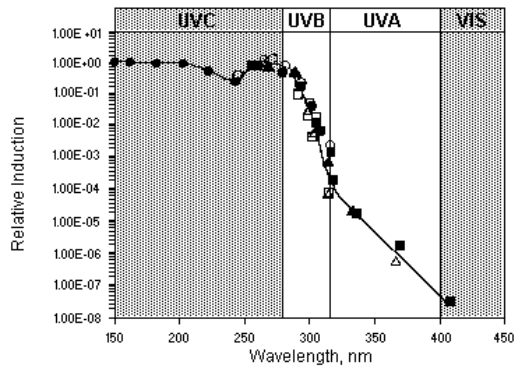
Figure 6.3 Action spectra for cyclobutane pyrimidine dimer formation in epidermal DNA. ■ Ley et al., 1983; ▲ Freeman et al., 1989 (courtesy of National Radiological Protection Board, UK)
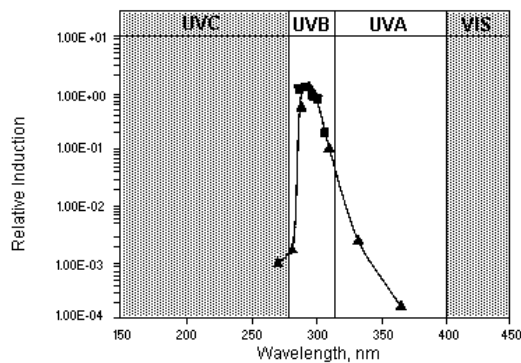
Thy (6-4) pyo photoproducts

A second type of pyrimidine dimer can be formed by UV (Varghese & Wang, 1967) which was originally termed a pyrimidine adduct and is now more commonly referred to as the thy (6-4) pyo photoproduct. More recently a pyrimidine nucleoside-cytidine lesion was recognized in highly reiterated sequences of human DNA (Lippke *et al.,* 1981) which is almost certainly the precursor of the thy (6-4) pyo photoproduct (Brash & Haseltine, 1982; Franklin, *et al.,* 1982). The (6-4) photoproduct is formed with much greater frequency between cytosines located 5' of adjacent pyrimidines. Action spectra that compare induction of cyclobutane-type pyrimidine dimers are all similar between 265 nm and 302 nm (Patrick, 1977; Chan *et al.,* 1986; Matsunaga, *et al.,* 1991; Rosenstein & Mitchell, 1987) as shown in figure 6.4. However, at longer wavelengths not all the spectra agree. At least for human skin fibroblasts the relative level of (6-4) photoproduct induction is only half that for cyclobutane-type dimers. The reason for this appears to be that the (6-4) photoproducts are converted to a Dewar pyrimidine isomer by UV radiation at wavelengths peaking in the UVB range. This has been confirmed in studies by Mitchell & Rosenstein (1987) using radio-immuno assays for the (6-4) photoproduct and its Dewar isomer.

Although (6-4) photoproducts form with 5-10 fold lower efficiency than cyclobutane type dimers, they may be formed with equal efficiency at certain sites (Kraemer *et al.,* 1988). Furthermore, in the UVB region, a significant level of Dewar pyrimidine isomers will be formed and the precise ratio and level of these three major types of base damage will depend on the wavelength(s) of radiation employed, as well as irradiation conditions.

Other types of dimeric base damage which include purines have been isolated from DNA heavily irradiated with UVC. These include the thymine-adenine dimer (Bose & Davies, 1984) and adenine dehydrodimer (Gasparro & Fresco, 1986). Such photoproducts occur at fairly low frequency (approximately 1 percent of that of pyrimidine-type dimers. The relative levels and significance of these photoproducts in the UVB or longer wavelength regions has not yet been determined.

Figure 6.4 Action spectra for pyrimidine (6-4) pyrimidone adduct formation in naked DNA and cultured cells. ▲ Chan et al., 1986; □ Rosenstein & Mitchell, 1987; ● Matsunaga et al., 1991 (courtesy of National Radiological Protection Board, UK).
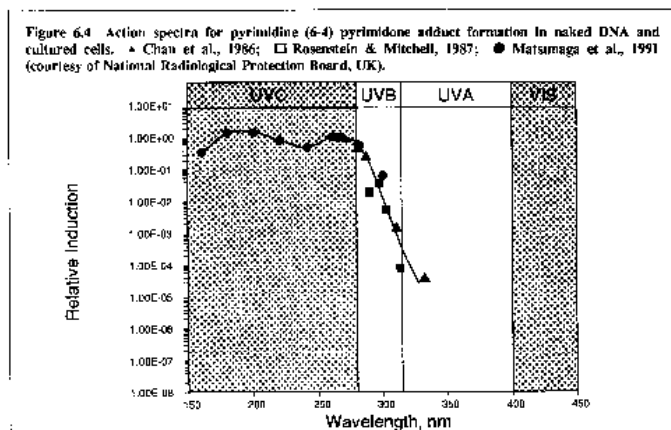
Monobasic DNA damage

Damage to a single base is a relatively low frequency event in UV damaged DNA. Simple hydrates of cytosine and thymine can certainly be formed (Fisher & Johns, 1976) but these low frequency events are unreliable and therefore extremely difficult to study from a biological viewpoint. They may be related to the low frequency cytosine photoproduct identified by sequencing techniques by Gallagher *et al.* (1989). Sequencing techniques in combination with endonuclease V treatment have also led to the detection of a class of rare and unidentified purine or purine-pyrimidine sites after broad spectrum UV irradiation (Gallagher & Duker, 1986).

A group of lesions induced by both UV and ionizing radiation are ring-saturated thymines of the 5, 6- dihyroxydihydrothymine type (thymine glycols). Although original measurements indicated that they were induced almost as frequently as pyrimidine dimers at 313 nm as against 21:1 at 254 nm (Cerutti & Netrawali, 1979), it has been concluded from more recent data using sequencing analysis (Mitchell *et al.,* 1993) that they do not occur at a significant rate in UVC or UVB irradiated DNA.

Increasingly sophisticated chemical methods are now becoming available to measure oxidative DNA damage (Cadet *et al.,* Methods in Enzymology, in press). Since the proportion of this type of damage will increase with increasing wavelength, such techniques will soon be applied to consolidate the picture of UV-induced based damage throughout the entire solar UV spectrum. Furthermore, an interesting enzyme has been isolated (Boiteux *et al.,* 1987) termed the Fapy glycosylase because of its ability to excise the ring-opened form of N7-methylguanine from DNA. The enzyme will also recognize DNA products generated in photosensitisation reactions involving singlet oxygen (Epe *et al.,* in press) and 8-hydroxyguanine may be a major component. Since the longer UV wavelength in sunlight clearly generate biologically relevant levels

of singlet oxygen and other active intermediates (Tyrrell, 1991;
Basu-Modak & Tyrrell, 1993), this type of analysis may also be
usefully applied to the solar UV spectrum. Certainly, near-visible
light alone is able to generate Fapy glycosylase-sensitive lesions
in the DNA of cultured mammalian cells and these, at least in part,
are probably 8-hydroxyguanine (Epe et al., 1993).

    DNA strand breaks

    Few DNA strand breaks are induced by UVC radiation but they
constitute an increasing proportion of the total lesions as

wavelength is increased. For example, in E. coli the ratio of DNA
strand breaks to pyrimidine dimers is 1:44 at 313 nm (Miguel &
Tyrrell, 1983) whereas at 365 nm one strand break is formed for
every two pyrimidine dimers (Tyrrell et al., 1974). Action spectra
have now been determined for the induction of DNA single strand
breaks in human skin cells which show that breaks occur throughout
the UVA and into the near-visible range (Peak et al., 1987). Since
break measurements involve alkaline denaturation, 10-20 percent of
the so-called breaks are due to the fragility of chemical bonds at
apurinic and apyrimidinic sites. It is important to note that unlike
most of the common forms of base damage, induction of strand breaks
is strongly dependent on oxygen throughout the UVB and UVA ranges
(Tyrrell, et al., 1974; Peak & Peak, 1982; Miguel and Tyrrell, 1983)
and at the longest wavelengths may involve generation of singlet
oxygen (Peak et al., 1987). Figure 6.5 gives the action spectra
for single strand breaks and figure 6.6 for double strand breaks in
cultured cells.

    DNA-protein cross links

    Photochemically induced DNA-protein cross links, mostly
involving cysteine are clearly formed in vitro (Smith, 1976;
Shetlar, 1980) and appear to be formed in vivo, particularly in
the UVA range (Bradley, et al., 1979; Peak & Peak, 1991). Despite
the obvious importance of this type of damage, there is little known
at the molecular level concerning the nature of the damage formed
 in vivo. Action spectra for DNA-protein cross links in cultured
cells is given in figure 6.7 (from Peak et al., 1985a, b).

    Ribonucleic acid

    Messenger RNA is readily susceptible to modification by UV
radiation. However, given the fairly rapid turnover of most
molecules of this type (half-lives generally of the order of minutes
and hours) and the capacity for de novo synthesis in the absence
of DNA damage, mRNA is not generally considered a critical target of
radiation damage in mammalian cells. Bacterial transfer RNA is often
extremely photosensitive because of the presence of an unusual
nucleoside 4-thiouridine and this leads to some fascinating
photobiological phenomena of ecological significance (Jagger, 1985).
However, such findings are of little significance to eukaryotic
cells.

Figure 6.5 Action spectra for single strand break formation in cultured cells. ▲ Peak et al., 1987;
■ Rosenstein & Ducore, 1983; ◆ Peak & Peak, 1991(courtesy of National Radiological Protection
Board , UK).

Figure 6.6 Action spectrum for double strand break formation in cultured cells. Peak & Peak, 1990 (courtesy of National Radiological Protection Board, UK).

Figure 6.7 Action spectra for DNA-protein cross links formation in cultured cells. ▲Peak et al., 1985a; ■Peak et al,. 1985b (courtesy of National Radiological Protection Board).

6.4.2 Membranes

      UV-induced changes in membrane permeability and membrane transport systems would be expected to have fairly dramatic consequences for human skin and eyes. Unsaturated fatty acids are readily oxidised to hydroperoxides. Several reports have now shown that UV radiation can peroxidise membrane lipids (Desai, *et al.,* 1964; Roshchupkin *et al.,* 1975; Putvinsky *et al.,* 1979; Azizova, *et al.,* 1980). Using liposomal models (Mandal & Chatterjee, 1980; Bose *et al.,* 1989), it has been shown that UVA radiation causes a dose-dependent increase in lipid peroxidation as measured by various techniques and that this can be largely inhibited by membrane antioxidants such as butylated hydroxytoluene. In *E coli,* sensitivity to UVA correlates with the levels of unsaturated fat in membranes (Klamen & Tuveson, 1982; Chamberlain & Moss, 1987). An agent which enhances singlet oxygen lifetime, deuterium oxide, enhances the level of membrane damage, sensitivity to UVA and lipid peroxidation. There are now reports that both UVB and UVA (Morlière *et al.,* 1991; Punnonen *et al.,* 1991; Vile *et al.,* 1994) radiation can cause lipid peroxidation at biologically relevant fluences in the membranes of human fibroblasts and keratinocytes.

      Cell leakage experiments have been used to assess membrane damage in yeast (Ito and Ito, 1983) and a similar technique has now been used to show UVA-mediated enhancement of membrane leakage in human skin fibroblasts (Gaboriau *et al.,* 1993; Vile *et al.,* 1994). UVA also causes changes in membrane fluidity as assessed using a lipophilic fluorescent probe. UVA-induced alteration of membrane transport systems received considerable attention in prokaryotes (see Jagger, 1985) but little information is available in mammalian cells. A recent study has demonstrated that UVA radiation inhibits both receptor-mediated (low density lipoprotein) and nonspecific (sucrose) uptake of exogenous molecules (Djavuheri-Mergny *et al.,* 1993). These findings may be related to other studies in human fibroblasts which have shown that broad spectrum UV sources cause cytoskeletal damage as manifested by dose-dependent microtubule disassembly (Zamansky & Chou, 1987).

6.4.3 Proteins

      As the wavelength is increased through the UVB and UVA regions damage to proteins becomes increasingly important because of the absorption properties of the aromatic amino acids relative to nucleic acids. In addition, many proteins that include the antioxidant enzymes catalases and peroxidases contain heme groups thus making them UVA chromophores and potentially photosensitisers. Indeed, catalase is sensitive to sunlight (Mitchell & Anderson, 1965), probably as a result of UVA absorption (Kramer & Ames, 1987). In bacteria there is evidence that endogenous catalase and possibly alkyl hydroperoxide reductase are actually photosensitisers (Eisenstark & Perrot, 1987; Kramer & Ames, 1987) but no similar

experiments to have been carried out in mammalian cells. Repair enzymes are also sensitive to UVA radiation and there is evidence that UV-induced repair disruption plays a role in cell death and mutagenesis (Haynes, 1966; Webb, 1977; Tyrrell, 1982). Considerable attention has been given recently to metal ion catalysed oxidation of protein since this is clearly a physiologically relevant process (for review see Stadtman, 1990). Numerous proteins have been shown to be modified by a free radical generating, system modelling those that cells are exposed to during normal metabolism or exogenous insult. It appears that active oxygen/free radical species are generated at specific metal binding sites on proteins and that this leads to reactions with amino acid residues at specific steric locations.

6.5 Cellular Defences

6.5.1 DNA

Even one or two pyrimidine dimers in the entire genome of a bacterium such as *E coli* may be lethal if DNA repair processes are defective. However, DNA repair processes are not only crucial for cell survival but also for the maintenance of genetic stability since DNA damage is continuously generated as a by-product of metabolism even in the absence of exogenous insults. Because of the availability of mutants, most of the original studies concerning removal of DNA damage employed bacteria and bacteriophage. The first process to be identified was photoreactivation later known as photoenzymatic repair. In this process, a DNA photolyase forms a specific complex with a pyrimidine dimer which can be split in the presence of UVA and/or visible light to leave the original pyrimidines in the DNA. The process has been widely used to correlate a specific type of DNA damage (the pyrimidine dimer) with a given biological effect (from cell death in bacteria to cancer in fish), although recent evidence for an enzyme which recognizes (6-4) photoproducts may cast doubt on the validity of this approach. Photoenzymatic repair is entirely error free (i.e. it does not lead to mutations) and occurs in a wide variety of single and multiple-celled organisms. Although photoenzymatic repair and associated photolyases occur in non-placental mammals such as the marsupials, evidence for photoreactivation in placental mammals, including humans, has been fragmentary and controversial. Recent evidence suggesting that photoreactivation of UV damage may not be a significant process in human skin (Li *et al.,* 1993) could be of crucial importance when considering potential interactions between wavelengths.

Evidence for two broad categories of DNA repair, originally denoted as dark repair processes, were revealed by bacterial studies (see Friedberg, 1984 for review). Post-replicational repair, as the name implies, can occur only after DNA synthesis and includes many of the complex pathways of genetic recombination. Humans with the

genetic disease Xeroderma pigmentosum (XP) of the variant complementation group are deficient in this type of repair. However, the SOS repair process in bacteria which involves the inducible activation of a post-replication error-prone (mutagenic) repair pathway, has no equivalent in humans. On the other hand, excision repair is the most widespread of DNA repair processes and occurs from bacteria to man. In excision repair, damaged or incorrect bases are excised from the genome and replaced by the correct nucleotides. The first step in the process involves recognition of the damage and incision at or close to the damaged site. This can occur by two distinct mechanisms. Damaged bases may be recognised by a series of specific glycosylases. In this case, incision occurs by a two-step reaction which involves the sequential activities of the DNA glycosylase and an apyrimidinic/apurinic endonuclease. However, a second mechanism of incision involves the direct action of a damage-specific DNA incising activity without the need for glycosylase action. At least in *E Coli,* incisions are made at either side of the damaged base so that exonucleolytic removal of bases is unnecessary in this case. Repolymerization of the gap created by endonuclease/exonuclease activity is an essential step and can take place using the undamaged strand as a template. The action of DNA ligase restores the original integrity of the double-stranded DNA.

DNA excision repair in humans is also an extremely complex process as evidenced by the considerable genetic heterogeneity in XP which is a rare but extensively studied disease whose cellular basis involves a defect in DNA repair. Genomic clones of several human DNA repair genes have now been derived by transfecting DNA from repair proficient human cells into a series of UV-sensitive mutant rodent cell lines (Westerveld *et al.,* 1984). A considerable amount of information is now available concerning the molecular genetics of eukaryotic DNA excision repair (Hoeijmakers & Bootsma, 1990). The repair genes isolated to date often have DNA binding and/or nucleic acid helicase domains. Most recently, a repair gene product has been identified as one of the components of a transcription factor complex involved in the transcription of polymerase II genes (Schaeffer *et al.,* 1993). This is currently an extremely active area of research and further genes are expected to be isolated.

In vitro repair systems are now available (Wood *et al.,* 1988). In addition, animal models are now being developed using homologous recombination techniques and genetic manipulation of embryonic stem cells.

6.5.2 Human excision repair disorders

Several human diseases involve defects in DNA repair. The most

studied example is the genetic disorder XP which actually involves
several types of excision repair defect as well as the variant form
which is defective in post-replication repair. These cell lines are

crucial to basic studies of DNA repair in humans. Cell lines derived
from the excision-defective individuals are many times more
sensitive to inactivation and mutation by UVC and UVB radiation
(Arlett et al., 1992). This appears to be directly correlated with
the fact that individuals with this disease are extremely prone to
tumours of the skin, eye and lips (Kraemer et al., 1987). Indeed,
it is the study of cancer incidence in these individuals which
provides the strongest evidence that the induction of photoproducts
in skin by UV is the first event in a sequence which eventually
leads to basal cell carcinoma, squamous cell carcinoma and melanomas
in man.

      The above conclusion is now complicated by studies with cells
from patients with the rare disease, Trichothiodystrophy. Although,
cells from most of the patients studied so far have a marked defect
in DNA excision repair, the patients do not show elevated evidence
of skin tumours. They are, nevertheless, sun-sensitive in terms of
their erythemal response (Bridges 1990). A partial explanation may
be that XP patients but not Trichothiodystrophy patients have
defects in both DNA repair and oxidative metabolism and both these
processes are involved in carcinogenesis (Vuillaume et al., 1992).

      Fibroblasts from patients with Cockayne's syndrome are
specifically defective in excision of dimers from DNA undergoing
active transcription (Mayne et al., 1988) and are sensitive to
killing and mutation by UVC radiation. (Arlett & Harcourt 1983).
However, these individuals are not exceptionally cancer-prone
(Barret et al., 1991).

6.5.3 Antioxidant pathways

      Small antioxidant molecules

      Recent reviews have evaluated the nature and importance of
small antioxidant molecules in human blood plasma (Stocker & Frei,
1991), the eye (Spector, 1991) and human skin (Fuchs & Packer 1991;
Tyrrell 1991).

      Glutathione is a major constituent of lens epithelial cells
(Rathbun 1989) and these cells have a high capacity for maintaining
glutathione in the reduced state because of extremely active hexose
monophosphate shunt activity. This compound may be involved in a
number of antioxidant reactions that are relevant to UV-mediated
oxidative stress including detoxification of hydrogen peroxide (as a
cofactor of GSH peroxidase), detoxification of free radicals,
reduction of protein disulphides, and competition with protein
thiols for oxidising species. The role of ascorbate as an effective
antioxidant in lens is less clear because of the potential of
ascorbate to be involved in the generation of deleterious components
(Spector, 1991). Vitamin E is also a potentially useful antioxidant

but there is no general agreement as to the usefulness of vitamin E
therapy for cataract.

      Free radical intermediates have been implicated in UV- induced
carcinogenesis in investigations originally stimulated by the
isolation of the putative carcinogen cholesterol epoxide from human
skin (Black 1987). Various components present in skin are potent
antioxidants including ascorbate, uric acid, carotenoids and
sulphydrils. Carotenoids have been shown to inhibit UV-induced
epidermal damage and tumour formation in mouse models (Mathews-Roth
& Krinsky, 1987). In cell culture models using human skin cells, it
has been clearly shown that glutathione depletion leads to a large
sensitization to UVA (334 nm, 365 nm) and near-visible (405 nm)
wavelengths as well as to radiation in the UVB (302 nm, 313 nm)
(Tyrrell & Pidoux, 1986,1988). There is a direct correlation between
the levels of sensitisation and cellular glutathione content.
Additional evidence that glutathione is a photoprotective agent in
skin cells is derived from experiments which have demonstrated that
glutathione levels in both dermis and epidermis are depleted by UVA
treatment (Connor & Wheeler, 1987).

      Water-soluble antioxidants in plasma include glucose, pyruvate,
uric acid, ascorbic acid, bilirubin and glutathione. Lipid soluble
anti-oxidants include alpha-tocopherol, ubiquinol-10, lycopene,
ß-carotene, lutein, zeaxanthin and alpha-carotene. Since, the long
wavelengths in sunlight can penetrate through tissue and into blood
at the longer wavelengths, these defenses may be critical under
certain circumstances.

      Antioxidant proteins including enzymes

      The major classes of antioxidant enzymes characterized to date
in eukaryotic cells are superoxide dismutase (which converts
superoxide anion to hydrogen peroxide), catalase (which destroys
hydrogen peroxide) and glutathione peroxide and associated enzymes
(which in addition to metabolizing hydrogen peroxide can also reduce
hydroperoxides such as those that result from lipid peroxidation).
Both glutathione peroxide and catalase are present in the lens,
although the latter is present at low levels and concentrated in the
epithelial cells (Bhuyan & Bhuyan 1983). Spector (1991) claims that
these enzymes are present at sufficient concentrations to handle the
normal levels of hydrogen peroxide generated in the lens. This
author suggests that the thioredoxin/thioredoxin-reductase system
may also be involved in the defense of lens against oxidative
stress. This system can quench free radicals and also reduce some

protein disulphides.

All the major antioxidant enzymes are present in skin but their
role in protecting cells against oxidative damage generated by UV
radiation has not been elucidated. Acute UV exposures lead to
changes in glutathione reductase and catalase activity in mouse skin

but insignificant changes in superoxide dismutase and glutathione
peroxidase (Fuchs *et al.,* 1989). Consistent with original studies
in bacteria, neither endogenous catalase nor superoxide dismutase
play a major role in protecting cells against the lethal effects of
UVA irradiation (Tyrrell & Pidoux 1989). Iron plays a critical role
in oxidative reactions as a catalyst in the Fenton reaction so that
cellular levels of free iron need to be kept low. The intracellular
storage protein, ferritin may therefore play a critical role in
cellular antioxidant defense. UVA radiation (and other oxidant
stress) leads to high levels of expression of the heme oxygenase 1
gene (HO1) (Keyse & Tyrrell 1989) which in turn leads to the
catabolism of heme and release of free iron. The increased ferritin
levels that result appear to be directly responsible for a
UVA-mediated adaptive response involving the protection of human
fibroblast membranes against subsequent UVA radiation damage (Vile
 et al., 1994).

6.5.4 Summary

Repair of UV-induced DNA damage is crucial in removing
potentially mutagenic damage from cells although errors in repair
can themselves lead to mutations. The repair capacity of human skin
cells therefore directly relates to the probability of initiation of
the carcinogenesis process and eventually tumour formation. At
longer UV wavelengths, an increasing component of oxidative damage
to DNA, membranes and proteins influences the biological effects.
Both endogenous and exogenous photosensitisers normally generate
active oxygen intermediates. Cellular antioxidant defense mechanisms
are therefore crucial for the prevention or removal of the damage
caused by the oxidising component of UV radiation.

6.6 Cellular Consequences of Damage

6.6.1 Membrane disruption

Lipid and protein damage by UV associated with cytoskeletal
damage may lead to severe disruption of plasma membrane functions
including a breakdown in the permeability barrier and interruptions
in active transport functions. Crucial signalling molecules such as
cytokines may be inappropriately released leading to aberrant cell
to cell communication and toxins present in the external cellular
environment may gain free access to the interior of the cell.
Critical ion pumps may be damaged, thereby influencing a wide range
of processes that rely on ion homeostasis. Breakdown of internal
lipid membranes in eukaryotic cells will also be highly disruptive
leading to many pathological consequences including mitochondrial
damage, leakage of proteases from disrupted lysosomes and breakdown
of the nuclear membrane permeability barrier. Details in this
important area of UV effects are sparse but it is clear that
consequences of UV damage to membrane components need to be better

understood and incorporated into current models for cellular and
organ damage.

6.6.2 Activation of genes

UV inducible defense pathways in bacteria and human cells

In bacteria, UVC radiation induces a large set of genes under
the regulatory control of the *rec A* gene which lead to enhanced
DNA repair, mutagenesis, prophage induction and inhibition of cell
division (for review see Walker, 1987). Many groups have sought a
similar SOS response in eukaryotic cells. Reactivation of several
different UVC damaged viruses (human cytomegalovirus or Herpes
Simplex virus) has been observed upon infection into UVC treated
cultured human skin fibroblasts. The effects are not generally large
(Dion & Hammelin, 1987; Abrahams *et al.,* 1984). In one study, a
parallel phenomenon has been observed using split doses of UV in
arrested cultures of human fibroblasts (Tyrrell, 1984). Cell
populations irradiated with low doses of UV developed enhanced
resistance to a second UV challenge dose with a maximum response
occurring between 2-4 days. The level of reactivation was much
higher in a repair deficient (XP variant cell line). As for viral
reactivation, protein synthesis is necessary. No mutation studies
have been carried out under similar conditions. Furthermore, these
phenomena have not been investigated in the solar UVB region
although it is likely that the response will be similar. Although
these adaptation responses appear to reflect enhanced gene
expression, there are few clues as to the molecular mechanism
underlying these observations.

Bacteria also respond strongly to oxidative stress by either
the oxyR pathway (Christman *et al.,* 1985) or the soxRS pathway
(Greenberg *et al.,* 1990) which is induced by superoxide-
generating redox cycling agents such as menadione and paraquat. The
oxyR pathway is induced by agents such as hydrogen peroxide and the
regulatory protein encoded by this gene controls expression of at
least 9 proteins including the antioxidant enzymes, catalase,
glutathione reductase and alkyl hydroperoxide reductase. This
pathway is emphasised here because it also appears to be involved in
protection of bacterial cells against the cytotoxic action of UVA
radiation (Kramer & Ames 1987). However, although several eukaryotic
genes are induced by both UVA radiation and hydrogen peroxide (see

below), none of them involves such a clear-cut direct activation of
antioxidant enzymes.

        Gene activation in mammalian cells by UVC and UVB radiations

        A large number of genes have been shown to be activated by UVC
radiation (listed in Table 1 of a review by Keyse 1993). However, in

many cases the doses required are very high, so that by the
criterion of colony-forming ability, the majority of the population
is dead. Although it is a reasonable assumption that the same genes
will be induced by UVB radiation, this has only been shown in
certain cases. Damage to DNA may be a critical intermediate in
triggering the response since induction of certain genes has been
shown to occur at much lower doses in mutant cell strains lacking
DNA repair. (Stein et al., 1989, Miskin & Ben-Ishai, 1981).
Furthermore, crude action spectra for induction of several genes by
UV radiation correspond to the action spectra for DNA damage
induction (Stein et al., 1989). However, at least for the
induction of the fos gene (see action spectrum in figure 6.8),
events at the membrane also appear to be involved (Devary et al.,
1992). There is still a controversy as to whether or not the initial
signal occurs in the nucleus and is then transduced to the membrane
or whether the crucial initiating events occur at the membrane
itself. UVC activation of the HIV-1 promoter also appears to involve
membrane events (Devary et al., 1993).

        Metallothioneins are also induced by both UVC and UVB radiation
(Angel et al., 1986). However, in general, the relationship
between UVC/UVB activation of genes and cellular defense against
short wavelength UV radiations remains obscure. The synthesis of a
constitutive damage specific DNA-binding protein has been shown to
be stimulated by UV radiation in both monkey and human cells
(Hirschfield et al., 1990). Although the binding activity was
shown to be absent in certain strains of XP (group E) (Chu & Chang
1988), subsequent studies showed that not all strains from this
group lacked the damage specific protein (Kataoka & Fujiwara 1991).

        Gene activation in mammalian cells by UVA radiation

        The eukaryotic genes induced by UVA radiation are, for the most
part, distinct from those induced by the shorter wavelengths. This
appears to be largely due to the fact that UVA radiation acts
indirectly by generating active oxygen intermediates rather than
being directly absorbed by biomolecules. Although UVA radiation can
activate antioxidant enzymes such as catalase in prokaryotic cells,
there is no evidence that UVA radiation can activate any of the
common antioxidant pathways in mammalian cells. In contrast to the
studies with UVB/UVC radiations, UVA radiation can activate genes at
doses which kill only a small percentage of the total population in
cultured cell models. This is crucial since it indicates that gene
activation by UVA radiation may actually relate to events in living
tissue and could reasonably be expected to be involved in protective
pathways.

Figure 6.8 Action spectrum for early phase of c-fos induction in cells. Stein et al., 1989a (courtesy of National Radiological Protection Board, UK).
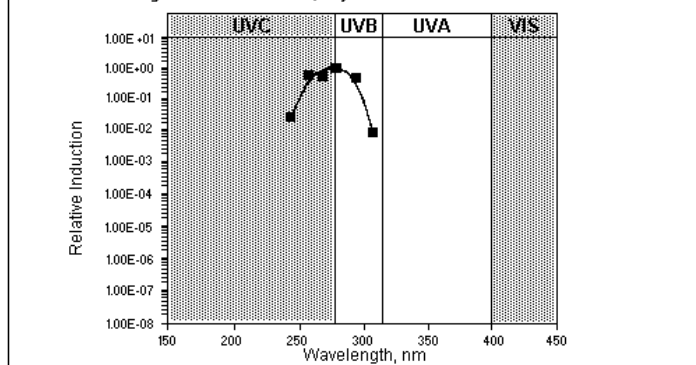
        For simplicity, we can distinguish three groups of genes that
are activated in cultured mammalian cells by UVA radiation. These
may involve secreted molecules in cell to cell interactions:
collagenase (Scharffetter et al., 1991) and intracellular adhesion
molecule 1; proteins involved in early cellular events and signal
transduction (protein kinase C, phospholipase A2, and a phosphatase,
see Keyse, 1993) or catabolic enzymes (currently only represented by
heme oxygenase 1). To date only heme oxygenase 1 has been implicated
in a cellular defense pathway in which human fibroblasts adapt to
oxidative damage to membranes (Vile et al., 1994).

        UV activation of viruses

        UV radiation has long been known to activate Herpes Simplex
virus. Experimental evidence now indicates that UVC and UVB
radiation can activate the promoter of the human immune deficiency
virus (see figure 6.9) as well as complete HIV (Valerie et al.,
1988). This activation may contribute to the faster development of
AIDS in seropositive individuals. Current evidence in both cell
systems and transgenic animal models have led to the conclusion that
UVA radiation cannot activate the virus (see Beer & Smudzka, 1991).

However UVA at solar radiation levels can clearly activate binding
of the NFKB transcription factors to the corresponding DNA binding
site which is present in several promoters including the long
terminal repeat of the HIV promoter (Tyrrell, R.M Personal
communication). This issue clearly merits further study in view of
the importance to human health.

6.6.3 Cell death

     Cells irradiated with UV may show changes in permeability,
inhibition of macromolecular synthesis, loss of ability to divide
and total metabolic disruption eventually leading to cellular
disruption. A discussion of how to define and measure cell death is
beyond the scope of this overview, but the most commonly accepted
parameter employed is the loss of the ability of a cell to divide
and form colonies. Many classical studies of UV effects were based
on these parameters and survival curves and their interpretation
have been extensively discussed (Jagger, 1985). Inactivation rates
can be derived from survival curves and used to construct action
spectra for inactivation of cultured organisms ranging from viruses
to human cells. Such survival curves are particularly useful for
defining sensitive and resistant cell populations, often an
indication of genetic defects in repair processes. Action spectra
for inactivation of cell populations generally follow DNA absorption
at wavelengths as long as 320 nm. However cells are killed more
efficiently than predicted by DNA damage at longer wavelengths as a
result of multiple effects of the longer wavelength including
disruption of DNA repair and the increasing importance of targets
such as the membrane.

Figure 6.9 Action spectrum for HIV-1 activation in cells. Stein et al, 1989b (courtesy of National Radiological Protection Board, UK).
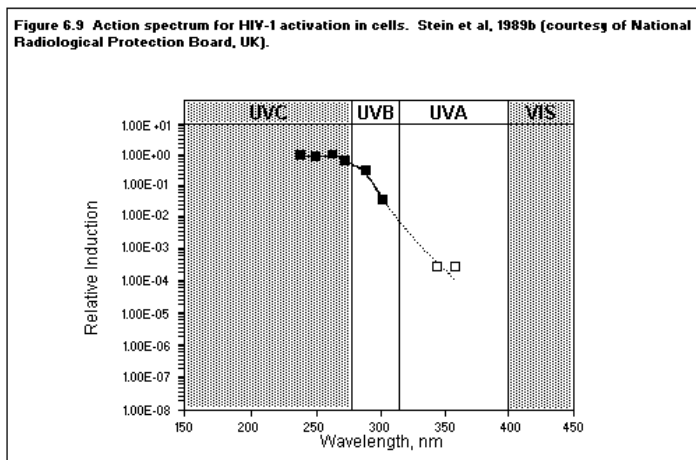
     At solar UV levels that lead to erythema and acute skin burn in
human beings, extensive cell death may occur. This may be
particularly important to the eventual appearance of melanomas which
have been linked to severe sunburn early on in life in
epidemiological studies. It should also be noted that action spectra
data taken together with solar spectroradiometric measurements and
the known transmission of human skin have led to the conclusion that
the UVA component of sunlight is a major factor in the cytotoxic
action of sunlight at the basal layer of the epidermis (Tyrrell and
Pidoux 1987).

6.6.4 Mutation, chromosomal damage and transformation

     Studies in microorganisms have unambiguously shown that damage
induced by UV throughout the whole range is mutagenic (Webb, 1977).
Until the present decade, UVB and UVA studies in mammalian cells
were much less conclusive because most of them employed broad
spectrum lamps and mutagenic effects could be partially or entirely
attributed to wavelengths at the short end of the emitted spectrum.
Nevertheless, a large body of work now supports the conclusion that
both UVC and UVB radiations are mutagenic to cultured human cells.
Studies using predominently UVA sources or monochromatic radiations
in three different cultured human cell systems have reported
positive (Enninga *et al.,* 1986), ambiguous (Jones *et al.,* 1987)
or negative (Tyrrell 1984) results. These results are clearly a
function of the system employed and merely underline the fact that
although pre-mutagenic lesions are induced by wavelengths longer
than 320 nm in human cells, the efficiency of mutation induction is
several orders of magnitude lower than that induced by the short
wavelengths. It should be stressed at this point that UVA radiation
is clearly carcinogenic in animal models (De Gruijl *et al.,* 1993).

     Most DNA photoproducts are likely to be pre-mutagenic lesions
because of the potential for error occurring during repair. Recent
attention has focused on the relative mutagenicity of the
cyclobutane type pyrimidine dimers compared with the second most
common DNA lesion formed by UVB and UVC radiation, the (6-4) pyo
photoproduct (reviewed by Mitchell *et al.,* 1993). Most of the
conclusions are based on the specific type of sequence changes
(transitions, tandem transitions) that occur in a variety of test
systems. In certain cases, clear evidence has emerged that the minor
(6-4) pyo photoproduct may be highly mutagenic relative to the
pyrimidine dimer (Leclerc *et al.,* 1991). Much additional study
will be required to resolve the mutagenic potential of each
photoproduct, especially considering the rapid expansion in numbers

of additional photoproducts that are now being recognised.

Except for UVC radiation, most of the studies of the chromosomal effects of UV radiation have been carried out with broad spectrum sources. The data has been extensively tabulated in a

recent evaluation of UV effects (IARC 1992). A similar comment applies to the studies on morphological transformation.

6.7 Conclusions

DNA is the most critical chromophore and target for damage by UVB and UVC radiation. The fraction of oxidative type damage involving other chromophores and additional targets increases with increasing wavelength. The determination of accurate action spectra in cultured cells and animal models is critical to obtaining clues as to the nature of these chromophores and for predictive evaluation in the many cases in which human data is lacking.

A considerable amount of knowledge is available concerning the interaction of UV radiation with nucleic acids. Controversy still exists as to which type of lesion constitutes the most important type of pre-mutagenic damage, although (6-4) pyo photoproducts and cyclobutane type pyrimidine dimers may both be relevant. Damage to membranes and other organelles is also being given increasing attention since non-DNA events may also be involved in UV mediated biological effects.

Studies of DNA repair defective disorders in humans have clearly established a link between UV induced DNA damage in skin and various types of cancer. A clear understanding of endogenous defense pathways including antioxidant defense is essential for understanding the origins of UV-related human disease and to the elaboration of adequate protective measures.

Cell death, chromosome changes, mutation and morphological transformations are observed after irradiation of prokaryotic and eukaryotic cells with UV. Many different genes and several viruses (including HIV) are activated by UV radiation. However, the genes activated by UVC and UVB are different from those activated by UVA radiation.

7. ANIMAL STUDIES

7.1 Skin Carcinogenesis

7.1.1 Domestic animals

Skin tumours have been reported in some domestic and food animals including cats, dogs, cows, sheep and goats (Dorn *et al.,* 1971; Emmett, 1973; Madewell *et al.,* 1981). That the tumours observed often develop in sparsely haired, light-coloured skin suggests that sunlight was involved. Cancers of the external membranes of the eye are also observed, particularly in cattle, and are thought to be related to sun exposure (Russell *et al.,* 1956).

7.1.2 Experimental animals

The experimental induction of skin cancers in mice following exposure to a mercury arc lamp was first reported by Findlay (1928). Since then, carcinogenicity of UV has been investigated in many experiments, mostly in mice, less often in rats, and infrequently in other species (Blum et al, 1959; Urbach *et al.,* 1974; Kripke & Sass, 1978; WHO, 1979; van der Leun, 1984; Epstein, 1985). Spontaneous skin tumours are rare in rodents but have been consistently observed following experimental UV exposure with a clear dose-response relationship in well-conducted studies. A recent review concluded that there was sufficient evidence that UV caused skin cancer in experimental animals (IARC, 1992).

Broad Spectrum UV

The carcinogenicity of sunlight was tested in two studies in mice and rats (Roffo, 1934; 1939). In the first study of 600 rats, 165 (70%) of 235 which survived the acute heat load of exposure to sunlight for 5 hours a day developed tumours of the skin (mainly squamous cell carcinomas on the ears) or conjunctiva (spindle cell sarcomas). No tumours developed when sunlight was filtered through glass. Similar results were obtained in a second study in 2 000 rats and mice.

"Solar-simulated radiation" has been studied in a number of experiments (Forbes *et al.,* 1982; Staberg *et al.,* 1983; Young *et al.,* 1990; Menzies *et al.,* 1991). In the study by Forbes *et al.* (1982), 1 000 hairless mice were exposed for up to 80 weeks to radiation from a xenon arc lamp passed through various filters to simulate sunlight. More than 90% of the mice developed tumours, particularly squamous cell carcinomas.

UVB

Many studies have been conducted with sources emitting mainly UVB radiation. A few of the more informative studies in different species are summarised below.

Mouse: Freeman (1975) exposed one ear of each haired albino mouse in groups of 30, three times a week, to one of four wavelengths of narrow band UVB (290, 300, 310 and 320 nm), produced by a high-intensity diffraction grating monochromator with a half-power band-width of 5 nm, at doses proportional to the MED of

each wavelength for untanned human skin. Tumours were produced in
about 50% of surviving animals at each wavelength except 290 nm
where no tumours were produced although all animals survived. Most
tumours were squamous cell carcinomas (SCC).

De Gruijl et al. (1983) exposed six groups of 22 to 44 (total
199) male and female Skh-hr 1 hairless albino mice to daily doses of
from 57 to 1 900 J m^{-2} of mainly UVB from Westinghouse FS40TL12
sunlamps. Most of the mice developed skin tumours, mainly squamous
cell carcinomas, even though the highest daily dose was
sub-erythemal. A power relationship (linear on log-log scales) was
observed between the daily dose and the time required for 50% of the
animals to develop tumours (figure 7.1). SCC developed in 71% of
mice in the lowest dose group and two skin tumours of different
types were observed late in the lives of 24 control mice (received
no UVB radiation).

Other Species: Stenbäck (1975a) exposed groups of shaven NMR
rats, Syrian golden hamsters and guinea pigs to mainly UVB from
Westinghouse FS40T12 sunlamps for 60 weeks at weekly doses of 5.4 to
10.8 J m^{-2}. Tumours developed in 16 of 40 rats (mainly papillomas
on the ears), 14 of 40 hamsters (mainly papillomas of skin not on
the ears) and 2 of 25 guinea pigs.

A number of experiments were carried out in which groups of a
South American opossum, *Monodelphis domestica,* were exposed to
mainly UVB from Westinghouse FS40 sunlamps. *M domestica* is unusual
in showing photoreactivation of cyclobutylpyrimidine dimers (Ley,
1985). Regular exposures of 250 mJ m^{-2} produced melanomas in 5 of
13 surviving animals by 100 weeks from commencement of the
experiment. No melanomas were seen in a much larger colony not
exposed to artificial UV (Ley et al., 1989). In other experiments,
nonmelanocytic skin tumours (mainly fibrosarcomas and squamous cell
carcinomas) and fibrosarcomas of the corneal stroma were produced
(Ley et al., 1987, 1989). The latter were delayed in appearance
and reduced in number when UV exposure was followed immediately by
photoreactivating light.

Figure 7.1 Relationship of the logarithm of relative UVB dose to
the logarithm of median time (t_m) to first detectable skin tumours
(threshold <1mm diameter) in albino hairless mice irradiated
with Westinghouse FS40TL12 sunlamps. The maximum daily
dose was measured at 190 mJ m^{-2} (From De Gruijl et al., 1983).
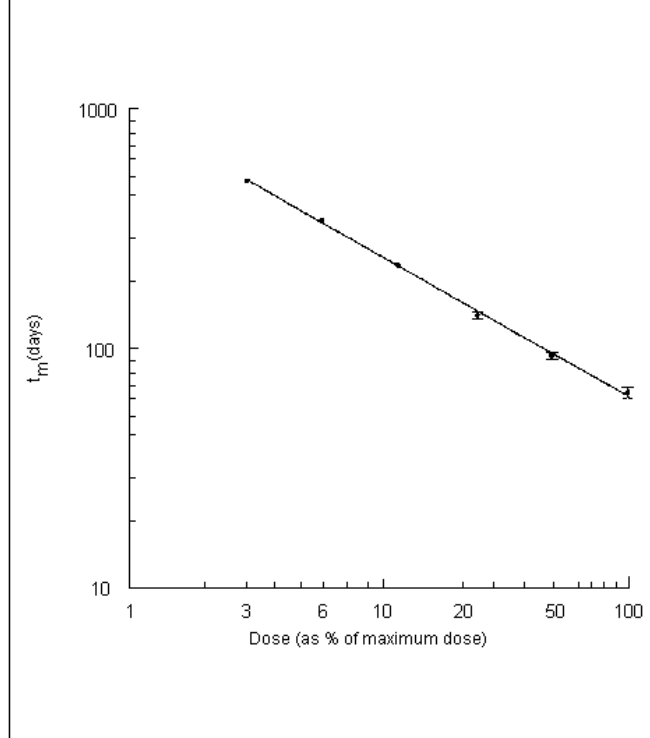
A group of 460 hybrid fish of two strains developed by crossing
platyfish (*Xiphophorus maculatus)* and swordtails (*Xiphophorus
helleri)* were exposed for 5 to 20 days to mainly UVB from
Westinghouse FS40 sunlamps filtered through acetate sheets
transmitting > 290 nm (150 or 300 mJ m^{-2}) and >340 nm (850 and
1700 J m^{-2}). Between 19% and 40% of exposed fish developed
melanocytic tumours compared with 12% and 2% in control fish (Setlow
 et al., 1989).

In an attempt to confirm a suspected association between
sunlight and cancer of the eye in cattle, four Hereford cattle were
exposed to mainly UVB from Westinghouse FS40 sunlamps. Visible
tumours developed in the eyes of three of them and one was confirmed

histopathologically as a preneoplastic growth (Kopecky *et al.,*
1979).

   UVC

    Experiments have been carried out in which animals have been
exposed to low-pressure mercury discharge germicidal lamps which
emit most of their radiation at 254 nm with weaker spectral lines in
the UVB, UVA and visible spectra (IARC, 1992). Examples are given
below.

    A group of 40 mice was irradiated with germicidal lamps at
weekly doses of 3 x 10^4 J m^{-2}. By 52 weeks, 97% of mice had
developed skin tumours, the majority of which were squamous cell
carcinomas (Lill, 1983). In another study, groups of 24 hairless
albino mice were irradiated daily at 230, 1460 or 7000 J m^{-2}. The
prevalence of tumour-bearing mice (with mainly squamous cell
carcinomas) increased with time to over 75% in each exposure group
(Sterenborg *et al.,* 1988). A comparison with other studies showing
response to exposure to UVB led the authors to conclude that the
small amounts of UVB emitted by the germicidal lamps could not
explain the response observed. Interaction between UVC and UVB could
not be excluded. Yields of keratoacanthoma like skin tumours,
proportional to dose, were observed in small groups of rats exposed
to radiation from Westinghouse G36T6L germicidal lamps (Strickland
 et al., 1979).

   UVA

    A number of studies have been conducted in which skin tumours
have been produced in hairless mice by UVA under conditions in which
the exclusion of UVB from the exposure was adequately documented

(IARC, 1992). For example, groups of 24 albino hairless mice were
exposed to UVA from Philips TL40W/09 fluorescent tubes filtered
through 10mm of glass, highly absorbent for UVB, for 12 h/day, seven
days a week, for one year. The daily dose was 220 kJ m^{-2}. Skin
tumours appeared in all animals and histopathological examination of
the larger lesions showed the majority to be SCC. On the basis of
the known dose-response to UVB, it was estimated that 100,000 times
more UVB than was residually present in the exposure would have been
necessary to produce the incidence of tumours observed (van Weelden
 et al., 1986, 1988). Similar findings were obtained in a study in
which UVA at > 340 nm was produced by passing radiation from
Philips HPA 400 W lamps through liquid filters (Sterenborg and van
der Leun, 1990).

7.1.3 Interactions between radiations of different wavelengths

    Simple photoaddition is commonly assumed for the interaction of
different wavelengths of UV in producing cancer. That is, exposure
at each wavelength contributes to the effective dose in an additive
way. Several studies, however, suggest that the true position is
more complex and the subject has been reviewed in detail by van der
Leun (1987, 1992).

    For exposures to UV at different wavelength ranges administered
simultaneously, or in close temporal proximity, both reductions and
increases in the carcinogenic effect have been reported by
comparison with what would have been expected on the basis of simple
addition. Following detailed review, these effects were described as
"nonexistent, unproven or small" (IARC, 1992) and this conclusion is
consistent with the results of a recent study (Berg *et al.,* 1993).
Such interactions play only a small role in the evaluation of risks
of UV (Health Council of the Netherlands, 1986).

    There is a well-established protective effect of visible light
against UV carcinogenesis (and other effects) in *M. domestica*
(Ley, 1993) and lower animals (see, for example, Setlow *et al.,*
1993) which possesses the photoreactivating enzyme, photolyase.
Whether or not humans possess a DNA photolyase or show
photoreactivation is controversial (Ley, 1993, Li *et al.,* 1993).

    Several experiments, with somewhat conflicting results, have
been carried out in which exposures to UV to one wavelength range
have been separated in time from exposures to another (Forbes *et
 al.,* 1978; Staberg *et al.,* 1983; Bech-Thomsen *et al.,* 1988a,
b; Slaper, 1987). On review of these studies, it was concluded that

the combined effects tend to be slightly less than what would be
expected from simple photoaddition (IARC, 1992).

7.1.4 Dose-response

    The accurate and quantitative description of the relationship
between UV and the occurrence of skin tumours, usually SCC, has been
based on experiments in which mice have been exposed regularly,
usually daily, to UV from standard sources. In most relevant
experiments, a UV dose, usually much lower than that of the outdoors
environment, was delivered daily or several times per week until
skin tumours developed. The UVB dose which induces tumours in mice
is lower than for acute reactions such as erythema or oedema and up
to 33 times lower in one experiment which produced an abundance of
skin cancers (De Gruijl *et al.,* 1983). The higher the dose given,
the less time it takes for tumours to appear. In most experiments,
the time taken for 50% of mice to develop tumours has ranged between
a few months and one year but can be brought down to as low as 18
days (IARC, 1992; Willis *et al.,* 1981).

Quantitative dose-effect relationships have been derived for
mice exposed regularly (usually daily) to UV. The median time to
first tumour (t_m) has been used as the measure of effect.
Dose-effect relationships of the following form have been proposed
(IARC, 1992):

$$t_m = k_1 \, D^{-r}$$

or, equivalently,

$$\log t_m = -r \log D + \log k_1 \; .$$

In these expressions, k_1 is a constant representing both the
susceptibility of the mouse strain and the effectiveness of the
radiation spectrum administered, D is the daily dose of radiation
and r is a numerical exponent giving the slope of the dose response
curve. Estimates of r vary between 0.5 and 0.6 in most experiments,
with broad-spectrum UV and broadband UVB; the value of 0.5 is
typical for large tumours, and 0.6 for small tumours (Blum *et al.*,
1959; de Gruiji, 1983). In one experiment with UVC a value r=0.2 was
found (Sterenborg, 1988). The relationship found by de Gruijl *et
al.* (1983) for the induction of skin tumours less than 1 mm in
diameter by UVB in albino hairless mice is shown in figure 7.1; the
value of r in this relationship is 0.6.

A corresponding expression for the dose-response relationship
in albino hairless mice is given by:

$$Y = k_2 \, D^c \, t^d$$

where Y is the average number of tumours per mouse (the yield), k_2
is a constant, D is the daily dose of UV radiation, t is the number
of days of exposure to UV and c and d are numerical exponents
describing the dose response relationship (van der Leun & der
Gruijl, 1993). By describing the response in terms of a measure of
incidence of tumours rather than time to tumour development, this
expression may be more useful for risk assessment in humans.

7.1.5 Effect of pattern of exposure

Tumours can be induced by a single dose of UV (Hsu *et al.*,
1975; Strickland *et al.*, 1979). In mice, this has required a dose
that caused ulceration of the skin which is known to be a tumour
promoter.

Two experiments have reported on the effects of pattern of UV
(mainly UVB) exposure in albino hairless mice. At constant
instantaneous intensity and constant weekly dose of UV, increasing
fractionation of the dose from once weekly to three times weekly to
five times weekly increased the incidence of tumours (Forbes *et
al.*, 1981). Similarly, with a constant daily dose of UV, incidence
of tumours increased with extension of the period of delivery (and
corresponding reduction in instantaneous intensity) from 1.25 to 4
or 12 hours (Kelfkens *et al.*, 1991); there was no appreciable
difference between exposures of 4 and 12 hours. Similar results had
been obtained by Forbes and Davies (cited in Kelfkens *et al.*,
1991).

7.1.6 Action spectrum

Ideally, to determine the action spectrum of UV carcinogenesis,
experiments would be carried out with monochromatic radiation to
determine the relationship between dose and median time to first
tumour for each wavelength. However, narrow-band monochromatic
sources suitable for experiments of these types are difficult to
achieve. An alternative approach is to conduct experiments with a
number of overlapping broad band sources and to derive an action
spectrum by appropriate mathematical analysis of the results.

Recently two large collections of data on carcinogenicity of UV
in albino hairless mice following exposure to multiple overlapping

sources in the UVC, UVB and UVA ranges, supplemented with results of
experiments using highly filtered UVA sources, have been combined to
produce what is probably the best estimate to date of the action
spectrum for skin carcinogenesis in any strain of animals (de Gruijl
 et al., 1993). As far as possible, the end point in the
experimental results used was the appearance of SCC.

The action spectrum produced is shown in figure 7.2. The upper
and lower dashed (- -) curves result from a sensitivity analysis
showing the boundaries of the effects of displacements of 5 nm
segments of the action spectrum that do not increase the chi^2 for
the fit of the spectrum to the data by more than 1.0. Effectiveness
rises as wavelength increases to a peak at about 295 nm, falls
steeply to an initial minimum at about 350 nm, rises again to 380 nm
and then appears to fall away sharply. The definition of this action
spectrum is very good in the UVB range, there is substantial
uncertainty in the UVA range and essentially no information below
280 nm except at 254 nm. Even with the uncertainty, if there is not
actually a second peak in the UVA range, there is at least a plateau
from about 340 to 380 nm. This action spectrum is very similar to
the action spectra for erythema in humans (McKinlay and Diffey,
1987) and the induction of oedema in the skin of mice (Cole *et al.*,
1986).

Recently, results have been reported on the action spectrum for
the production of melanomas in hybrid fish (Setlow *et al.*, 1993).

Groups of between 20 and 124 fish were exposed to single doses, at two to six exposure levels, of UV or visible light at wavelengths of 302 nm, 313 nm, 365 nm, 405 nm and 436 nm. Narrow band radiation was produced by use of a grating monochromator and, for the higher wavelengths, various filters to eliminate any radiation at substantially lower wavelengths. The experiment was terminated after four months and all fish examined for melanomas which occurred in 5% to 24% of control fish and 24% to 45% of irradiated fish. The estimated action spectrum obtained is shown in figure 7.3 superimposed on published action spectra for mammalian cell mutagenicity and cytotoxicity. Relative to an effectiveness in producing melanomas of 1.0 for UV at 302 nm, the effectiveness at 313 nm was 0.16 and that at 365 nm, 0.32; for visible light, the relative effectiveness were 0.017 at 405 nm and 0.023 at 436 nm. The effectiveness of UVA in producing melanoma in this model relative to the effectiveness of 300 nm radiation was some 3 orders of magnitude greater than the effectiveness of UVA, relative to the same baseline, in producing SCC in hairless albino mice (figure 7.2; de Gruijl *et al.,* 1993). An action spectrum has not yet been determined for production of melanoma in *M. domestica.*

Figure 7.2 Estimated action spectrum (called the SCUP action spectrum) for induction by UV of SCC in the skin of albino hairless mice (Skh-hr 1). The dashed lines (--) show the upper and lower limits for 5nm displacements of the action spectrum that do not increase the χ^2 for fit of the spectrum to the data by more than 1.0 (Reprinted with permission from de Gruijl et al., 1993).

Figure 7.3 Estimated action spectrum for induction by UV and visible light of melanocytic tumours in hybrid fish of the genus *Xiphophorus* compare with published action spectra for mammalian cell mutagenicity and cytotoxicity. o, cytotoxicity; ●, mutagenicity; ■ , induction of melanocytic tumours (Reprinted with permission from Setlow et al., 1993).
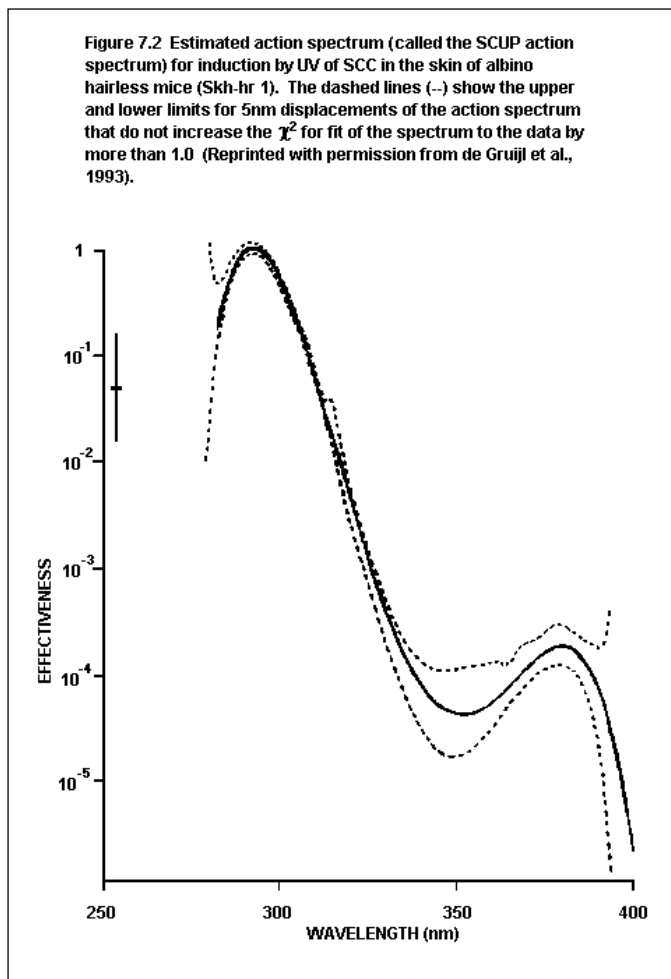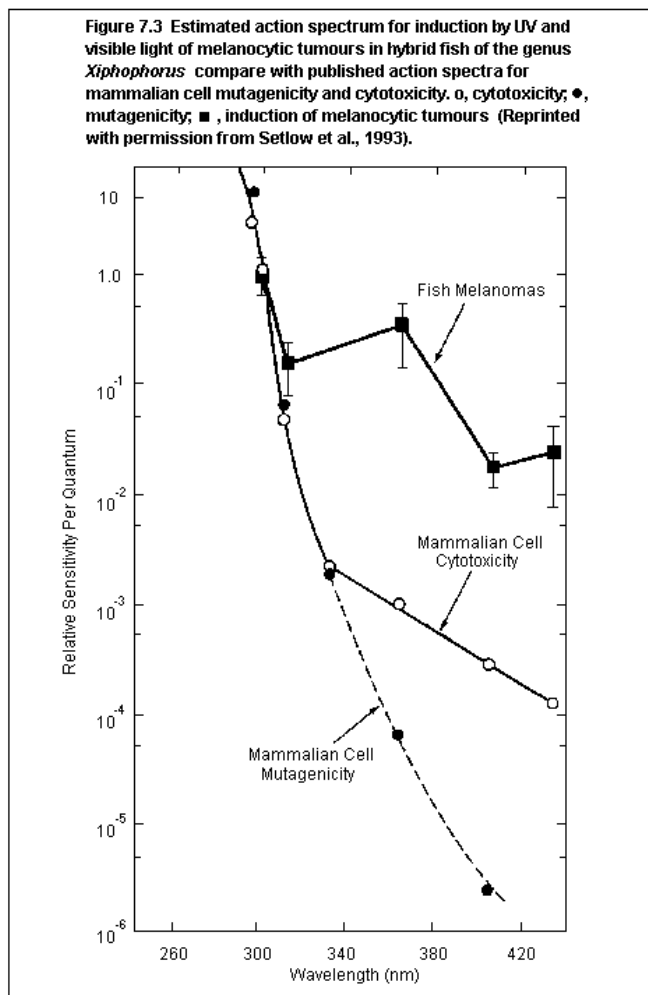
7.1.7 Interaction between UV and chemicals

Interaction with chemical carcinogens

A number of studies have been carried out in which UV has been administered before or after administration of a known chemical carcinogen. A period of irradiation with UVB before application of 3,4-Benzo[a]pyrene to the skin of mice increased the carcinogenic response to high-dose 3,4-Benzo[a]pyrene (Gensler & Bowden, 1987; Gensler, 1988). A number of studies in which mice were irradiated with UV after application of 7,12-Dimethylbenz[a]anthracene (DMBA) to the skin showed an increase in tumour production over that produced by DMBA alone (Epstein & Epstein, 1962; Epstein, 1965; Reeve *et al.,* 1990; Husain *et al.,* 1991). Of particular interest in this regard is the production of melanoma-like lesions in mice by the combination of DMBA and UV. In a number of experiments, DMBA alone has produced benign pigmented naevi. Subsequent administration of UVB, UVB + UVA, and UVA alone caused these naevi to grow into lesions that had the appearance of malignant melanoma; these lesions did not develop in mice treated with DMBA alone (Epstein, 1965; Epstein *et al.,* 1967; Husain *et al.,* 1991). Irradiation with UVB from Westinghouse FS40 sunlamps before application of DMBA and the promoter 12-O-tetradecanoylphorbol 13-acetate (TPA) reduced the incidence and number of tumours produced in CDF_1 mice both when the site of subsequent application of the chemicals was irradiated and when a distant site was irradiated (Gensler and Welch, 1992). This effect, therefore, appeared to be mediated systemically.

Both croton oil and TPA, applied to skin after irradiation with UV, have been shown to increase the carcinogenic response to UV (Epstein & Roth, 1968; Pound, 1970; Stenbäck, 1975b; Strickland *et al.,* 1985). Of two other, suspected cancer promoters, one, methyl ethyl ketone peroxide increased tumour production (Logani *et al.,* 1984) and the other, benzoyl peroxide, did not (Epstein, 1988; Iversen, 1988).

Interaction with other chemicals

In several experiments, mice exposed to either solar- simulated radiation or UVA and topical application of 5- methoxypsoralen showed higher incidences of skin papillomas or SCC than did mice exposed to UV or 5-methoxypsoralen alone (Zadjela & Bisagni, 1981; Cartwright & Walter, 1983; Young *et al.,* 1983). Methoxsalen (8-methoxypsoralen) shows the same effects when given with UV (IARC, 1980).

7.1.8 Mechanisms of UV carcinogenesis

DNA damage

There is abundant evidence that UV causes DNA damage, both by direct photochemical effects (for example, the production of cyclobutylpyrimidine dimers and 6-4 photoproduct) and by oxidative effects leading to DNA strand breakage and DNA-protein cross-linkage (see Chapter 6).

There is evidence that UV-induced DNA damage, and particularly the formation of pyrimidine dimers, is one step in the mechanism whereby UV can cause cancer in experimental animals. First, Hart *et al.* (1977) showed, in the clonal fish, *Poecilia formosa,* that the transplantation of UVC irradiated thyroid cells from one fish to another induced thyroid tumours in the host fish. If irradiation of the thyroid of the donor fish was followed immediately by application of photoreactivating light (which monomerizes the pyrimidine dimers), the development of thyroid tumours was almost completely prevented. Second, and similarly, Ley *et al.* (1991) showed that exposure to photoreactivating light, after exposure to UV, delayed and reduced the yield of skin tumours produced in *M. domestica* by irradiation with Westinghouse FS40 sunlamps. The same result was obtained for corneal tumours but, unexpectedly, exposure to photoreactivating light was as effective in reducing carcinogenesis when given immediately before UV as when given after. There is evidence that photoreactivating light may also inhibit the production by UV of melanocytic lesions in the skin of *M. domestica* (Ley *et al.,* 1989). Third, Yarosh *et al.* (1992) applied liposomes containing T4 endonuclease V, an enzyme that specifically repairs cyclobutyl pyrimidine dimers, to the skin of albino hairless mice, three times a week, after they had been irradiated with Westinghouse FS20 sunlamps. The incidence of skin tumours observed in the mice fell in proportion to the quantity of active liposomes applied.

There is also evidence that activated oncogenes and a mutated tumour-suppressor gene are present in some skin cancers induced experimentally by UV. Husain *et al.* (1990) reported studies of expression of the cHa-ras oncogene in three papillomas and three carcinomas from among lesions that developed in 17 of 90 Sencar mice following a single exposure, at 7×10^4 J m^{-2}, to UVB from Westinghouse FS20 sunlamps. RNA preparations from all six tumours showed elevated levels of Cha-*ras*-specific messenger RNA sequences, suggesting overexpression of this oncogene. DNA from the carcinomas, but not the papillomas, was able to induce transformation of NIH-3T3 cells which demonstrated overexpression and amplification of the Cha-ras oncogene. Subsequently, in their studies of melanocytic tumours produced by DMBA and UV in hairless mice (Skh-hr 2), Husain *et al.* (1991) found mutations in codon 61 of the N-*ras* oncogene in three of eight precursor naevi and one

melanoma. The base transitions, however, were not of a type to suggest that they had been caused by UV. Kress *et al.* (1992) screened exons 5 to 8 of the p53 tumour-suppressor gene for mutation in 35 epidermal tumours induced in four strains of mice by UV from Westinghouse FS40 sunlamps. Mutations were found in seven tumours. All mutations occurred at dipyrimidine sequences. C -> T and CC -> TT transitions were present in five of the seven tumours with mutations, strongly suggesting that these mutations were due to UV.

Oxidative processes

Oxidative processes in the skin may also mediate the carcinogenicity of UV, particularly UVA (Morlière *et al.,* 1992), in skin, either by direct oxidative damage to DNA or by way of potentially carcinogenic intermediates, such as cholesterol-5,6-epoxide (Black, 1987; Morin *et al.,* 1991). A number of studies have shown that relative increases in dietary polyunsaturated fatty acids, which may lead to lipid peroxidation, can increase the tumour response to exposure to UV in experimental animals and that this effect can be inhibited by the simultaneous feeding of antioxidants (Reeve *et al.,* 1988; Black *et al.,* 1992). In addition, the feeding of antioxidants, such as tocopherol, can reduce the tumour response to UV in the absence of any manipulation of dietary fat (Black & Chan, 1975; Gerrish & Gensler, 1993).

Immune-suppression

UV-induced immune-suppression appears to play a major role in UV carcinogenesis in mice. A review of the literature on the association between UV-induced immune suppression and increased susceptibility to tumours may be found in section 7.3.2.

There is evidence also that administration of immunosuppressive drugs will increase the carcinogenic response to UV in experimental animals (IARC, 1992). Experiments have been carried out with anti-lymphocyte serum, azathioprine, cyclophosphamide, cyclosporine and 6-mercaptopurine. Consistent increases in the carcinogenic response to UV over two or more experiments were seen with azathioprine and cyclosporine (Reeve *et al.,* 1985; Nelson *et al.,* 1987; Servilla *et al.,* 1987; Kelly *et al.,* 1987, 1989).

7.1.9 Conclusions

From a review of the animal studies one can conclude the following about UV exposure of the skin:

Carcinogenesis by sunlight is a widespread phenomenon among domestic and food animals. Most tumours found are squamous cell carcinomas (SCC). In experimental animals skin cancer is mainly caused by UV radiation. Again, most tumours induced are SCC. For the

induction of SCC in albino hairless mice, the effectiveness is a
function of wavelength:

-    the effectiveness is found to peak in the UVB range;
-    UVA is also carcinogenic, but at a much lower level of
     effectiveness - similar to what is found for erythema and
     tanning;
-    the effectiveness in the UVC range is unknown, except for one
     wavelength, 254 nm; at that wavelength the effectiveness is
     lower than that in the UVB peak
-    it is still unknown if there is any effectiveness of visible
     light.

     For the induction of SCC in hairless mice by daily exposures to
UVB the dose effect relationship was found to be a power function.
It showed no indication of a threshold dose, even at doses as low as
3% of that required for an acute reaction, such as oedema.
Radiations of different wavelengths can cooperate in the induction
of SCC.

     Melanomas are much less common among animals. Only two animal
models have been found where exposure to UV induced melanomas:

-      the South American opossum *M. domestica,* and

-      a hybrid fish, derived from the swordtail and platyfish.

     An initial action spectrum was determined for the hybrid fish.
It peaks in the UVB range but also shows a high effectiveness in the
UVA. An action spectrum for the induction of melanoma in *M.
 domestica* has not been determined.

     Basal cell carcinomas are uncommon in animals. Suitable animal
models for the induction of BCC are not available.

7.2 Immune Responses

7.2.1 Immune function assays

     The immune system depicted in figure 7.4 is composed of primary
lymphoid organs (bone marrow and thymus), secondary lymphoid organs
including spleen and lymph nodes, and several cell types. In
addition a number of mediators including cytokines, antibodies and
complement regulate and/or are produced by the immune system. A
number of studies have shown that exposure to UV suppresses contact

hypersensitivity (CHS) and other delayed-type hypersensitivity (DTH)
responses of the immune system. Both of these responses provide a
measure the competence of T lymphocytes, suppression of which would
be expected to compromise host resistance to infectious agents such
as viruses and mycobacterium. Unless otherwise indicated animal
studies have utilized FS sunlamps (see Chapter 3 for spectral
characterization) and exposed shaved skin.

     Two types of experiments have been described in the literature.
In experiments designed to investigate local immune suppression,
mice were exposed to UV and a hapten chemical such as
dinitrofluorobenzene (DNFB) was applied to the site of irradiation.
After an incubation period of several days, animals were challenged
by painting the chemical on the ear, and the immune response was
assessed by measuring ear thickness, which is an expression of CHS.
Mice exposed (usually for 4 successive days prior to chemical
application) to doses of UV, which might cause a minimal erythemal
response in an untanned human, failed to show ear swelling (Toews
 et al., 1980; Noonan & De Fabo, 1990; Jeevan *et al.,* 1992a). The
failure to respond appeared to be due to the development of
suppressor T cells which rendered the mouse tolerant to the
particular antigen. This concept was supported by the observation
that the same mice could not be sensitized with the same chemical
through unirradiated skin 14 days later. Moreover, antigen-specific
unresponsiveness could be adoptively transferred to naive mice by
spleen and lymph node cells obtained from mice skin-painted with
DNFB through UV-irradiated skin (Elmets *et al.,* 1983). It should
be noted that the precise nature of the activity of these suppressor
cells remains the subject of some debate.

     In a second type of experiment the effects of UV on systemic
immune responses were demonstrated by irradiating mice at one site
and subsequently (3-5 days later) exposing them to a contact
allergen (CHS) or injecting a protein antigen (DTH) at an
unirradiated site. These mice failed to respond when subsequently
challenged on the ear (CHS) or in the footpad (DTH) with the same
antigen (Noonan *et al.,* 1981a, Kim *et al.,* 1990; Ullrich *et
 al.,* 1986a; Ullrich, 1986; Jeevan & Kripke, 1990; Howie *et al.,*
1986; Denkins *et al.,* 1989; Giannini, 1986a,b). Again
unresponsiveness was attributed to the development of antigen
specific "suppressor T cells" (Noonan *et al.,* 1981b; Ullrich
1985). These experiments suggest that immune suppression could occur
even when the site of entry for the antigen was not the same as the
site of UV exposure.

Figure 7.4 Schematic of the immune system. The immune
system is composed of primary lymphoid organs (bone marrow
and thymus), secondary lymphoid organs (not shown) and several
cell types. A number of mediators including cytokins, antibodies,
and complement regulate and/or are produced by the immune
system. The above schematic depicts some of the interactions
that occur when the immune system responds to an antigen.

Noonan *et al*. (1981a) reported a 50% suppression of CHS in
BALB/c mice after a single dose of 2 KJ m^{-2} UV. She also reported
that there was no difference in the dose response curves for
UV-induced local and systemic immunosuppression of CHS responses;
however, the dose of UV required to suppress CHS in C57BL/6 mice was
6.4 times less than that required to produce similar immune
suppression in BALB/c mice (Noonan & De Fabo, 1990). Also, while
local suppression could be demonstrated in mice sensitized
immediately after irradiation, systemic suppression occurred only if
the sensitizer was applied 3 or more days after radiation (Noonan &
De Fabo, 1990).

Fifty percent suppression of CHS and DTH has been reported at
doses ranging from 2.3 kJ m^{-2} to 20 kJ m^{-2}, (Kim *et al.,* 1990;
Jeevan & Kripke, 1990; Jeevan *et al.,* 1992b) levels which produce
minimal or no edema. The dose needed to produce 50% suppression
varies depending on the strain of mouse and type of antigen used,
and on the laboratory producing the data. Suppression of
virus-specific DTH was observed in mice exposed to a suberythemal
dose of UVB 3-7 days prior to infection with Herpes simplex virus
(HSV) but not 14 days and persisted for at least 3 months after
irradiation (Howie *et al.,* 1986). Elimination of wavelengths below
315 nm with a mylar filter either eliminated or greatly reduced the
suppression of CHS following exposure to UV indicating that most if
not all the suppression is due to UVB (Noonan *et al.,* 1981b;
Noonan and De Fabo, 1990). Using narrow bands of UV at 10
wavelengths from 250 to 320 nm, it was reported that maximum
suppression of CHS occurred between 260 and 270nm, there was a
shoulder in the action spectrum from 280-290 nm and then a steady
decline to 3% of maximum at 320 nm (De Fabo and Noonan, 1983).

There are two subpopulations of T helper cells, designated Th1
and Th2 which appear to be differentially affected by UV exposure.
These two populations are thought to regulate different sets of
immune responses. Th1 cells produce interleukin (IL) 2 and gamma
interferon (gamma IFN) as well as other cytokines, promote
delayed-type hypersensitivity (cell mediated, type IV) responses
such as CHS, provide help for certain antibody subtype responses
including complement-fixing antibodies, activate macrophages, and

may be particularly important for dealing with antigens expressed on cell surfaces, such as viral and tumour antigens (Coffman *et al.,* 1988). Th2 cells produce a different array of cytokines including IL-4 and IL-5 which promotes antibody responses. Only Th2 cells can stimulate a primary IgE response which is mediated by IL-4 and inhibited by gamma IFN (Coffman *et al.,* 1988). Thus, Th2 cells may be particularly important in responding to certain parasitic infections, and also play an important role in immediate-type hypersensitivity including reactions to common allergens such as pollen and dust mite.

Recent studies have suggested that both local and systemic immune suppression induced by UV may be the result of an inability to present antigen to and hence activate Th1 cells (Simon *et al.,* 1990, 1991; Araneo *et al.,* 1989).

Suppression of systemic CHS and DTH responses similar to that observed following UV exposure have been obtained by injecting mice with supernatant from UV-irradiated keratinocytes (Kim *et al.,* 1990; Rivas & Ullrich, 1992; Jeevan *et al.,* 1992c). Among factors derived from keratinocytes, the cytokines tumour necrosis factor alpha (TNF alpha) (Yoshikawa & Streilein, 1990; Vincek *et al.,* 1993) and IL-10 (Rivas & Ullrich, 1992) are thought to be important in UV-induced immunosuppression. Also, cis-urocanic acid, the product of UV isomerization of urocanic acid located in the stratum corneum, when injected subcutaneously or painted on the epidermis, produces immunosuppressive effects which mimic UVB-induced immunosuppression (Ross *et al.,* 1986), and the action spectrum of UV-induced immune suppression closely follows the absorption spectrum of urocanic acid (De Fabo and Noonan, 1983). In all three cases it is thought that these mediators act by modifying antigen presentation (Vermeer & Streilein, 1990; Rivas & Ullrich, 1992; Noonan *et al.,* 1988).

In summary, it appears that UVB causes the release of mediators from the skin which alter the antigen presenting capability of Langerhans cells as well as antigen presenting cells at other sites, resulting in the development of "suppressor T-cells". It may be that these suppressor T cells are Th2 cells. The net result is the failure to activate Th1 cells and suppression of DTH responses thought to play an important role in host defences against certain types of tumours and microbial infections. The immune suppression is antigen specific, (i.e. only responses to antigens administered within 7 days after irradiation are affected) and is long lasting (at least 3 months).

In addition to DTH and CHS responses, UV affects several other immune functions frequently included in the standard protocols for immunotoxicity testing. Spleen cells taken from UV-exposed mice (single exposure, 54 kJ m^{-2}) failed to respond in a mixed lymphocyte response assay *in vitro* (Ullrich, 1985), and spleen cells from tumour-implanted UV-treated (10 kJ m^{-2}, 3 times/wk, for 3 months) mice were not cytotoxic *in vitro* against UV-induced tumours (Fisher & Kripke, 1977). In contrast, exposure to approximately 2-3 kJ m^{-2} day^{-1}, for 23 days did not affect responses of spleen or inguinal lymph node cells to the mitogens, phytohaemagglutinin, concanavalin A or bacterial lipopolysaccharide. Similarly, lymphocyte responses to these mitogens and peritoneal macrophage phagocytic and tumouricidal activities were unaffected by exposure to 10 kJ m^{-2}, 3 times per week, for up to 6 months (Funnell & Keast 1985; Norbury *et al.,* 1977).

Kripke *et al.,* (1977) reported no effect of UV (in mice exposed to 10 kJ m^{-2}, 3 times per week for up to 6 months) on the primary haemagglutonin antibody response to sheep red blood cells; however in another study, the IgM and IgG plaque forming cell responses of lymph node cells to sheep red blood cells given intradermally (through irradiated skin) were suppressed (Funnell & Keast, 1985). Also, suppressor cells generated by irradiating mice with a single exposure of 30-40 kJ m^{-2}, 5 days prior to sensitization with trinitrochlorobenzene prevented the development of hapten specific antibody-forming cells when injected intravenously along with hapten conjugated sheep red blood cells into syngeneic recipients (Ullrich *et al.,* 1986b).

UV exposure enhanced poly I.C augmented natural killer cell (NK) activity in mice (Lynch & Daynes, 1983); however, suppression of NK activity in rats has been reported following exposure to suberythemal doses of UV (Garssen *et al.,* 1993). Hence, in laboratory animals UV exposure appears to affect mixed lymphocyte responses, cytotoxic T cell activity, possibly NK activity, and in some circumstances antibody responses. With the exception of NK activity all of these responses are antigen specific responses. In contrast UV does not appear to alter several non-specific responses including macrophage phagocytic or tumouricidal activities, or T or B cell responses to mitogens. However, unlike CHS and DTH, none of these responses has been studied in detail in rodents, and dose response information is not available.

7.2.2 Susceptibility to tumours

Interest in the immunosuppressive properties of UVB was first sparked by the observations of Kripke and associates that UV exposure induced highly antigenic tumours which did not grow when transplanted into syngeneic, immunocompetent mice but did grow when transplanted into immunosuppressed or UV treated mice (Kripke 1974; Kripke & Fisher, 1976). The precise nature of the tumour antigens has not been defined. Mice treated with 1.8 kJ m^{-2}, 3 times per

week, for 3 months were unable to reject UV-induced syngeneic
tumours when challenged subcutaneously at any time from 2 weeks into
the irradiation exposure regimen to as late as 5 months after the
end of UV treatment (Kripke & Fisher, 1976). Hence susceptibility to
tumour challenge was detectable well before the appearance of
primary skin cancers induced by the UV and persisted long after
exposure ended. Similarly, more UV-induced fibrosarcoma tumour
colonies were detected in the lungs following i.v injection of
tumour cells in mice treated with 7 kJ m^{-2}, 3 times per week, for
5 weeks (Kripke & Fidler 1980) as compared to unirradiated controls.
Susceptibility to tumour challenge was directly proportional to dose
of UV and a dose fractionated over time was no more effective than
the same total dose given as a single treatment (Kripke & Fidler
1980; De Fabo and Kripke 1979).

In BALB/cAnN mice 50% tumour incidence following subcutaneous
tumour challenge at an unirradiated site occurred at a dose of
approximately 40 kJ m^{-2}. Enhanced tumour incidence was observed in
mice exposed to 21.6 kJ m^{-2} as much as 32 weeks before tumour
challenge. A number of studies (Fisher & Kripke, 1977; Daynes &
Spellman, 1977; Daynes *et al.,* 1977; Spellman & Daynes, 1978;
Spellman *et al.,* 1977; Ullrich & Kripke, 1984, de Gruijl and van
der Leun 1982, 1983) have demonstrated that susceptibility to
challenge with UV-induced tumours following UV exposure, like
suppression of CHS and DTH, is mediated by antigen specific
"suppressor T cells" which are present in spleen and lymph nodes of
UV-irradiated mice. As with suppression of DTH and CHS responses,
enhanced susceptibility to UV-induced tumours is antigen specific
and long lasting.

While it is very clear that UV increases the susceptibility of
mice to UV-induced tumours, much less work has been done on the
effects of UV on susceptibility to other types of tumours. UV
treated mice that were unable to reject syngeneic UV- induced
tumours were able to reject 2 types of non-UV-induced tumours, B16
melanoma tumours and a spontaneous mouse leukaemia tumour (Kripke
et al., 1977). Roberts and Daynes (1980) reported that mice
irradiated with subcarcinogenic doses of UV for 3 weeks prior to
treatment with either benz[a]pyrene or methycholanthrene at an
unirradiated site had reduced latency periods for the development of
these chemically-induced tumours. Also, chemically induced tumours
from these UV-treated mice appeared to be more antigenic than those
induced in untreated mice in that they were incapable of progressive
growth when transplanted into normal (immunocompetent) syngeneic
mice but were capable of progressive growth in UV-treated mice. The
authors suggested that decreased selective pressures exerted by the
host (due to UV-induced suppressor cells) at the time of tumour
induction allowed more immunogenic tumours to emerge and progress.

7.2.3 Susceptibility to infectious disease

Several types of infectious disease models have been developed
to study the effects of UV exposure: 1) the infectious agent was
injected through irradiated skin, 2) exposure to the infectious
agent occurred at a site distant from the site of irradiation, or 3)
in the case of some herpes simplex virus (HSV) studies, exposure to
UV occurred after infection. The first exposure scenario is
representative of vector-borne infections and some vaccinations
while the second exposure regimen is representative of infections
which do not necessarily enter the host via the skin. The third
scenario was designed to mimic reactivation of HSV in humans
following sun exposure. In all cases the focus has been on microbial
agents that are controlled, at least in part, by DTH responses.

An example of the first type of model is that of *Leishmania
major* infection in mice (Giannini 1986a, 1986b, 1987, 1992). Mice

were irradiated only on the tail with suberythemal doses (0.06-6 kJ
m^{-2}), 3 times/week, for 1 month and were infected intradermally
through the irradiated surface of the tail 24 hr after the first UV
exposure. In UV-treated mice the DTH response to *L. major* antigens
2 and 6 weeks post infection was suppressed, the number of organisms
recovered from skin at the injection site was (Giannini, 1986a) and,
a larger number of parasites was observed in the draining lymph node
(Giannini, 1987, 1992). Finally, mice which were infected through
irradiated skin failed to develop protective immunity such that
lesions following reinfection at an unirradiated site were
significantly larger when compared to lesions of previously infected
but unirradiated mice (Giannini, 1986b).

In a similar model mice treated with 13 or 33 kJ m^{-2} for 4
consecutive days and infected intradermally with HSV at the site of
irradiation had a higher incidence of zosteriform lesions than
unirradiated mice, and at the higher exposure level 100% mortality
was observed as opposed to no mortality in unirradiated mice
(Yasumoto *et al.,* 1987). A decreased DTH response to viral antigen
was observed and appeared to result from the induction of suppressor
T cells (Yasumoto *et al.,* 1987, Aurelian *et al.,* 1988). Also,
following *in vitro* exposure to UV, a defect in the ability of
Langerhans cells to present HSV antigen to lymphocytes was
demonstrated (Hayashi & Aurelian, 1986).

In contrast, no effect of UV on either parasite specific DTH
responses or recovery of parasite from internal organs was observed
following percutaneous injection of *Schistosoma mansoni* through
UV-irradiated (0.4 kJ m^{-2}, 4 consecutive days) skin (Jeevan *et
al.,* 1992a). In this same study, suppression of microbe specific
DTH responses were not observed following intradermal injection of

Mycobacterium bovis (BCG) or subcutaneous injection of *Candida albicans* at the site of irradiation; however, the number of viable mycobacteria recovered from the lymphoid organs of BCG-infected mice was increased significantly in the UV treated mice for a period of more than 2 months post infection.

BCG has also been used as an infectious disease model to illustrate systemic effects of UV immunosuppression. In this model mice were irradiated on the back and injected with BCG subcutaneously in the footpad. Mice exposed from 1 to 15 times (3 times/week for up to 5 weeks) to one minimal erythemal dose (2.25 kJ m^{-2}) showed significant suppression in their DTH response to tuberculin (PPD) and increased numbers of live bacteria in the spleen and lymph node compared to unirradiated controls (Jeevan & Kripke, 1990). However, when exposures were continued beyond 5 weeks, the DTH response recovered and mice challenged with bacteria at that point did not exhibit increased numbers of organisms in the spleen and lymph node, suggesting that eventually some sort of adaptation to exposure occurs. Significant suppression of DTH was observed in mice which received a single dose as low as 1.4 kJ m^{-2}

3 days prior to infection and significant increases in bacteria in spleen and lymph node were observed in mice which received as little as 0.7 kJ m^{-2}. Similar effects were observed when supernatants from keratinocyte cultures exposed to UV *in vitro* were injected intravenously 3 days prior to infection (Jeevan *et al.,* 1992c).

In a similar model, mice treated with a single high UV dose (45 kJ m^{-2}) 3 days before infection with *Mycobacterium lepraemurium* exhibited significant suppression of DTH responses to mycobacterial antigen 3 and 6 months after infection and had significantly more bacteria in the infected footpad, lymph node, and spleen 3-6 months post infection (Jeevan *et al.,* 1992b). This high dose also reduced the median survival time in mice infected i.v. With a lower exposure dose (2.3 kJ m^{-2}) 50% suppression of the DTH response to mycobacterial antigen was observed 3 months post infection, and increased numbers of bacteria were observed in the footpad, spleen and lymph node of mice exposed to UV doses greater than or equal to 5.6 kJ m^{-2}. When mice were treated with 2.25 kJ m^{-2}, 3 times/week from 3-15 times, the DTH response to *M. lepraemurium* was suppressed, but as with BCG, the DTH response was normal in mice which received more than 15 exposures.

Effects of systemic UV-induced immune suppression have been demonstrated in mice infected with HSV, 3 days after irradiation with 1 kJ m^{-2}, at a site distant from the site of infection. In this model suppression of DTH was mediated by modulation of epidermal antigen presenting cells and the development of suppressor T cells (Howie *et al.,* 1986, 1987). Subcutaneous injection or epidermal application of UV-treated urocanic acid produced similar immune suppression (Ross *et al.,* 1986). Effects of UV on the actual progression of disease in this model have not been reported.

While most of the work to date has been done in mice, recent work in the rat suggests that suberythemal doses of UV also suppress immune responses. In addition rats exposed to suberythemal doses of UV had higher levels of microorganisms in target organs following oral infection with *Trichinella spiralis* or intraperitoneal infection with cytomegalovirus (Garssen *et al.,* 1993).

In summary, exposure to suberythemal doses of UV has been shown to exacerbate a variety of infections in rodent models. Both infections which are initiated at the site of UV exposure and infections initiated at distant sites have been affected. While most of the infections test, have evolved in some manner more recent work indicates that systemic infections without skin involvement may also be affected. Enhanced susceptibility appears to result from suppression of T-helper-1 cell activity. The mechanisms associated with this suppression appear to be the same as those identified in association with suppression to CHS responses.

Reactivation of latent HSV infections can be induced in mouse and guinea pig by exposure of the previously infected site to sub- or minimal erythemal doses of UV. However, the role that immune suppression plays in this reactivation has not been established (Blyth *et al.,* 1976; Norval *et al.,* 1987; Laycock *et al.,* 1991).

7.2.4 Susceptibility to immunologically-mediated diseases

Several studies have suggested that stimulation of Th2 cells may remain intact or be enhanced in UV-exposed mice (Simon *et al.,* 1990; 1991; Araneo *et al.,* 1989). Since Th2 cells are the only cells that can stimulate a primary IgE response (Coffman *et al.,* 1988), it is possible that UV exposure may increase the risk of immediate-type hypersensitivity. This possibility has not yet been studied, but deserves attention in light of the increasing incidence of morbidity and mortality due to asthma, which is often triggered by allergic responses (NIH, 1991; Danielle, 1988).

Acceleration of autoimmunity following UV exposure has also been reported in mice. Both acute (2 hr/day, for 7 days) and chronic (3 hr/wk, for 4 wks) exposure to 20 J m^{-2} s^{-1} enhanced mortality in an autoimmune strain of mice (NZB X BZW F$_1$). These exposures also caused increased serum antibodies to single stranded DNA, enhanced polyclonal B-cell activity in the spleen, and caused more severe renal glomerular inflammatory changes (Ansel *et al.,* 1985),

all hallmarks of autoimmunity. It is unclear whether there is a relationship between these reactions and the effects of UV on immunological processes described above.

7.2.5 Conclusions

Exposure of mice to UV radiation impairs certain immune responses, enhances susceptibility to a variety of infectious agents and UV-induced tumours. While fewer studies have been done in rats, similar effects have been observed. Suppression of contact and delayed type hypersensitivity responses have been studied most extensively; however, several other cell mediated responses are also affected. Suppression of these immune responses appears to be mediated by release of soluble mediators from UB exposed skin which alter antigen presentation by Langerhans (and other) cells such that they fail to activate TH 1 cells. The resulting immune suppression is antigen specific, can occur regardless of whether antigen is applied at the site of exposure or not, and is relatively long lasting.

Enhanced susceptibility to a variety of infections in mice and rats corresponds to suppression of DTH responses to microbe specific antigens. UV exposure also prevents the development of protective immunity to these infections.

7.3 Ocular Studies

7.3.1 Introduction

The large number of animal studies enhances our understanding of both acute and delayed ocular effect from UV exposure (Zigman 1993; Andley 1987; Dillon *et al.,* 1990). Studies of the action spectrum of delayed or permanent effects such as cataract or retinopathy and UV damage mechanisms in the cornea, lens and retina are only possible in animal models.

7.3.2 General effects

Photokeratitis is an acute reversible radiation-induced injury of the corneal epithelium. It is analogous to acute sunburn of the skin. Animal studies have clearly demonstrated that exposure to an artificial source of UVB can lead to acute photokeratitis, and action spectra have been determined (Cogan & Kinsey, 1946; Pitts *et al.,* 1977; Zuclich and Kurtin, 1977). Pitts (1974; 1978) estimated the mean threshold of UVB (290-315 nm) for photokeratitis was 35 J m^{-2} at 270 nm.

Damage to corneal endothelium has been reported in rabbits (Doughty & Cullen, 1990). The effects on the corneal stroma have also been observed in rabbits, where reversible damage to the stromal keratocytes has followed exposure to UV (Ringvold & Davangar, 1985). This histological study showed that keratocytes disappear following UV exposure and later reappear. More recent animal studies have reported the use of a UVB filtering contact lens or the application of UVB absorbing chromophores to the cornea of rabbit eyes protects against photokeratitis (Bergmanson *et al.,* 1988; Oldenburg *et al.,* 1990).

7.3.3 Cataractogenesis

There is substantial evidence that exposure to UV induces discrete opacities in the anterior lens of experimental animals. Several studies have shown that UVB, but not UVA, induces anterior opacities in animals (Bachem, 1956; Pitts *et al.,* 1977; Jose & Pitts, 1985; Söderberg 1990). Supra threshold doses of UVB at 300 nm cause a Na-K shift between the lens and the surrounding (Söderberg (1991). This leads to swelling and disruption of lens cells, probably causing zones of deviating refractive index within the lens observed as opacities (Söderberg 1989). Anterior lens opacities have developed in albino mice after daily exposure for 1-2 months to mixed UVA and UVB source (290-400 nm), but not when the source was filtered to remove radiation <320 nm (Jose & Pitts, 1985). Anterior cataract have also been produced in young albino mice exposed to black light (predominantly UVA, with some UVB) (Zigman *et al.,* 1974). With more prolonged exposure of mice, cortical and posterior subcapsular opacities have been induced (Zigman *et al.,* 1975;

Jose, 1986). By contrast, a dose of 2 kJ m^{-2} applied every day produced anterior polar cataract within 8 weeks. Extension of the irradiation to 5 months created an opacity in the deeper cortex (Weager *et al.,* 1989). In testing possible cataractogenic efficacy of UVA and UVB, UVB alone was cataractogenic, whereas, UVA showed the same effect only when other cataractogenic factors were added (e.g. X-ray) (Schmitt *et al.,* 1988).

Ham *et al.* (1989) irradiated rhesus monkeys to 1 mW cm^{-2} daily for three years to UVA radiation (UVB radiation was carefully excluded) and was unable to detect lenticular opacities.

7.3.4 Retinal effects

It is well accepted that short wavelength visible non-coherent and coherent light, as well as UVA, can cause photochemical, mechanical and thermal damage to the retina and the pigment epithelium (review: Ham *et al.,* 1984; Organisciak & Winkler, 1993). Aphakic monkeys revealed retinal lesions after exposure to UVA (Guerry *et al.,* 1985). Exposure of aphakic albino rats to UVA created acute retinal lesions with 50-80% more effectiveness than blue light (Rapp & Smith 1992). Mechanical and thermal lesions are

almost entirely limited to exposure to high energy laser light.
Photochemical damage can occur through two different light exposure
regimes: short term, high irradiance (minutes to hours) and
long-term (days to weeks) low irradiance (Kremers & van Norren,
1988; Remé *et al.,* 1991; Rapp & Smith, 1992). Whereas damage
thresholds differ depending on the animal species, basic mechanisms
at the molecular and structural level are essentially the same (for
review: see Organisciak and Winkler, 1993). Photochemical lesions
are strongly dependent on wavelength, i.e. the absorbing chromophore
and its quantum efficiency, obey, at least within a certain time
frame, the reciprocity of intensity and exposure duration (e.g.
Kremers & van Norren, 1988).

     Action spectra for high irradiance short exposure duration
lesions have been obtained in several studies (e.g. Ham *et al.,*
1984). Action spectra for prolonged exposure to relatively low light
levels are less clear and were first evaluated by Noell *et al.*
(1966). Prolonged exposure to low light levels may elicit secondary
tissue responses that may not be directly related to the initial
action spectrum. These tissues responses include acute cellular
necrosis and apoptotic cell death, an inflammatory response with
oedematous changes and macrophage invasion, and tissue proliferation
with scar formation and neovascularization (e.g. Hoppeler *et al.,*
1988; Yoshida *et al.,* 1993). Action spectra, tissue responses,
preventive measures as well as enhancing factors, which are all
intensively investigated in many laboratories, are likely to be
similar to the human.

     Studies of photochemical retinal injury in aphakic rhesus
monkeys have extended the action spectrum for short-wavelength light
damage down to 310 nm (Ham *et al.,* 1984). These studies showed
that the retina, if exposed, is up to six times more vulnerable to
photochemical damage in the UV than in the visible. These results
are therefore of direct relevance to pseudophakic individuals
without a UV-protective lens, and may also indicate a contributory
role to light damage from the small fraction of UV that reaches the
retina of the normal eye.

8. HUMAN STUDIES: THE SKIN

8.1 Characteristics

8.1.1 Structure and optical properties

     The skin is a large organ with an area of more than 1.5 m^2 in
adults. It provides the first stage of protection for chemicals,
radiations, xenobiotics and also prevents the evaporation of water
and the loss of ions and proteins. The skin has developed specific
mechanisms for photoprotection and biological responses to UV as
discussed below.

     Skin is composed of three very different parts (as shown in
figure 4.1): the epidermis, dermis and subcutaneous tissue. The
epidermis is the outermost layer of the skin and varies in thickness
from 50 μm to 600 μm (palmoplantor skin). The fibrous proteins known
as keratin are produced in the keratinocytes of the epidermis. It is
keratin that serves as a major protective tough substance in the
skin; hair and nails are composed almost entirely of keratin. The
daughter cells of the keratinocytes in the basal layer (stratum
basale) of the epidermis differentiate and become "prickle cells" of
the malpighian layer of the epidermis - the *stratum malpighii*. As
these cells migrate outward, changes continue to occur; granules
appear in the cytoplasm of each cell; the cells tend to flatten and
form the *stratum granulosum*. Still later, the cells lose their
nuclei, die, dehydrate and flatten out to form the tough *stratum
corneum* (horny layer). It is generally agreed that the entire
process of cell migration from the basal layer of the epidermis to
final shedding from the surface of the stratum corneum takes 28 days
in normal skin. Of this 28-day period, the cell spends about 14 days
in the epidermis and 14 days in the stratum corneum.

     The skin contains millions of tiny glands, including: apocrine
(sweat) glands which discharge sweat into hair follicles, eccrine
(sweat) glands which carry saline from the dermis and subcutaneous
layer directly to the skin surface, and sebaceous glands which
secrete sebum - an oily substance which lubricates hairshafts and
maintains a slightly acidic, oily film over the stratum corneum. The
collection of eccrine sweat glands plays a major role in the body's
thermoregulatory mechanism, since evaporative cooling is the most
efficient means the body has for removing excess heat, as long as
the humidity is not 100%. More than two litres of sweat can be
discharged in one day. On average, the skin contains about as many
sebaceous glands as eccrine sweat glands, except that there are few
sebaceous glands on the palms of the hands and soles of the feet.

     The dermis, or corium, is much thicker than the epidermis, but
consists of much larger cells. The dermis is largely connective
tissue which gives the skin its elasticity and supportive strength.
Nerve cells, blood vessels and lymphatic glands are found in the

outermost dermal layer - the papillary dermis. Unlike the epidermis,
the thickness of the dermis is not at all uniform throughout the
body; it varies from 1 mm to 4 mm.

     The basal layer of the epidermis is delineated from the dermis
by a complex basement membrane. The keratinocytes are anchored to
the basement membrane by semi desmosomes. This is the only layer
where cell division takes place. The division of keratinocytes,
under normal conditions, occurs every 17 to 38 days. The division

rate may vary in different parts of the body.

Melanocytes are formed in the basal layer of the epidermis loosely attached to the neighbouring keratinocytes (ratio 1 melanocyte for 46 keratinocytes). The melanocytes synthesize the pigment melanin which matures into melanosomes. Then the melanosomes are transferred to the keratinocytes where they are digested if their size is below 1 cubic micron. Large melanosomes, as in dark skin, are not digested but transferred intact to the stratum corneum with the normal shedding of the epidermis.

Melanocytes are cells of nervous origin which have migrated during the 10th week of embryonic life in the epidermis and in the hair roots. These cells divide very slowly (one division every 3-5 years). There is a boost of division when new hairs are growing or after exposure to UV light.

Chemically, melanins are bipolymers: red melanins contain sulphurs and are soluble at PH 7.2, black melanins are insoluble. The ratio of red and black melanins within a melanocyte is genetically determined. Mixed types of melanins are deposited on a protein matrix contained in the melanosomes. Both types absorb UV and participate in the screening effect of the whole epidermis. Two major steps in the melanin synthesis take place: the enzymatic (tyrosinase) oxidation of the tyrosine to produce dopa (di-hydroxyphenylalanine) and the spontaneous oxidation of dopa in quinones.

Black melanin absorbs UV. In the presence of oxygen, it produces a free radical which, in sufficient quantities, can be deleterious to the melanocytes and the cellular environment, including keratinocytes or in the dermis, fibroblasts and fibres.

A third type of cell is present in the upper layers of the stratum Malpighi: the Langerhans cell. It is a migrating dendritic cell which is able to recognise foreign or abnormal structures. This cell plays a major role in immunological recognition and its activity is very sensitive to UV. Its function is impaired by a UV dose as low as one half of a minimal erythema dose.

The innermost layer of the skin is generally known as the subcutaneous layer. It is composed largely of fatty tissue that

serves a shock-absorbing and insulating role. The thickness of this layer varies considerably from one body region to another and from one person to another.

Skin optics are governed by two basic processes, the absorption and scattering of light. Absorption is the loss of a photon when its energy is reduced within the atom or molecule, and more specifically in a target species called a chromophore. UV absorption occurs in wavelength bands where the molecules have characteristic absorption spectra. The absorbed photon energy is dissipated as heat or reemission of light when the excited molecules return to their ground state, or the energy is spent on photochemical reactions. Scattering is a process where the direction of propagation of UV is altered, especially at boundaries of refractive index. Scattering and absorption of the photons limit the depth of penetration of UV in the skin (see section 4.2 and figure 4.1).

In the white skin, the change in the refractive index causes 5% of the normally incident light to be reflected. The remaining 95% is absorbed or reflected at the dermis. The back-scattered light is reflected again at different interfaces. This phenomenon explains why, in the epidermis and in the upper papillary dermis, the strength of the light becomes several times that of the incident light itself.

The transmission of UV through isolated epidermis is strongly dependent on the chromophores contained in the structure. Aromatic amino acids (tryptophan, tyrosin, phenyl-alanine) absorb strongly near 275 nm, urocanic acid and melanins play the role of endogenous sunscreens. The DNA absorbs 260 nm wavelengths. Melanin is the unique chromophore with an absorption extending into the UVA and visible regions.

8.1.2 Skin types

The sensitivity of skin to UV has been defined by six phototypes: types I to IV are characteristics of caucasoid populations; type V represents mongoloid Middle Eastern populations (Fitzpatrick *et al.,* 1974); and type VI represents African and American negroid populations. The capacities to acquire natural tan or to present naturally a deep pigmentation are keys to the response to UV exposure. Among caucasians, there is a general correlation between skin type and resistance to sunburn and capacity to tan.

8.2 Beneficial Effects

8.2.1 Vitamin D3

An established beneficial effect of UV exposure is the synthesis of vitamin D3 (Adams *et al.,* 1982). In adults, the epidermis contains nearly 50% of the total concentration of

7-dihydrocholesterol in the skin. UVB exposure causes the provitamins D3 to be isomerized to pre-vitamin D3. During continual exposure to sunlight, the pre-vitamin D3 forms by photo-isomerization the biologically inert photo-products lumisterol and tachysterol. Once formed, the pre-vitamin D3 spontaneously

isomerizes into vitamin D3 (reaction with a maximum efficacy at 37°C), a more stable form. After crossing the basal membrane of the epidermis, vitamin D3 is linked to a circulating alpha1-globulin: vitamin D-binding protein. The protein linked vitamin D3 is transformed to 25-OH-T3 which can be measured in the blood. Transported to the kidney, it is metabolised to 1,25 dihydroxy vitamin D3 which is the biologically active form.

Vitamin D3 is required for the intestinal absoprtion of calcium (Davies 1985). After a single whole body exposure to one MED the circulating vitamin D3 level increases by an order of magnitude (2 ng/ml to 24 ng/ml within 24 hours) and returns to normal levels within a week (Holick 1985). Since active vitamin D3 is metabolised by the kidney, it was expected that in the circulating blood it does not change dramatically after repeated solar exposures. Chronically reduced vitamin D3 synthesis may lead to a deficit in active vitamin D3, as was found in elderly subjects (Omdahl *et al.,* 1982).

The use of sunscreens was found to suppress cutaneous vitamin D3 synthesis (Matsuoka *et al.,* 1988). This was also found in children, pregnant or lactating women and debilitated patients with poor intestinal absorption. Widespread use of sunscreens could lead to vitamin D deficiency in some groups and inadequate fixation of calcium (Prystowsky 1988). More recently, receptors for the active form for vitamin D3 were found in the keratinocytes of the epidermis. Vitamin D3 inhibits the proliferation of cultured keratinocytes and induces them to terminally differentiate (Smith *et al.,* 1986). The topical or oral administration of 1, 25-OH-D3 has proved to be effective for the treatment of psoriasis, in replacement or in addition to the classical PUVA treatment. This is a new approach for the treatment of this condition and a possible explanation for the success of the heliotherapy (Morimoto and Kunihiko, 1989).

For the entire system of vitamin D3 production the amount of UV radiation reaching the skin is critical. The doses needed are small, and daily exposures of the face and hands to sun and light for 15 minutes is considered sufficient. The minimum dose requirement was estimated to be equivalent to 55 MED per year (Health Council of the Netherlands, 1986). When too little UVB reaches the skin, deficiencies of vitamin D may occur, resulting in a weakening of the bones. Groups at risk are particularly dark-skinned children in high latitude cities and elderly people living entirely indoors. Supplementation of vitamin D3 in the diet is then recommended.

8.2.2 Skin adaptation

Another beneficial effect of modest exposure to UVB radiation is the maintenance of the ability of the skin to sustain further UV exposures. Loss of this adaptation forms an important component in photodermatosis, skin diseases where the lesions are caused by light. These patients can be treated by regular exposures to UVB. The doses required are in the same range as that needed for the synthesis of vitamin D3.

8.2.3 Other benefits

It has been suggested that beneficial effects of UV exposures may occur such as: improvement of cardiopathy and functions, and better microorganism defense. These effects have not been confirmed in well designed studies. Bright light therapy for winter depression is most likely to be the consequence of visible light stimulating the ocular system. Because of the high illumination needed for this treatment special care is needed to avoid the emission of UV light by these sources (Terman *et al.,* 1990).

Treatment of portwine stains and pigment dyschromia by lasers are applications of selective absorption of some wavelengths by specific chromophores contained in the lesion. Phototherapy by specific dyes absorbed by tumour cells or specific structures, is currently a growing field.

8.3 Acute Effects

8.3.1 Erythema and sunburn

In its mildest form, sunburn consists of a reddening of the skin (erythema) that appears up to about 8 h after exposure to UV and gradually fades after a few days. In its most severe form, it results in inflammation, blistering, and peeling of the skin. The degree to which a person will experience sunburn depends critically on skin type. For fair-skinned people, the relative effectiveness of UV for tanning and for erythema are approximately the same over the entire UVB and UVA ranges of wavelengths (Parrish *et al.,* 1982).

The most important factors that define if a dose of UV will induce erythema are the wavelength of the radiation, the skin type, and the pigmentation of the subject. UVA, UVB and UVC are all able to induce the erythema.

The relative effectiveness of the different wavelengths to induce erythema is expressed as an erythema action spectrum (McKinlay and Diffey 1987). For minimal erythema, the most erythemogenic wavelengths are in the 250-290 nm range and a decrease in effectiveness is observed as the wavelengths increase. Erythema occurs 3-5 hours after UV exposure and reaches a maximum intensity

between 8 and 24 hours, fading over 3 days. The vasodilatation of capillary vessels within the papillary dermis can be observed before the erythema becomes visible, and occurs in the same way for

children, adults and elderly. However, the exposure time required to
produce UVB erythema increases after about 60 years of age.

Histologic alterations from erythema are observed in the
photodyskeratotic keratinocytes as well as intercellular edema with
exocytosis (lymphocytes in the epidermis). Superficial vascular
plexus, endothelial cell enlargement, perivenular edema, red blood
cells in the capillary are characteristic features observed between
3 hours and 72 hours after UV exposure. Dermal neutrophils appear
immediately after irradiation reaching a peak level at 24 hours.

DNA may be the primary chromophore involved in the induction of
erythema (Ley, 1985, Wolf *et al.,* 1993). Subsequently, a number of
inflammatory mediators are induced. Cutaneous blisters have been
used extensively to study these mediators. Prostaglandin (E_2 and
F_2) levels were elevated in these blisters within 6 hours, peaked
at 24 hours and returned to control levels by 48 hours after UV
exposure, although erythema persisted beyond that time. Indomethacin
suppressed prostaglandin formation, however, blood flow was only
slightly altered by this treatment suggesting that other factors
must play an important role in UVB induced inflammation (Greaves *et
al.,* 1978). Similarly while elevated histamine levels have been
observed, antihistamines have little effect in diminishing UV
induced erythema (Gilchrest *et al.,* 1981).

Finally, UV exposure causes keratinocytes, to release the
cytokines interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF
alpha) both of which are potent mediators of inflammation (Oxholm
 et al., 1988; Rasanen *et al.,* 1989). UVB exposure also causes
up-regulation of adhesion molecule such as ELAM-1 which facilitates
inflammatory cell infiltration (Murphy *et al.,* 1991).

Irradiation of human skin with 3 MED is associated with
increased levels of transforming growth factor, suggesting a role of
this molecule in keratinocyte proliferation, epidermal hyperplasia
and angiogenesis.

8.3.2 Skin pigmentation and tanning

When skin is exposed to UV, two distinct tanning reactions
ensue. Immediate pigment darkening (IPD) begins immediately on
exposure to UV and is caused by the darkening of the pigment melanin
that is already present in the skin; it is normally seen only in
people who have at least a moderate constitutive tan. Such
pigmentation begins to fade within a few hours after cessation of
exposure. UVA is regarded as being most effective for IPD.

Delayed tanning (melanogenesis) takes about three days to
develop and is more effectively produced by UVB than by UVA (Parrish
 et al., 1982; Gange *et al.,* 1985). Delayed tanning is more
persistent than IPD and results from an increase in the number, size
and pigmentation of melanin granules. Exposure to UVB results also
in an increase in the thickness and scattering properties of the
epidermis (outer layer of the skin). Because UVA does not produce
thickening of the epidermis, the tan obtained from it, while perhaps
cosmetically acceptable, is not as effective in protecting against
further exposure to UV as the equivalent pigmentation induced by
exposure to UVB or solar radiation.

8.3.3 Photosensitization

The use of certain medicines may produce a photosensitizing
effect on exposure to UVA as may the topical application of certain
products, including some perfumes, body lotions, etc. Many
medications and other agents contain ingredients that may cause
photosensitivity, which is defined as a chemically induced change
that makes an individual unusually sensitive to light. An individual
who has been photosensitized may develop a rash, sunburn, or other
adverse effect from exposure to light of an intensity or duration
that would normally not affect that individual.

Reactions to photosensitizing agents involve both photoallergy
(allergic reaction of the skin) and phototoxicity (irritation of the
skin) after exposure to ultraviolet radiation from natural sunlight
or artificial lighting (particularly from tanning booths). This
photosensitization of the skin may be caused by creams or ointments
applied to the skin, by medications taken orally or by injection, or
by the use of prescription inhalers.

In addition to an exaggerated skin burn, itching, scaling,
rash, or swelling, exposure to UV in combination with certain
medications may result in (FDA 1992); Skin cancer, Premature skin
aging, Skin and eye burns, Allergic reactions, Cataracts, Reduced
immunity and Blood vessel damage.

This can result in photoallergic or phototoxic reactions that
are accelerated by UV exposure. Phototoxic contact dermatitis often
occurs clinically as exaggerated sunburn but occasionally blisters
may also occur on the erythematous areas. Most phototoxic
sensitizers have an action spectrum in the UV from 280-430 nm.
Window glass which absorbs UV below 320 nm will protect patients
from phototoxic compounds with absorption below 320 nm, but fails to
protect against photosensitizers such as tar and psoralens which are
efficient at longer wavelengths. Examples of photocontact drugs and
substances are given below in table 8.1.

Table 8.1 Some photosensitizing substances
         (CIE, 1990, FDA, 1992)

```
              Sulphonamides
              Salicylanilides
              Coal-Tar derivatives
              -     acridine
              -     anthracene
              -     phenanthrene
              Dyes
              -     anthraquinone
              -     eosin
              -     methylene blue
              -     rose bengal
              Psoralens
              Some fragrances
              Cyclamate (artificial sweetener)
              Non-steroidal anti-inflammatory drugs (pain reliever,
              antiathritics)
              Deodorant and bacteriostatic agents in soaps
              Fluorescent brightening agent for cellulose, nylon or wool
              fibres
              Phenothiazines (major tranquilizers, anti-emetics)
              Sulfonylureas (oral anti-diabetics, hypoglycemics)
              Sunscreen ingredients
                   -    6-Acetoxy-2,4,-dimethly-m-dioxane (preservative)
                   -    Benzophenones
                   -    Cinnamates
                   -    Para-aminobenzoic acid (PABA)
                   -    Paba esters
              Tetracyclines (antibiotics, anti-infectives)
              Tricyclic antidepressants
```

The concentration of drugs needed to elicit a photoallergic reaction is much lower than that needed to cause a phototoxic reaction. On the other hand, photoallergic reactions occur only in a small proportion of exposed individuals while phototoxic reactions may occur in anyone, given sufficient exposure. Generally, no clinical reaction occurs on first exposure to an agent causing subsequent photoallergy. Even sunscreen agents used to protect against photocontact dermatitis may be photoallergenic. A small number of individuals who develop photocontact dermatitis may retain a persistent reactivity to light (including UV) long after exposure to the photosensitizing compound.

8.4 Chronic Effects on the Skin Other than Cancer

UV radiation causes a number of chronic degenerative changes in the skin, mainly in caucasian populations, as a result of its action

on keratinocytes, melanocytes and components of the dermal stroma including fibrous tissue (collagen and elastin) and blood vessels. These changes include freckles (ephelides), melanocytic naevi, lentigines, telangiectasia, skin wrinkling and atrophy, yellow papules and plaques on the face, colloid milium (firm, small, yellow, translucent papules on the face, forearms and hands), diffuse erythema, diffuse brown pigmentation and ecchymoses (Goldberg & Altman, 1984). These or related changes are sometimes grouped into syndromes such as cutis rhomboidalis nuchae (thick, yellow, furrowed skin, particularly on the back of the neck), Favre-Racouchot syndrome (yellow, thick comedones and follicular cysts of the periorbital, malar and nasal areas) and reticulated poikiloderma (reddish brown reticulated pigmentation with telangiectasia and atrophy and prominent hair follicles on the exposed chest and neck). With the exception of freckles and melanocytic naevi, these changes are also referred to collectively as "photoageing" (Gilchrest, 1990) because of their association with increasing age but presumed correlation with total accumulated exposure to the sun rather than with age per se.

In the US National Health and Nutrition Examination Survey (Engel et al., 1988), age-adjusted prevalence proportions of senile elastosis, actinic (solar) keratosis, fine telangiectasia, localized hypermelanism, senile (solar) lentigines and freckles, in whites 1 to 74 years of age, were associated with lifetime exposure to the sun as estimated by dermatologists.

Freckles and solar lentigines

Freckles and solar (also called senile) lentigines are pigmented macules occurring on the sun exposed skin of caucasians. Their prevalence is increased in those with highly sun-sensitive skin (Azizi et al., 1988). Freckles occur most commonly in children while the frequency of solar lentigines increases with age and is greatest in those over 60 years of age (estimated at 75% in the USA: Rhodes et al., 1991). They show similar histological patterns: their are increased numbers of melanocytes and an increased concentration of melanin in the basal layer of the epidermis (Rhodes et al., 1991). Melanocytic atypia has been observed in both. An increased risk of melanoma has been observed in relation to freckling in childhood and an increased risk of non-melanocytic skin cancer in relation to both freckling and prevalence of solar lentigines (see sections 8.4.1 and 8.4.2).

Melanocytic naevi

Melanocytic naevi are benign proliferations of melanocytes usually beginning in the basal layer of the epidermis and later extending into the dermis. They are common in white populations and rare in black and Asian populations (Armstrong & English, 1988; Gallagher et al., 1991), are associated, in white populations,

with phenotypic indicators of constitutional sensitivity to the sun,

particularly fair skin colour (Green *et al.,* 1988b; Gallagher *et al.,* 1990b), occur mainly on body sites that are maximally or intermittently exposed to the sun (Kopf *et al.,* 1978, 1985; Augustsson *et al.,* 1990; Gallagher *et al.,* 1990a), occur more commonly in Australian than British children (Green *et al.,* 1988b) and in persons born in Australia than immigrants who arrived in Australia after about 15 years of age (Armstrong *et al.,* 1986), and somewhat inconsistently with measures of sun exposure, including sunburn in early life (Armstrong *et al.,* 1986; Gallagher *et al.,* 1990c; Coombs *et al.,* 1992). They are associated with an increased risk of cutaneous melanoma (see section 8.4.2).

Solar keratoses

Solar keratoses are benign proliferations of epidermal keratinocytes. They are very common on exposed body sites in older people in caucasian populations living in areas of high ambient solar irradiance (see for example, Marks *et al.,* 1983 and Holman *et al.,* 1984a). Solar keratoses have been reported to be associated with phenotypic indicators of cutaneous sun sensitivity (Vitasa *et al.,* 1990), to be more common in people born in Australia than in migrants to Australia (Goodman *et al.,* 1984), to be associated with estimates of total and occupational sun exposure (Goodman *et al.,* 1985; Vitasa *et al.,* 1990), and to be associated with other benign indicators of cutaneous sun damage (Holman *et al.,* 1984b; Green 1991). Their number on the skin is strongly associated with risk of non-melanocytic skin cancer (see section 8.4.1).

8.5 Cancer

Epidemiological evidence relevant to the effects of UV on risk of cancer in humans derives mainly from study of the effects of sun exposure (presumably solar UV but not separable from other solar radiation) on cancer risk. There are four general lines of evidence available from which it may be inferred that sun exposure causes any particular cancer. They are that: the cancer in question occurs more frequently in people who are sensitive to the sun, occurs mainly at sun-exposed body sites, is increased in residents of areas of high ambient solar irradiance, and is increased in people with high personal sun exposure.These lines of evidence will not apply to all cancers that may be linked to sun exposure. They form nonetheless, a useful framework within which most of the relevant evidence can be described. To this framework will be added a consideration of evidence relating to artificial sources of UV when it is available.

The most direct evidence of the carcinogenicity of UV in humans should come, in principle, from observation of the effects of personal exposure to the sun. In practice, it is very difficult to make measurements of personal sun exposure accurately. Most often

they are made by questionnaire and require recall of rather non-salient details of life over 60 or more years. This is a very difficult task (Kricker *et al.,* 1993). A difficulty is presented by the fact that people who have sun sensitive skin and are at higher risk of skin cancer will tend to expose themselves less to the sun. To obtain an accurate measure of the effects of personal sun exposure, this confounding with sun sensitivity should be controlled - this has not always been done. It may not be surprising, therefore, that measures of personal exposure to the sun have not been consistently associated with risk of cancers thought to be related to the sun and that more indirect evidence has proved to be stronger.

8.5.1 Nonmelanocytic skin cancer

Introduction

There are two major histopathological types of nonmelanocytic skin cancer: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). BCC is the commoner type in white populations.

The epidemiology of nonmelanocytic skin cancer is difficult to describe accurately. Its routine recording is often not attempted by cancer registries because of the large numbers of cases involved and, if attempted, is invariably incomplete because of the rarity with which primary nonmelanocytic skin cancers require hospital treatment and the frequency with which probable nonmelanocytic skin cancers are not sent for histopathological verification of the diagnosis (Muir *et al.,* 1987).

These difficulties have influenced the quality of the epidemiological evidence relating nonmelanocytic skin cancer to sun exposure. In addition, most of the earlier cross-sectional and case-control studies of nonmelanocytic skin cancer , and some of the more recent ones, (see, for example, table 11 in IARC, 1992) are deficient in that the control series were rarely population-based, appropriate effect measures or p values were often not estimated, and confounding by age and sex were not controlled in the analysis. In the narrative that follows, little reliance will be placed on these studies which include those reported by Lancaster & Nelson (1957), Gellin *et al.* (1965), O'Beirn *et al.* (1970), Urbach *et al.* (1974), Aubry & MacGibbon (1985), O'Loughlin *et al.* (1985), Herity *et al.* (1989), Hogan *et al.* (1989) and Gafa *et al.* (1991).

The results of most of the studies referred to below have been described and their results tabulated in detail in other publications (e.g., IARC, 1992) thus only the immediately salient features will be described here.

Sun-sensitivity

Race

Nonmelanocytic skin cancer is much less frequent in populations
with dark skins than those with light skins (Fitzpatrick & Sober,
1985; Hoffman, 1987; Urbach, 1987). Data from cancer registries
represented in Cancer Incidence in Five Continents Volumes II-VI
(Doll *et al.,* 1970; Waterhouse *et al.,* 1976, 1982; Muir *et al.,*
1987; and Parkin *et al.,* 1992) in which direct comparisons of
nonmelanocytic skin cancer incidence in different ethnic groups can
be made within a single geographical area show that the incidence
rates in the light skinned populations are consistently the highest.
Similarly, in the 1977-78 US survey of nonmelanocytic skin cancer;
rates in whites were 232.6 per 100 000 person years compared with
3.4 in blacks (Scotto *et al.,* 1983).

Available evidence suggests that BCC occurs less frequently
than SCC among dark skinned populations. The opposite is the case in
light skinned populations. BCC was the most common nonmelanocytic
skin cancer reported in South African whites in 1949-1975 but was
rare among black Africans, occurring mainly in albinos (Oettlé,
1963; Oluwasanmi *et al.,* 1969; Rippey and Schmaman, 1972; Isaacson
et al., 1978). SCC, principally on the lower limb and associated
with previous trauma, was the commoner of the two in blacks (Oettlé,
1963; Oluwasanmi *et al.,* 1969; Rippey and Schmaman, 1972; Isaacson
et al., 1978; Rose, 1973). Melanesians (Foster & Webb, 1988) and
Polynesians (Paksoy *et al.,* 1991) had less BCC than SCC, while no
BCCs were reported in the Melanesians of North Samoa, a particularly
heavily pigmented people (Foster & Webb, 1988).

Ethnic background is an important determinant of risk of
nonmelanocytic skin cancer in Caucasians. In people of southern
European ethnic origin born in Australia, relative to other people
born in Australia, risk of BCC was 0.56 (95% CI 0.14-1.65) for those
with one southern European grandparent, 0.17 (0.00-1.05) for two and
0.00 (0.00-0.86) for three or four (p for trend 0.002; Kricker *et
al.,* 1991a). No subject with SCC in this study had any southern
European grandparents (RR 0.00, 0.00-1.23).

Individual sun sensitivity

Among recent cross-sectional, case-control and cohort studies
several have reported significantly elevated relative risk (RR)
estimates for red or light hair colour with BCC (RRs between 1.5 and
2.9; Hunter *et al.,* 1990; Green & Battistutta, 1990; Kricker *et
al.,* 1991a) and SCC (RR=2.4; Kricker *et al.,* 1991a). However, a
light complexion was significantly associated only with SCC (RR=3.3;
Kricker *et al.,* 1991a), and high RRs (of 3.4) for light hair
colour with BCC and SCC were reported in only one study (Vitasa *et
al.,* 1990).

Sensitivity of the skin to the sun, as measured by ability to
tan and susceptibility to sunburn, was more consistently related to
risk of BCC and SCC than hair, skin and eye colour. RRs of 2.0 or
more for BCC were found with a skin that burns rather than tans
(Marks *et al.,* 1989; Vitasa *et al.,* 1990; Hunter *et al.,* 1990;
Kricker *et al.,* 1991a). For SCC, the evidence of an increased risk
with sun-sensitive skin was somewhat weaker, with RRs around 2.0 and
95% confidence intervals (CI) that were wide and included 1.0, in
the two studies that reported RRs adjusted for age, sex, and other
relevant confounders (Vitasa *et al.,* 1990; Kricker *et al.,*
1991a).

Xeroderma pigmentosum and albinism

Xeroderma pigmentosum (XP) is a recessively inherited syndrome
characterised by clinical and cellular hypersensitivity to solar
radiation and a defect in the capacity to repair UV-induced damage
in DNA (Fitzpatrick *et al.,* 1963, Cleaver, 1973). Evidence of
cutaneous sun damage may appear as early as 1-2 years of age in the
absence of specific protection from the sun, and skin cancers are
very frequent (Kraemer *et al.,* 1987). In a survey of 830 cases of
XP located through published case reports, 45% were reported to have
had skin cancers (Kraemer *et al.,* 1987). The median age of
diagnosis of the first skin cancer was 8 years. Ninety seven per
cent of BCC and SCC were on constantly exposed sites, that is, the
face, head, and neck, compared with an estimated 80% in the general
US population. In 220 XP patients in whom the number of skin cancers
was stated, half had more than two cancers and 5% had more than 30;
79 patients were described as having BCC and 112 SCC (Kraemer *et
al.,* 1987).

Albinism is an inherited disorder of melanin metabolism with a
decrease in or complete absence of melanin; as a result, the skin of
albinos is highly sensitive to the sun. The most common type of
albinism occurs in 1 in 15,000 American blacks, 1 in 40,000 European
or American Caucasians, and has estimated frequencies as high as
1:3,900 in Soweto, South Africa (Kromberg and Jenkins, 1982), and 1
in 1,000 in Nigeria (Cervenka *et al.,* 1979). African albinos have
been reported to have a high incidence of SCC and a somewhat lower
rate of BCC (Cervenka *et al.,* 1979; Luande *et al.,* 1985;
Kromberg *et al.,* 1989).

Body-site distribution

It is commonly stated that the site distributions of
non-melanocytic skin cancers, particularly SCC, correspond well to
what would be expected from the exposure of different body sites to

the sun. They do generally conform to this pattern with more than
60% of lesions occurring on the head and neck (Kricker et al.,
1993). It is consistently observed, however, that the proportion of
SCC on the upper limbs is higher than that of BCC while BCC has the

higher proportion (some 10% or more) on the trunk (Scotto et al.,
1983; Osterlind et al., 1988a; Giles et al., 1988; Glass &
Hoover, 1989; Levi et al., 1988; Karjalainen et al., 1989;
Kricker et al., 1990; Gallagher et al., 1990a; Roberts, 1990;
Magnus, 1991; Serrano et al., 1991; Kricker et al., 1993). At
the sub-site level, BCCs are almost completely absent on the heavily
exposed backs of hands, and infrequent on the forearms compared with
the upper arms (Brodkin et al., 1969; Scotto et al., 1983;
Goodman et al., 1984; Kricker et al., 1990); in addition, this
subsite distribution on the face is not highly correlated with the
distribution of UV erythema on the face (Diffey et al., 1979).

     Residence in areas of high ambient solar irradiance

        Geographical variation

     Annual incidence rates of nonmelanocytic skin cancer in 29
populations of mainly Western European origin in Cancer Incidence in
Five Continents, volume 6 (Parkin et al., 1992) show little
evidence of any consistent relationship between incidence and
latitude. The highest incidence rates were in the populations of
Tasmania, Australia (42°S) (213.2 per 100,000 in men and 113.1 per
100,000 in women) and British Columbia, Canada (49°N) (134.1 in men
and 91.2 in women), and were also comparatively high in Switzerland
(47°N) (78.7 in men and 50.2 in women) and Southern Ireland (53°N)
(71.5 in men and 48.0 in women).

     In contrast to these international patterns, incidence rates of
nonmelanocytic skin cancer within countries do appear to increase
with proximity to the equator as indicated by broad place of
residence, latitude, or measures of solar irradiance. Geographical
variation in nonmelanocytic skin cancer incidence in the USA has
been described in three National Cancer Surveys (Mountin & Dorn,
1939; Dorn, 1944a, 1944b; Auerbach, 1961; Haenszel, 1963; Scotto et
 al., 1974) and several related studies (Scotto et al., 1982,
1983; Serrano et al., 1991). Incidence of all types increased with
increasing proximity to the equator, with similar gradients for men,
women and all ages. The same pattern is seen in Australia (Marks et
 al., 1993)

        Migrants

     The nonmelanocytic skin cancer experience of light-skinned
migrants from areas of low to areas of high ambient solar irradiance
has generally been consistent with an effect of sun exposure on skin
cancer incidence. In Australia, incidence and mortality were found
to be lower in migrants, most of whom had come from the UK, an area
of lower sun exposure, than in those born in Australia (Armstrong
 et al., 1983; Giles et al., 1988). Kricker et al. (1991a)
examined in some detail the relationship between BCC and SCC and
migration to Australia. Migrants (excluding those from southern

Europe who may be at lower constitutional risk for skin cancer) had
a lower risk of BCC and SCC (RRs around 0.3) than did those born in
Australia. In addition, for BCC (which had sufficient cases to
analyze) the RR in those who migrated in the first 10 years of life
(1.05) was the same as that in those born in Australia (1.0) but
then fell to low levels in those who migrated later in life (RR
about 0.2). Hunter et al., (1990) observed an association between
risk of BCC and residence in southern parts relative to elsewhere in
the USA (RRs of 1.6 for residence in California and 2.1 for
Florida).

     Personal sun exposure

        Total sun exposure

     Reported measurements of total current or accumulated sun
exposure in studies of nonmelanocytic skin cancer are likely to be
subject to substantial error not only because of the difficulties in
recalling sun exposure over periods of 60 years or more (Kricker et
 al., 1993) but also because of the use of broad summary variables
such as "estimated average daily outdoor exposure" (Gellin et al.,
1965). The two studies which attempted a more quantitative measure
found no evidence of a positive association between estimates of
total sun exposure and risk of BCC (RRs of 1.0 or less) (Hunter et
 al., 1990; Vitasa et al., 1990). Only one of these studies
included SCC (with only about 50% confirmed histopathologically);
for sun exposure above the 75th centile the estimated RR was 2.5
(95% CI 1.2-5.4) (Vitasa et al., 1990).

        Occupational sun exposure

     Early clinical reports associated skin cancer with outdoor
occupation (Molesworth, 1927; Blum, 1948; Emmett, 1973). However,
the relationship between occupation and skin cancer has been
examined adequately in relatively few studies and the evidence for
an association is weak. At the population level, the best conducted
studies which attempted to classify occupational sun exposure on the
basis of occupational title found only small differences in skin
cancer incidence between outdoor and indoor workers. Several
population studies reported associations with employment in
agriculture (Atkin et al., 1949; Whitaker et al., 1979; Teppo
 et al., 1980) and outdoor employment generally (Beral & Robinson,
1981; Vågerö et al., 1986) but their interpretation is complicated

by incomplete and potentially biased case ascertainment (Vågerö *et al.,* 1986; Teppo *et al.,* 1980), inclusion of other cancers (Atkin *et al.,* 1949), and confounding between occupation and social class (Beral & Robinson, 1981).

There have been few well-conducted studies of occupational sun exposure at the individual level. They show a generally consistent but not strong association between BCC and SCC and various crude

measures of outdoor employment, e.g., "indoors", or "outdoors" occupation. The RRs have generally been under 2.0 for BCC (Hogan *et al.,* 1989; Marks *et al.,* 1989; Green and Battistutta, 1990; Gafa *et al.,* 1991). One study reported a high RR for SCC with an "outdoors" occupation but with an extremely wide confidence interval (Green and Battistutta, 1990). Other studies found RRs close to 1.0 (Aubry and MacGibbon, 1985, Hogan *et al.,* 1989; Marks *et al.,* 1989; Gafa *et al.,* 1991) and only one appeared to be statistically significant (Hogan *et al.,* 1989).

Recreational exposure

The relationship of exposure to sunlight in non-working hours (largely recreational sun exposure) with nonmelanocytic skin cancer has been described in only two studies. One study reported an RR below 1.0 for BCC in those with "mainly outdoor leisure" and a positive but not statistically significant association for SCC: RR of 3.9 (95% CI 0.5-30.9) (Green & Battistutta, 1990). In the study of Aubry & MacGibbon (1985), the highest category of a "non-occupational exposure score" showed an elevated risk of SCC (RR 1.6; p-value=0.07).

Sunburn

Risk of BCC was significantly increased in subjects with a history of sunburn in one of two recent studies. Hunter *et al.* (1990) observed an increasing risk with increasing frequency of painful sunburns (RR 2.91, 95% CI 2.37-3.58, for 6+ occasions). Green and Battistutta (1990), on the other hand, found no discernible association between BCC and number of painful sunburns. The risk of SCC, however, was increased with any history of painful sunburn in this study: RRs 3.3 (95% CI 0.9-12.3) for 1-5 sunburns and 3.0 (0.7-12.2) for 6+.

Other sun-related skin conditions

Cutaneous microtopography (a measure of loss of the fine skin markings on the backs of the hands presumed due to loss of dermal collagen; Holman *et al.,* 1984a), prevalence of solar elastosis of the neck, solar telangiectasia and solar lentigines and a history of solar keratoses have been taken as indicators of a high level of total accumulated exposure to the sun in those who have BCC or SCC. The evidence that sun exposure causes these conditions, however, is no stronger, and may be weaker, than the evidence that it causes BCC, SCC or cutaneous melanoma.

Increasingly severe sun-related skin damage as measured by cutaneous microtopography was associated with increasing risks of both BCC (RR 3.1, 95% CI 1.5-6.4 for the highest grade) and SCC (RR 1.8, 95% CI 0.8-4.2 for the highest grade) (Kricker *et al.,* 1991a). Other indicators of sun damage to the skin (e.g. freckles,

telangiectasia, and elastosis) were also strongly related to risk of both BCC and SCC, whether considered separately (Green and Battistutta, 1990; Kricker *et al.,* 1991a) or together (Holman *et al.,* 1984a; Green *et al.,* 1988a), and including when adjusted for cutaneous sun sensitivity (Kricker *et al.,* 1991a). The RRs associated with the presence of 40 or more solar keratoses were 10.4 (95% CI 5.8-18.8) for BCC and 34.3 (95% CI, 14.0-84.0) for SCC (Kricker *et al.,* 1991a).

Exposure to artificial sources of UV

Any use of a sunlamp was associated with a statistically significantly increased risk of SCC in the study of Aubry & McGibbon (1985) but three other studies (O'Loughlin *et al.,* 1985; Herity *et al.,* 1989; Hogan *et al.,* 1989) found no association with "artificial sunlight" or use of sunlamps or sunbeds.

8.5.2 Cutaneous Melanoma

Introduction

Cutaneous melanoma began to be studied epidemiologically in 1948 when it was separated from other primary malignancies of the skin in the 6th Revision of the International Statistical Classification of Diseases (WHO, 1948), and Eleanor MacDonald published the first population-based study, covering 272 incident cases of melanoma in Connecticut (MacDonald, 1948). Because of its likely fatality if not treated, melanoma is much more likely to come to medical attention and to be diagnosed histopathologically than nonmelanocytic skin cancer. It has, therefore, been more readily recorded on a population basis than nonmelanocytic skin cancer and better studied epidemiologically. Thus, while generally considered less clearly associated with sun exposure, a series of large and well-conducted studies in different countries over the last 10 years have served to clarify this issue.

Sun-sensitivity

Race

Melanoma is a disease primarily of light-skinned populations and occurs much less frequently in people with darker skins. In the United States, the incidence in whites is ten fold or more higher than in blacks living in the same areas (Parkin et al., 1992). Rates are lowest (less than 0.7 per 100 000 person years) in parts of Asia (eg Japan, Singapore, India, China, Philippines) while in Los Angeles, USA, incidence was less than 1 per 100 000 in Japanese and Chinese people compared with slightly higher rates, around 2.0, in blacks (Parkin et al., 1992).

Among Caucasians, ethnic background is an important determinant of melanoma incidence. The incidence is substantially lower among Hispanics than among other whites in the United States. 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 100,000 (Muir et al., 1987). In several case-control studies, subjects with a southern or eastern European background had substantially lower risks than those of northern European or United Kingdom origins (Elwood et al., 1984; Holman and Armstrong, 1984a; Graham et al., 1985).

Individual sun sensitivity

Blue eyes, fair or red hair, and pale complexion in people of European origin are well established risk factors for melanoma. These pigmentary characteristics were documented in most melanoma case-control studies (see table 16 in IARC, 1992 and, as examples, Elwood et al., 1984, Holman & Armstrong, 1984a, and Green et al., 1985). Relative risk for light skin colour ranged from a little more than 1.0 to about 3. Compared with those with dark brown to black hair, those with fair hair generally had a less than two-fold increase in risk, but those with red hair usually had a 2 to 4-fold increase in risk. Eye colour was generally a weak risk factor with relative risks less than 2, and what increased risk there was generally disappeared after adjustment for the other traits.

Increased risks of melanoma in those with a reduced ability to tan and an increased tendency to sunburn were observed in all case-control studies in which these sun-sensitivity measures were examined (see, for example, Elwood et al., 1984, Holman & Armstrong, 1984a, and Green et al., 1985).

Xeroderma pigmentosum and albinism

In a review of reports of 378 patients with XP in which cancer was mentioned, 37 patients had a melanoma (Kraemer et al., 1987).

African albinos have been reported to have a low rate of melanoma (Cervenka et al., 1979; Luande et al., 1985; Kromberg et al., 1989). Levine et al. (1992) state that there have been only 16 documented cases of melanoma in albino patients reported in the English language literature. Since albinos generally have a normal number of melanocytes (Dargent et al., 1992), the rarity of melanoma in them may indicate that melanin plays an important role in the genesis of this cancer.

Body site distribution

The distribution of melanoma appears to favour sites which are less heavily sun exposed, that is the back and face in Caucasian men and the lower limbs in women (Crombie, 1981). However, when

whole-population series of cancer cases have been examined and body surface area taken into account, sites that were usually covered by clothing had lower rates than those usually exposed, with the exception of the forearms and hands for which the rates per unit area were low (Elwood & Gallagher, 1983; Green et al., 1993). The anatomic site distribution of melanoma in blacks is quite different from that in Caucasians with the majority of melanomas on the soles of the feet (Higginson and Oettlé, 1959; Lewis, 1967; Fleming et al., 1975).

Residence in areas of high ambient solar irradiance

Geographical variation

Internationally, the incidence of melanoma varies over 100-fold. Among countries included in Cancer Incidence in Five Continents, Volume VI, the lowest rates reported around 1983-87 were 0.1-0.2 per 100 000 person years in China (Qidong), Japan (Osaka), India (Bombay), and in Kuwaitis in Kuwait, while the highest were about 25 per 100 000 person years in parts of Australia (Parkin et al., 1992). In the USA and Australia, which have reasonably homogeneous populations of mainly European origin distributed across a wide latitude range, melanoma incidence increases with increasing proximity to the equator or with increasing measured, annual ambient UV irradiance (Scotto & Fears, 1987; Jones et al., 1992).

A simple latitude gradient for melanoma is not evident in Europe. Armstrong (1984) showed that the incidence of melanoma in Europe decreased from about latitude 35°N to a minimum around 55o N and then rose with increasing latitude because of high rates in Scandinavian and Scottish populations. The gradient of risk for melanoma from north to south in northern Europe matches the increasing natural pigmentation of the skin and may also, in part, be due to differing patterns of sun exposure, particularly recreational and vacation sun exposure.

Migrants

If a person migrates in childhood to a country of high ambient
solar radiation such as Australia, Israel, and New Zealand, their
risk of melanoma is observed to be similar to that in those born in
the country to which they migrate, whereas if they migrate after
this age their risk is substantially less than that in the
locally-born population (Katz *et al.,* 1982; Cooke and Fraser,
1985; McCredie & Coates 1989; Steinitz *et al.,* 1989; Khlat *et
al.,* 1992). Overall, British immigrants to Australia and New
Zealand, where the populations are of predominantly British origin,
had incidence and mortality rates of melanoma of about a half the
levels in those born in these countries (Cooke and Fraser, 1985;
Khlat *et al.,* 1992).

   Residence history

   Studies of individual lifetime ambient solar radiance, based on
latitude, location (eg, tropical, near coast), or average sunshine
hours of all places of residence are consistent in showing an
increased risk of melanoma with increased average radiance (Green &
Siskind, 1983; Holman *et al.,* 1984b; Graham *et al.,* 1985;
Osterlind *et al.,* 1988b; MacKie *et al.,* 1989; Weinstock *et al.,*
1989; Beitner *et al.,* 1990). RRs for the highest category of
ambient solar radiance were 2.8 for mean annual hours of bright
sunlight at places of residence in Australia (Holman *et al.,*
1984b), between 1.4 and 2.6 for a southerly latitude in the USA
(Graham *et al.,* 1985; Weinstock *et al.,* 1989), or a tropical or
Mediterranean residence (MacKie *et al.,* 1989; Beitner *et al.,*
1990). RRs differed greatly for residence near the coast in Denmark
(RR=1.7; Osterlind *et al.,* 1988b) and Australia (RR=5.0; Green &
Siskind, 1983).

   Personal sun exposure

   Lifetime total exposure

   Inconsistent results have been obtained in studies in which
lifetime total sun exposure were assessed by questionnaires. RRs for
the highest exposure category were between 0.6 and 5.3 (see table 18
in IARC, 1992). Two of five studies showed a statistically
significant positive association with RRs of 3.4 and 5.4 (Grob *et
al.,* 1990; Lê *et al.,* 1992) while one study showed a significant
negative association (RR 0.6; Graham *et al.,* 1985). The other two
RRs were 1.1 (Dubin *et al.,* 1986) and 5.3 (95% CI 0.8-30.8; Green,
1984).

   Usual or recent total exposure

   In this context, total means exposure from all sources (i.e.
occupational and non-occupational) rather than the total over some
period of time. This concept has been measured in a variety of ways.
For example, it has been common to enquire about present "usual"
exposure to the sun or usual exposure in some time period in the
fairly recent past. The evidence of any effect of such exposures on
risk of melanoma is weak. Of five studies, four had relative risks
for the highest categories of exposure ranging from 0.7 to 1.2
(Elwood *et al.,* 1985b; Dubin *et al.,* 1986; Holman *et al.,*
1986; Cristofolini *et al.,* 1987). The remaining study found a
relative risk of 2.5 (p < 0.001) for the highest category of
exposure of average daily sun exposure 10-20 years ago (Rigel *et
al.,* 1983).

   Occupational exposure

   Four studies of melanoma have shown statistically significant
positive associations with estimated lifetime occupational exposure
to the sun (see table 20 in IARC, 1992) with RRs ranging up to 6.0
(95% CI, 2.1 to 17.4) for outdoor employment (Paffenbarger *et al.,*
1978; Dubin *et al.,* 1986; Garbe *et al.,* 1989; Grob *et al.,*
1990). On the other hand, four studies showed statistically
significant results in which the RR for the highest category of
exposure was < 1.0 (Elwood *et al.,* 1985b; Holman *et al.,* 1986;
Osterlind *et al.,* 1988b; Beitner *et al.,* 1990). The remaining
studies have shown RRs around 1.0.

   Recreational exposure

   Recreational exposure to the sun has generally been measured by
either the type of recreational activity or the frequency or
duration of outdoor recreation (see table 22: in IARC, 1992). Some
studies have also recorded sun exposure during vacations separately
from other recreational sun exposure. At least one statistically
significant positive association was found in 11 of 16 studies in
which recreational exposure was considered (Adam *et al.,* 1981; Lew
et al., 1983; Rigel *et al.,* 1983; Elwood *et al.,* 1985b; Dubin
et al., 1986; Holman *et al.,* 1986; Osterlind *et al.,* 1988b;
Zanetti *et al.,* 1988; Beitner *et al.,* 1990; Grob *et al.,* 1990;
Nelemans *et al.* 1993). The RRs in the highest categories of
exposure were generally between 1.5 and 2.5. Only one study has
shown a negative association with recreational exposure: MacKie &
Aitchison (1982), in Scotland, observed an RR of 0.4 (95% CI
0.2-0.9) for the highest category of hours a week in outdoor
recreation. Their statistical model, however, included socioeconomic
status and history of sunburn, both of which may measure sun
exposure; thus overadjustment of the estimate of RR is likely. All
measures of number or frequency of vacations in sunny places were
positively associated with risk of melanoma. The RRs for the highest
category of this variable ranged from 1.2 to 5 and the finding was
statistically significant in six of eight studies (Lew *et al.,*
1983; Elwood *et al.,* 1985b, Osterlind *et al.,* 1988b, Zanetti *et*

al., 1988; Beitner *et al.,* 1990; Nelemans *et al.,* 1993).

     Sunburn

     Fifteen of seventeen studies of melanoma in which sunburn was
recorded (see table 23 in IARC, 1992) showed a statistically
significant, moderately to strongly positive association with a
history of sunburn (MacKie & Aitchison, 1982; Lew *et al.,* 1983;
Elwood *et al.,* 1985a; Green *et al.,* 1985; Sorahan & Grimley,
1985; Elwood *et al.,* 1986; Holman *et al.,* 1986; Holly *et al.,*
1987; Osterlind *et al.,* 1988b; Zanetti *et al.,* 1988; MacKie *et
al.,* 1989; Weinstock *et al.,* 1989; Beitner *et al.,* 1990;
Elwood *et al.,* 1990; Nelemans *et al.,* 1993) (see table 23: IARC,

1992). Twelve of these studies showed RRs greater than 2.0 for the
highest category of sunburn. Positive associations were obtained for
both sunburn in childhood and sunburn at any age. The greater
consistency of the relationship of melanoma with sunburn compared to
that with other exposure variables may indicate a specific
association with sunburn per se or simply that sunburn is a more
accurately measured indicator of sun exposure.

     Presence of other sun-related skin conditions

     Cutaneous microtopography

     Severity of sun damage to the skin as measured by cutaneous
microtopography was strongly associated with risk of melanoma in
Western Australia. The RR for the most severe grade of damage was
2.7 (95% CI 1.4-5.0; p-value for trend=0.003; Holman *et al.,*
1984b). There was no similar relationship, however, in a study in
Denmark, in which similar methods were used (Osterlind *et al.,*
1988b).

     Freckling of the skin has been shown to be associated with an
increased risk of melanoma in several studies (see for example,
Elwood *et al.,* 1986, 1990, Osterlind *et al.,* 1988b; Dubin *et
al.,* 1986).

     Solar keratoses and other skin cancers

     The risk of melanoma was significantly increased in association
with a past history of nonmelanocytic skin cancer with RRs of 3.7
(95% CI 2.1-6.6) in Australia (Holman *et al.,* 1984b) and 3.8
(1.2-12.4) in the USA (Holly *et al.,* 1987). Relative risks for a
history of solar keratoses or "actinic tumours on the face" were
similarly high (Green & O'Rourke, 1985; Dubin *et al.,* 1986).

     Exposure to artificial sources of UV

     Several studies have reported increased risks of cutaneous
melanoma in users of sunlamps or sunbeds (IARC, 1992). In the most
recent of these studies (Walter *et al.,* 1990), the relative risks
for any use of sunbeds or sunlamps were 1.9 (95% CI 1.2-3.0) in men
and 1.5 (95% CI 1.0-2.1) in women. Relative risk increased with
increasing duration of use: for more than 12 months use the relative
risks were 2.1 (0.9-5.3) in men and 3.0 (1.1-9.6) in women. Positive
associations were found in two of four other case-control studies in
which these exposures were studied (Swerdlow *et al.,* 1988; MacKie
et al., 1989; see also IARC, 1992). Sun exposure is a potential
confounding variable in studies of sunlamps and sunbeds but has not
been taken into account. Specifically it was considered by Walter
et al. (1990). Exposure to a group of other artificial sources of
UV, including plan printers, laboratory equipment emitting UV,
insect tubes, black lights and photocopiers, was not associated with

melanoma in one case control study in Australia (Holman *et al.,*
1986) but for a similar group plus welding the RR was 2.2 (95% CI
1.0-4.9) in Canada (Elwood *et al.,* 1986). Siemiatycki (1991) found
no association between arc welding or other occupational exposure to
UV in a study of occupation and cancer in Canada.

     A number of case-control studies have examined the association
between melanoma and exposure to fluorescent lighting. Only the
first such study found a statistically significant positive result
(Beral *et al.,* 1982). Six subsequent studies found little or no
evidence of a positive association (IARC, 1992).

8.5.3 Cancer 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 SCC and occur on the lower lip
(Keller, 1970; Lindqvist, 1979), a site more heavily exposed to the
sun than the upper lip (Urbach *et al.,* 1966). The inclusion of
adjacent oral mucosa in the definition of cancer of the lip raises
the possibility of confounding of tobacco and alcohol use (well
established causes of cancer of the mouth; Tomatis, 1990).

     The incidence of cancer of the lip is much more common in men
than women. Among men in the USA, it is some 20 times more common in
whites than blacks and it is rare in black and Asian populations
worldwide (Parkin *et al.,* 1992). Incidence of and mortality from
cancer of the lip are substantially lower in migrants to Australia
and Israel, who come from places with potentially lower sun
exposure, than those born in these countries (Armstrong *et al.,*
1983; McCredie & Coates, 1989; Steinitz *et al.,* 1989).

     The incidence of cancer of the lip is higher in rural than
urban areas (Doll, 1991) and descriptive studies have consistently

reported higher incidence or mortality rates of this cancer in men
with outdoor occupations such as farmers, agricultural labourers and
fishermen. (Atkin *et al.,* 1949; Clemmesen, 1965; Gallagher *et
al.,* 1984; Olsen & Jensen, 1987; Lynge & Thygesen, 1990). Four
case-control studies of varying quality have examined the
association between outdoor work and cancer of the lip. Keller
(1970) compared 301 men with cancer of the lip with 301 oral cancer
controls. Crude RRs for employment as a farmer or in any outdoor
work were 4.0 and 2.6 respectively. The use of patients with oral
cancer as controls allowed a rough adjustment for confounding with
tobacco and alcohol use in this study. Spitzer *et al.* (1975)
compared 339 men with cancer of the lip with 199 matched population
controls. The relative risk for any outdoor work was 1.52 and, for
employment as a fisherman, 1.50 (p < 0.05 in both cases). Pipe
smoking but not alcohol drinking was controlled in the analysis. The
other two studies also showed a positive association between outdoor
work and cancer of the lip (Lindqvist, 1979; Dardanoni *et al.,*

1984) but did not control for smoking and alcohol use and showed
other methodological difficulties (IARC, 1992).

8.5.4 Ocular cancers

     Ocular melanoma and other ocular cancers are dealt with in
Chapter 10.

8.5.5 Other cancers

     Observations of increasing mortality with increasing latitude
have formed the basis of suggestions that cancers of the breast,
colon and prostate may be prevented by increasing exposure to the
sun (Garland & Garland, 1980; Gorham *et al.,* 1989, 1990; Garland
 et al., 1989, 1990; Hanchette & Schwartz, 1992), perhaps through
proposed anti-carcinogenic actions of vitamin D (Eisman *et al.,*
1980; Colston *et al.,* 1989; Schwartz & Hulka, 1990; Ainsleigh,
1993). Variation with latitude in medical care, death certification
practices, diet and other lifestyle factors are alternative
explanations for the latitude gradients in these cancers. These
observations, therefore, can be taken only to raise hypotheses about
indirect anti-carcinogenic effects of UV which require testing by
other means.

8.5.6 Action spectrum

     There are few data from which the action spectrum of UV
carcinogenesis in humans can be inferred. For practical purposes,
therefore, reliance is placed on action spectra which have been
determined in experimental animals (see chapter 7).

     If, as is argued below, it is accepted that the formation of
cyclobutylthymidine dimers is a step in the production of mutations
that are associated at least with BCC and SCC, then it would be
reasonable to accept the action spectrum for production of thymidine
dimers in humans as possibly indicative of the action spectrum for
production of nonmelanocytic skin cancer (figure 8.1). This action
spectrum was determined by Freeman *et al.* (1989) who irradiated
untanned gluteal skin of 30 caucasian volunteers with 1 or 2 MED of
narrow band UV at 275 nm, 282 nm, 290 nm, 296 nm, 304 nm, 334 nm and
365 nm. At least five subjects were irradiated at each wavelength.
Following irradiation, shave biopsies were taken of the irradiated
skin, DNA extracted and incubated with Micrococcus luteus
endonuclease to determine the frequency of endonuclease sensitive
sites which indicate the presence of thymidine dimers. Figure 8.1
shows that the effectiveness of UV in producing dimers increased

from 275 nm to a peak at 296 to 304 nm and then fell by four orders
of magnitude to the lowest measured level at 365 nm. This fall is
quite consistent with that observed in the relative effectiveness of
UV for carcinogenesis in mouse skin over the same wavelength range.
The authors reported, also, that observations had been made at 385
nm and 405 nm and that these wavelengths were "largely ineffective"
in net production of dimers.

     Some indication of the effectiveness of UVA in causing skin
cancer could be obtained from the experience of people exposed to
high doses of UVA from sunbeds or in tanning salons. There is some
evidence to suggest that these exposures are associated with an
increase in risk of nonmelanocytic skin cancer, cutaneous melanoma
and ocular melanoma (see above). In none of the studies carried out,
however, has exposure to mainly UVA sources been distinguished from
sources that emit both UVA and UVB. In addition, confounding with
sun exposure is a possibility in all these studies.

8.5.7 Dose-response

     In theory, the best way to estimate the dose-response
relationship between UV and cancer in humans would be to measure the
lifetime exposure to the sun of each member of a population and
relate this measurement, by way of a cohort or a case-control study,
to their probability of developing skin cancer. In practice this is
very difficult. First, measurement of lifetime exposure to the sun
generally requires recall of amount and pattern of sun exposure and
use of protective measures against the sun for as long as 40 or more
years in the past.

     Second, exposure in early life may be particularly important in
determining risk of skin cancer, at least, and this is to a large
extent outside the range of accurate recall. Third, while problems
of recall could be solved by conduct of a cohort study, such a study
would require measurements of sun exposure beginning in the first

few years of life and repeated periodically throughout life to the age at which UV-related cancers become common. Such a study would be logistically and economically impracticable. The whole process is complicated by the fact that a simple measure of lifetime exposure may be insufficient for adequate description of dose-response. The evidence that period and pattern of exposure may be important determinants of some UV-related cancers (see below) means that to model incidence correctly as a function of exposure it would be necessary to collect data on dose-rate of UV and its variation throughout life.

Figure 8.1 Action spectrum for the formation of pyrimidine dimers in human skin on exposure to UV between 275 nm and 366 nm as measured by the formation of micrococcus luteus endonuclease sensitive sites (ESS). Each point (●) represents one subject, circled points indicate two subjects with identical dimer yields. ph = photon, kb = kilobase. (Reprinted in modified form with permission from Freeman et al., 1989).

One attempt has been made to estimate the dose-response relationship between UV and SCC and BCC in a retrospective cohort study of Chesapeake Bay watermen (Strickland et al., 1989). The watermen work mainly in traditional fishing tasks that are regulated by law and have undergone few changes in the past 80 years. They presented, therefore, better prospects than most populations for the accurate recall of past sun exposure. Briefly, 808 caucasian subjects among 1 250 licensed watermen aged 30 years or more participated in an interview and skin examination. Present skin cancers were identified at examination and a history of past skin cancer was taken and; as far as possible, histological confirmation of the diagnosis was obtained for both present and past skin cancer. Totals of 47 SCC in 35 subjects, 60 BCC in 33 subjects and 344 solar keratoses in 202 subjects were identified. About a half of the SCC and BCC had been diagnosed before the survey examination while over 90% of the solar keratoses were diagnosed at the examination. Histological confirmation was available for at least one lesion in 51% of subjects with SCC, 72% with BCC and 13% with a solar keratosis (Vitasa et al., 1990). The average annual exposure of facial skin to solar UVB was estimated for each subject by the combination of data from a personal history of mainly occupational outdoor exposure from 16 years of age to the interview, estimates of ambient UV radiance in the area in which the watermen lived and worked, based on the US network of Robertson Berger meters (Berger & Urbach, 1982), and field measurements of individual exposure to UVB under working conditions as recorded by polysulphone film dosimeters. Annual average ambient UVB for the area was estimated at about 1.14×10^6 J m^{-2} or 3260 MED assuming 350 J m^{-2} to be equivalent to 1 MED. Personal annual average exposure of facial skin ranged from about 1% to 8% of ambient UVB, i.e., 33 to 260 MED a year.

The dose-response relationships obtained are shown in figure 8.2. They were derived from the following mathematical model:

prevalence = $(\text{exposure})^a \, (\text{age})^b$

or, equivalently,

log (prevalence) = a log (exposure) + b log (age).

Figure 8.2 Relationship of cumulative incidence of nonmelanocytic skin cancers and solar keratoses to individual estimated average annual exposure of the face to UVB since 16 years of age. O, solar keratosis; △, SCC; □, BCC. (Reproduced with permission from Strickland et al., 1989).
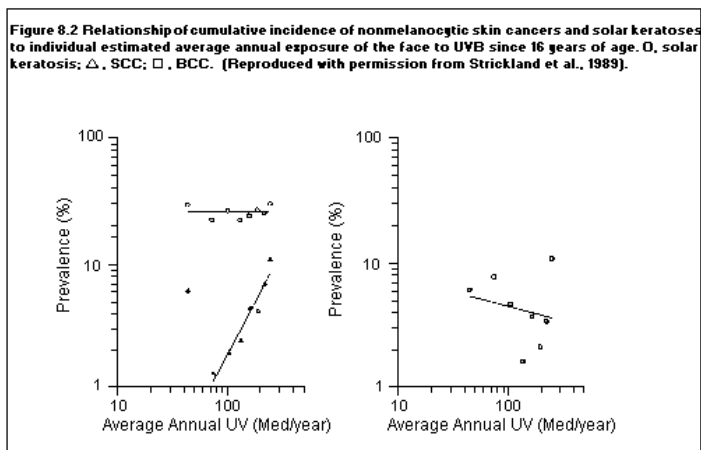
While prevalence is stated in the above expressions and the y axis in figure 8.2 is labelled as prevalence, it is believed that the figures are cumulative incidence proportions in which each subject with more than one of a particular type of lesion was counted only once. Only cumulative incidence of SCC appeared to increase with increasing estimated exposure to solar UVB. The value of a for SCC was 1.7. It should be noted however, that 4 subjects with SCC among 64 men in the lowest sun exposure category were excluded from the regression because of the anomalously high incidence in this group and because of the possibility that these subjects may have been hypersusceptible to UV. Apart from all having solar keratoses, however, they did not consistently show phenotypic features of high susceptibility to UV and it was not possible on any basis, therefore, to remove hypersusceptible subjects from the higher dose categories. The values of a for BCC and solar keratoses were -0.2 and 0.005 respectively. It was suggested that because of the high sun exposure of all men in the study the cumulative incidence of BCC may have reached a saturation point at the lowest level of sun exposure such that further increases in exposure did not lead to further increases in incidence.

An alternative approach to estimating dose-response relationships has been to examine the relationship, geographically, between incidence or mortality of skin cancers in whole populations and estimated or measured ambient UV (Armstrong, 1993). This work has been done in the context of estimating the increase in skin cancer that might be expected from some increment in ground-level UV caused by depletion of stratospheric ozone. It has made the fundamental assumption that the observed geographical variations in incidence or morbidity rates of skin cancer is due largely to geographical variations in UV. The results have commonly been expressed in terms of the biological amplification factor (BAF) defined as follows (de Gruijl and van der Leun, 1980).

There are substantial uncertainties regarding the dose-response relationships shown in figure 8.2. First, the estimates of dose were based on exposure of the face only, excluded dose in the first 16 years of life and did not take account of dose-rate or pattern of exposure. Second, there is likely to have been appreciable underascertainment of cancers diagnosed before the survey and high proportions of all lesions were not confirmed histopathologically. Third, the exclusion of four men with SCC must have had an

appreciable effect on the value of a for SCC. Fourth, no mention is made of having controlled in the analysis for potential negative confounding between cutaneous sun sensitivity and sun exposure. Such confounding might be expected to reduce the slope of the dose-response relationships. Finally, no measure of precision was given for the values of a; given the small numbers of subjects with SCC and BCC, those for these two cancers must have had quite wide 95% confidence intervals. This study gives only a hint, therefore, as to what the dose-response relationship between solar UVB and nonmelanocytic skin cancer might be at one end of the human exposure range. No similar observations are available for cutaneous melanoma.

  BAF = (dI/I)/(dD/D)

where dI equals a small increment in the existing incidence of skin cancer, I, which results, in the steady state, from a small increment dD in the existing biologically effective ambient level, D, of solar radiation (i.e., spectral dose weighted by the action spectrum for production of skin cancer).

The best known and most commonly used geographical relationships between skin cancer incidence and ambient UV used for dose-response estimation are those established from data on nonmelanocytic skin cancer collected in a special survey in the USA in 1977 and 1978 and UV measurements collected through the US network of Robertson-Berger meters (Scotto *et al.*, 1983).

Corresponding relationships were later established between melanoma
incidence measured by the US SEER cancer registries and the
Robertson-Berger meter data (Scotto and Fears, 1987). The
relationship for melanoma is shown in figure 8.3. In this figure,
the logarithm of age-adjusted annual incidence of melanoma is
plotted against the logarithm of the annual average Robertson-Berger
meter counts at each location. The lowest annual average meter count
was 95×10^4 units at Seattle and the highest, Albuquerque, New
Mexico, at 197×10^4 units. These values translate, approximately,
into 0.75×10^6 and 1.56×10^6 J m^{-2} respectively. The
estimated slopes of the regression lines were 0.7 in males and 0.8
in females which are also the estimated BAFs for melanoma from these
data.

Figure 8.3 Relationship of average annual age-adjusted incidence of cutaneous melanoma in whites
in seven areas of the United States in 1978-81 to average annual ambient UV as measured by
Robertson-Berger meters. ■.males; □.females.(Reproduced with permission from Scotto & Fears
1987).
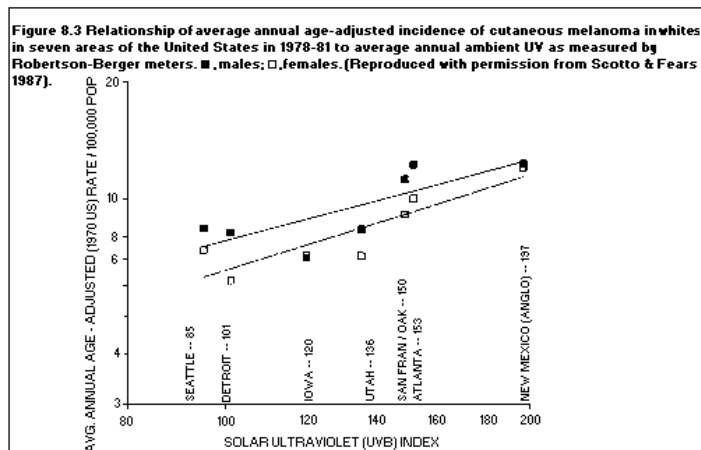
Table 8.2 summarises the most recent estimates of the BAFs for
nonmelanocytic skin cancer (BCC and SCC) and cutaneous melanoma from
data in the USA and Scandinavia. These estimates were based on
various action spectra: the response spectrum of the Robertson-
Berger meter (Scotto *et al.,* 1983; Scotto & Fears, 1987; Pitcher &
Longtreth, 1991), the CIE reference spectrum of McKinlay and Diffey
(1987), Moan *et al.* (1989), Moan and Dahlbach, (1992), and the
Sterenberg-Slaper action spectrum for UV radiation of skin cancer in
albino hairless mice (de Gruijl and van der Leun, 1991). Generally,
the BAF for BCC lay between about 1.5 and 2.0. For SCC and melanoma,
there was much greater variation in estimates. Those for SCC were
between about 2.0 and 4.0 when based on the US data but between 1.0
and 2.0 when based on Norwegian data. Similarly, BAFs for melanoma
were between 0.3 and 0.5 when based on US data but between about 1.0
and 3.0 when based on Scandinavian data. While an attempt had been
made to adjust the US estimates for confounding with population
constitutional sensitivity to the sun and sun-related behaviour,
even the unadjusted estimates (ranging from 0.6 to 1.0; Scotto &
Fears, 1987; Pitcher & Longstreth, 1991) were considerably less than
those for Scandinavia. The most likely reasons for the differences
between the estimates is differences in their error.

Table 8.2 Recent estimates of the biological amplification factors (BAF) for
nonmelanocytic skin cancer and cutaneous melanoma based on geographical correlations
between average annual ambient UV and skin cancer incidence or mortality.

Authors	Region	Sex	BAFs for BCC Incidence	BAFs for SCC Incidence
Nonmelanocytic skin cancer				
Scotto et al, 1983	USA (8 centres)	M	1.3-2.6[a]	2.1-4.1
		F	1.1-2.1	2.2-4.3
de Gruijl & van der Leun 1991	USA (8 centres)	MF	1.4	2.5
Moan et al 1989	Norway (6 areas)	M	1.5-2.0[a]	1.2-1.5
Melanoma				
Scotto & Fears, 1987	USA (7 areas)	M	0.4[c]	
		F	0.5[c]	
Pitcher & Longstreth, 1991	USA 215 SMAs	M		0.4[d]
		F		0.3[d]

Table 8.2 (contd).

Authors	Region	Sex	BAFs for BCC Incidence	BAFs for SCC Incidence
Moan & Dahlback, 1992	Norway	M	1.9	
		F	3.2	
	Finland	M	1.3	
		F	2.2	
	Sweden	M	1.9	

[a] Exponential model used in which the value of the BAF varies with ambient UV, thus range of values given.

[b] Same data as used by Scotto et al (1983) except that a power model was used instead of an exponential model and the most recent action spectrum for UV carcinogenesis in mouse skin was assumed.

[c] Adjusted for population estimates of ethnic origin, pigmentary characteristics, use of sunscreens, and hours per week of outdoor exposure.

[d] Adjusted for population estimates of ethnic origin, household income, outdoor occupation and education.

      This approach to estimation of dose-response has assumed, among other things, that: the correct action spectrum has been used to weight spectral UV irradiance when producing a single figure for ground level UV in each area; all members of the populations giving rise to the incidence rates have lived their whole lives in their present environment; the skin cancer incidence rates have been measured accurately and, in particular, that their error does not correlate with ambient UV radiance; and that possible confounding of ambient UV with constitutional sensitivity to the sun and sun-related behaviour is either unimportant or has been taken adequately into account. None of these assumptions is likely to be correct in any of the estimates of BAF made so far and the estimates are all likely, therefore, to be inaccurate (Armstrong, 1993).

      It should be noted that even if dose-response relationships between UV and skin cancer incidence determined at the population level are accurate, they may not reflect dose-response relationships at the individual level. This is because of the averaging of exposure and risk that occurs at the population level. The actual population exposure of the skin at any level of ambient UV is an average of many different exposures and the actual population incidence of skin cancer is an average of many individual risks of skin cancer. The association of individual risk to individual exposure may be quite complex (as has been postulated for melanoma; Armstrong, 1988) but at the population level this could still

translate into a simple exponential or power relationship between ambient exposure and incidence.

      No attempts have been made to estimate the dose-response relationships for UV and cancers other than skin cancers that may be caused by UV.

8.5.8 Effects of pattern of exposure

      There are a number of aspects of the epidemiology of cutaneous melanoma in European populations that appear inconsistent with a simple relationship between it and sun exposure (English & Armstrong, in press). First, in many populations, melanoma occurs as commonly in women as in men, although men are more likely to work outdoors; second, there is a relative peak in incidence in middle life, which is not the pattern to be expected from life-long exposure to an environmental agent; third, it most frequently occurs on the back in men and lower limbs in women, sites which are not maximally exposed to the sun; finally, melanoma is more common in indoor than outdoor workers and in those of higher socioeconomic status than those of lower status.

      These observations led to postulation of the "intermittent exposure hypothesis" for the relationship of sunlight to melanoma. This hypothesis states that incidence of melanoma is determined as much (or more) by the pattern of sun exposure as by the total accumulated dose of sun exposure and, specifically, that infrequent or intermittent exposure of untanned skin to intense sunlight is particularly effective in increasing incidence of melanoma (Armstrong, 1988). If, as seems plausible, this postulated effect of intermittency of sun exposure is due to protective thickening and pigmentation of the epidermis with more continuous sun exposure, then intermittent exposure would be maximally effective if it occurred at intervals longer than the time it takes for the skin to return to its prior level of sensitivity after a single episode of sun exposure (two to three weeks).

      The epidemiological evidence, summarised above, that risk of melanoma is apparently not increased with total or occupational exposure to the sun but is increased with increasing non-occupational exposure to the sun, in particular increasing time spent in sun-related vacations in populations with otherwise comparatively low sun exposure (Klepp & Magnus, 1979; Lew *et al.,* 1983; Elwood *et al.,* 1985b; Osterlind *et al.,* 1988b; Beitner *et al.,* 1990; Zanetti *et al.,* 1992), and episodes of sunburn (IARC, 1992) is consistent with this hypothesis.

      There are less grounds for believing that pattern of UV is important in causing nonmelanocytic skin cancer than there are for melanoma. Specifically, nonmelanocytic skin cancer as a whole, and BCC and SCC separately, are more common in men than women (Kricker

 et al., 1990; Parkin *et al.,* 1992; Marks *et al.,* 1993) and, in the largest, well-collected, population-based incidence series available, they showed steadily increasing incidence rates with age, except for a downturn in older age-groups possibly due to underascertainment (Scotto *et al.,* 1983). On the other hand, recent series of BCC have shown unexpectedly high proportions on the trunk (Kricker *et al.,* 1990; Magnus, 1991) and, as reviewed above, the relationship of nonmelanocytic skin cancer with occupational exposure to the sun is not at all clear. Moreover, there is some

evidence of an association between sunburn and other indicators of
intermittent exposure and BCC (Hunter *et al.,* 1990; Kricker *et
al.,* 1991b).

8.5.9 Interactions between UV and other agents

     5-methoxypsoralen and 8-methoxypsoralen (methoxsalen)

     Methoxsalen, 5-methoxypsoralen and some other psoralens
(hereafter referred to collectively as psoralens) are used in
combination with UVA (referred to as PUVA) for the treatment of
psoriasis and to produce repigmentation in vitiligo. A working group
of International Agency for Research on Cancer concluded in 1987
that there was sufficient evidence that PUVA (defined as
8-methoxypsoralen plus long-wave UV radiation) causes cancer in
humans, based mainly on evidence of its association with SCC.

     Recent studies have confirmed and extended this conclusion.
Stern & Lange (1988) reported on 5 to 10 year follow-up of patients
treated with PUVA in the USA. In 13 384 person years of follow-up of
1 380 people, 100 people had developed 391 SCC and 94 had developed
218 BCC. There were statistically significantly increasing risks of
both BCC and SCC occurring more than 58 months after entry into the
cohort with increasing number of treatments with PUVA. Risk of BCC
rose to 6.9 (95% CI 3.2-13.1) with 260 or more treatments and risk
of SCC rose to 50.1 (95% CI 24.9-89.5). Therapeutic exposure to
ionizing radiation, high doses of tar and UVB was unrelated to
number of treatments with PUVA and, therefore, did not confound the
observed dose-response relationship. Lindelöf *et al.* (1991)
reported on follow-up for an average of 6.9 years of 4 799 Swedish
patients treated with PUVA. Risk of SCC increased with increasing
number of treatments with PUVA. In those who received 200 or more
treatments, the relative risk, with reference to the general Swedish
population, was 30.7 (14.7-56.5) in men and 18.5 (0.5-103.2) in
women. BCC were not recorded in this study.

     Cases of melanoma have been reported in patients treated with
PUVA but the rates of melanoma in US and Swedish PUVA cohorts were
little higher than those expected on the basis of population
incidence rates. In the US cohort the relative risk was 1.46 (95% CI
0.3-7.3; Gupta *et al.,* 1988), while in the Swedish cohort it was

1.1 (0.2-3.2) in men and 0.8 (0.1-3.0) in women (Lindelöf *et al.,*
1991).

     It is not possible in any of these studies to estimate what the
risk of skin cancer would have been if the patients had been treated
with UV alone. It would seem reasonable to assume, however, on the
basis of the evidence from experimental animals (see above) that
administration of psoralens potentiated the effect of UV. In
addition analysis of clinical data even suggests that this
carcinogenicity of PUVA exceeds that of UVB treatment by an order of
magnitude (Slaper, 1987).

     Ionizing radiation

     Ionizing radiation causes nonmelanocytic skin cancer, mainly
BCC, generally after a long latent period (Shore, 1990; Fragu *et
al.,* 1991; Hogan *et al.,* 1991; Sadamori *et al.,* 1991; Moller
et al., 1993). Incidence in the atomic bomb survivors was related
strongly to exposure, although not for those closest to the blast
(Sadamori *et al.,* 1991). There is evidence that ionizing radiation
and UV may act synergistically in causing skin cancer. In a study of
skin cancer following irradiation of the scalp for ringworm, Shore
et al. (1984) found a substantial excess of BCC in white subjects.
In blacks, no skin cancers were observed when 13 would have been
expected from the rate on the UV-shielded scalp in whites. This lack
of skin cancers in irradiated blacks suggest that UV radiation
contributes more than additively to the production of these cancers
in irradiated whites. This inference is supported by the observation
that the excess of BCC around the UV-exposed fringe of the scalp in
irradiated whites was some four to five times higher per unit dose
and area than that on the UV-shielded hairy scalp (Shore *et al.,*
1984). Further, Modan *et al.* (1993) observed, in a separate cohort
of people irradiated for ringworm of the scalp, that sunbathing
increased the risk of skin cancer 2.6 times (95% CI 1.1-6.1). All
except one of 39 cancers were BCCs and 60% were on the scalp, thus
suggesting that the ionizing radiation had also contributed to their
causation. However, no formal analysis of interaction was reported
from this study.

     Other agents

     One or more SCCs occur in 30% to 50% of patients with
epidermodysplasia verruciformis, a rare chronic skin disease in
which there are multiple benign skin lesions caused by a variety of
different types of human papilloma viruses (HPV; Quan & Moy, 1991).
HPV DNA sequences have been identified in the SCC occurring in these
patients and most of the cancers occur on sun-exposed sites. This
coincidence suggests that the UV interacts with the virus in causing
these cancers. Benign warts are also increased in frequency in renal
transplant patients and it is possible that they, with UV, are
involved in causing the excess of nonmelanocytic skin cancers that

occur in these patients (Bouwes-Bavinck, 1992). These cancers, too,
occur mainly on sun-exposed sites.

8.5.10 Mechanisms of UV carcinogenesis

     Precursor lesions

Solar keratoses are very strongly related to risk of
nonmelanocytic skin cancer (Kricker *et al.,* 1991a) and it is a
matter of clinical observation that SCC often occurs in lesions
which, previously, had the clinical appearances of solar keratoses.
There is evidence that solar keratoses are, themselves, caused by
exposure to the sun. Thus solar keratoses could be the visible
expression of an early, UV-caused, mutational step in the pathway to
skin carcinogenesis.

Analogously with solar keratoses, benign melanocytic naevi are
commonly observed in clinical or histopathological contiguity with
melanomas and have been found, epidemiologically to be strongly
related to risk of cutaneous melanoma (Holman & Armstrong, 1984a;
Armstrong & English, 1988). Naevi may, therefore, represent an
early, UV-caused, mutational step in the development of melanoma. In
this regard, it is interesting to note that the most active
development of naevi occurs during the first 15 years of life, thus
providing a possible link to early life sun exposure as suggested by
migrant data (see above). The appearance of naevi in children who
have received chemotherapy for cancer may indicate that they can be
caused by mutagens other then UV (Hughes *et al.,* 1989; Baird *et
al.,* 1992; Green *et al.,* 1992).

DNA damage

The evidence of much increased incidence rates of BCC, SCC
cutaneous melanoma and tumours of the anterior eye in patients with
xeroderma pigmentosum (XP) (see above) strongly suggests that
unrepaired, UV-induced photoproducts in DNA form part of the genesis
of these cancers. Almost all forms of XP have an inherited
deficiency in excision repair of DNA photoproducts (Kraemer *et al.,*
1987). The position is made somewhat less clear, however, by the
existence of two other inherited syndromes involving deficiency in
DNA excision repair, trichothiodystrophy and Cockaynes syndrome,
that are not associated with increased incidence rates of skin
cancer (Bridges, 1990; Barrett *et al.,* 1991).

There is evidence also that low levels of DNA repair may be
associated with skin cancer in the general population, although
there is some disagreement in the results so far obtained .
Munch-Petersen *et al.* (1985) studied 29 patients with multiple
skin neoplasms, 19 with multiple BCC only and 10 with both BCC and
squamous lesions (SCC, solar keratosis, or Bowen's disease), and 25
control subjects with roughly the same age and sex distributions.

Patients with both BCC and squamous lesions had much higher
UV-induced DNA synthesis in lymphocytes, as measured by
incorporation of [3H]thymidine following irradiation with a Philips,
TUV, 6 watt lamp (peak emission at 254 nm), than did controls.
Patients with multiple BCC were not different from controls. The
authors attributed this difference to possible defects in the DNA
ligation process. Roth *et al.* (1987) studied the rate of loss of
dithymidine dimers in DNA of cultured fibroblasts that had been
irradiated with a Philips 6-V germicidal lamp with peak emission at
254 nm. Dimers were measured with a monoclonal antibody highly
specific for the conformational change in DNA caused by the dimers.
No significant difference was seen between 16 BCC cases and 30
controls in the rate of loss of dimers. In ten melanoma patients,
however, the mean percentage of bound antibody at 60 minutes was
50.5 (SD 18.2) compared with 29.8 (SD 5.7) in controls (p=0.001)
thus suggesting that average dimer repair capacity was less in the
melanoma patients than the controls. Alcalay *et al.* (1990)
compared 22 patients with a history of one (13 patients) or more BCC
in the past with 19 healthy volunteers. Each subject was irradiated
at two locations on the lower back with 1 MED of UV from a 150 W
xenon arc solar UV simulator from which wavelengths < 295 nm had
been removed by a 1 mm WG 320 filter. Shave biopsies of skin were
taken from one of the sites immediately and the other 6 hours after
irradiation and the concentrations of pyrimidine dimers in DNA
measured by the micrococcus luteus endonuclease assay. Dimer yields
immediately after irradiation were similar in BCC patients and
controls but, after 6 hours, the proportion of dimers that had been
repaired was 22% in the BCC patients compared with 33% in the
controls (p=0.06). Wei *et al.* (1993) measured DNA repair capacity
in 88 patients with a history of one or more histologically
confirmed BCCs and 135 control subjects. Repair capacity was
measured by assaying the capacity of lymphocytes to repair
UV-induced damage in DNA of a nonreplicating recombinant plasmid.
Damage was induced by irradiating the plasmid with either 3500 J
m^{-2} or 7000 J m^{-2} of UV at 254 nm. The BCC cases had a
significantly lower mean DNA repair capacity (p=0.047) than controls
only when 29 controls with a family history of BCC or who themselves
had an actinic keratosis were removed from the comparison.

It now seems highly likely that UV can mutate the p53 tumour
suppressor gene in human skin and that UV-induced mutations in this
gene may be involved in the aetiology of some human cancers. First,
a recent study has shown that mutations that are strongly suggestive
of a UV effect, CC-TT changes at dipyrimidine sites, could be found
in 17 of 23 (74%) samples of sun-exposed normal skin in Australian
skin cancer patients compared with 1 of 20 (5%) samples of skin from
sites not exposed to the sun (Nakazawa *et al.,* in press). Focal
overexpression of p53 protein has also been observed in normal, sun
exposed skin adjacent to BCC in 37 of 39 subjects but only in one
keratinocyte in 14 samples of buttock skin from the same subjects
(Shea *et al.,* 1992). Second, several studies have found mutations

at dipyrimidine sites in the p53 gene in 36% to 56% of BCC (Rady *et*

al., 1992; Molès *et al.,* 1993; Ziegler *et al.,* 1993). In three
similar studies of SCC one found these mutations in 14 (57%) of 24
cases (Brash *et al.,* 1991) one in two of 10 cases (Pierceall *et
al.,* 1991) and, the other, none of 13 (Molès *et al.,* 1993). The
more detailed findings of these five studies are summarised in table
8.3. Mutations were found in the p53 gene, following examinations of
varying extent, in 46% of BCC and SCC, the majority of which (88%)
were base substitutions or one or two base deletions at dipyrimidine
sites (the proportion expected by chance is 75%). The highest
proportions of these mutations resulted from C -> T, CC -> TT and
C -> A base changes which is consistent with what would be expected
if they had been caused by UV (Brash *et al.,* 1991). Several
studies have found p53 protein by immunostaining (evidence of
overexpression of possibly abnormal p53 protein) in from 42% to 83%
of BCC and 56% to 65% of SCC (Barbareschi *et al.,* 1992; Shea *et
al.,* 1992; Stephenson *et al.,* 1992, Ro *et al.,* 1993) and are
thus reasonably consistent with the observations as to prevalence of
mutations.

The position with respect to p53 mutation is much less clear
for other cancers possibly caused by UV. A number of studies have
reported on the prevalence of detectable p53 protein in primary
melanomas: the proportions have varied from 3.6% to 97% (see, for
example, Stretch *et al.,* 1991; Akslen & Morkve, 1992; Lassam *et
al.,* 1993; Ro *et al.,* 1993). There has been only one report of a
p53 mutation in melanoma, a C -> T transition in codon 248 of the
gene in the melanoma cell line SK-MEL-13 (Volkenandt *et al.,*
1991). The comparative lack of evidence of expression of p53 protein
in melanocytic naevi (Yu *et al.,* 1992; Lassam *et al.,* 1993)
would suggest that if p53 gene mutation is important in the genesis
of melanoma it is not the earliest mutation. The protein product of
p53 was detected in 12 of 18 (67%) choroidal melanomas (Tobal *et
al.,* 1992) but none of 7 choroidal naevi. The DNA of exons 5, 7
and 8 of the p53 was sequenced from two of the strongly positive
choroidal melanomas: a mutation was found in each, one G -> T and
one C -> G.

Mutations in the ras oncogenes appear to be less frequent than
in the p53 gene in nonmelanocytic skin cancers. Mutations were
sought in one or more codons of Ha-ras, Ki-ras and N-ras in 77 BCC
and found in five (6%) (van der Schroeff *et al.,* 1990; Lieu *et
al.,* 1991; Campbell *et al.,* 1993). There were two mutations, one
in a dipyrimidine site, in codon 61 of Ha-ras and three mutations at
dipyrimidine sites in codon 12 of Ki-ras; two mutations were C ->
A, one was C -> T and one was A -> T. These mutations were also
sought in 79 SCC and found in 7 (9%) (van der Schroeff *et al.,*
1990; Corominas *et al.,* 1991; Lieu *et al.,* 1991; Campbell *et
al.,* 1993). There were three mutations in dipyrimidine sites in
codon 12 of Ha-ras, three, but none in dipyrimidine sites, in codon
61 of Ha-ras and one at a dipyrimidine site in codon 12 of Ki-ras;

three mutations were C -> A, one was C -> T and three were T ->
A. Overall, 8 of 12 (67%) mutations were at dipyrimidine sites.
There is nothing about the pattern of base changes that would favour
UV as the cause of the mutations. The comparative rarity of ras gene
mutations in nonmelanocytic skin cancers is supported by a study of
26 such tumours in Japanese patients with xeroderma pigmentosum
(Ishizaki *et al.,* 1992). Only one mutation was found, an A -> T
change in codon 61 of Ki-ras.

Mutations in ras oncogenes have been demonstrated in some human
cutaneous melanomas. In three series totalling 59 primary melanomas
(van't Veer *et al.,* 1989; Shukla *et al.,* 1989; Albino *et al.,*
1991), ras gene mutations were found in 11 (19%). The mutations
occurred in codon 61 of N-ras (6), codon 13 of N-ras (4), codon 12
of Ki-ras (3) and codon 12 of Ha-ras (1) (two mutations were found
in each of 3 melanomas). Ten of the 13 mutations (77%) were at
dipyrimidine sites and nine were C -> A, three C -> T, one T -> C
and one T to A or G (IARC, 1992). The pattern of base changes is not
such as to suggest that UV was responsible for the mutations.
Mutations were sought but not found in codons 12, 13 and 61 of
Ha-ras, Ki-ras and N-ras in up to 68 uveal melanomas (Mooy *et al.,*
1991; Soparker *et al.,* 1993).

Table 8.3 Summary of results of detection of mutations in the p53d
gene of BCC and SCC (Brash et al, 1991; Pierceall et al 1991; Rady
et al., 1992; Molès et al., 1993; Ziegler et al., 1993).

Mutations Detected	BCC	SCC
	(60)[a]	(46)
Any mutation	52%	39%
Base substitutions or 1 or 2 base deletions at a dipyrimidine site	45%	35%
Types of base substitutions or 1 or 2 base deletions at dipyrimidine sites [b]	52%c	38%
C -> T	13%	19%
CC -> TT	13%	31%
C -> A	10%	6%
C -> G	3%	0%

Table 8.3 (contd.)

Mutations Detected	BCC	SCC
T -> C	3%	0%
T -> A	3%	0%
G -> C	0%	6%
C deleted	3%	0%
CC deleted		

[a] Total numbers of cancers examined.
[b] In consistency with the format adopted by Brash et al (1991) and
     Ziegler et al (1993), four base substitutions reported as G -> A
     (Pierceall et al, 1991; Rady et al, 1992) were represented as
     C -> T and two reported as G -> T (Pierceall et al, 1991; Molès
     et al, 1992) were represented as C -> A.
[c] Proportions of all point mutations at dipyrimidine sites.

    Oxidative processes

    Oxidative effects are an important consequence of exposure to
UV, especially UVA (see Chapter 6) and if they are involved in
mediating its carcinogenic effects in humans it might be expected
that anti-oxidant vitamins would reduce the risk of UV-related
cancers. There is some evidence of such effects, mainly for
cutaneous melanoma. Risk of melanoma was slightly but not
significantly reduced by high intakes of vitamin E and carotene and
high plasma concentrations of -carotene and -tocopherol in a
case-control study in the USA (Stryker et al., 1990). More
persuasively, a nested case-control study in a cohort study in
Finland showed significantly lower serum concentrations of -carotene
and -tocopherol in 10 cases of melanoma and 18 controls (Knekt et
 al., 1991). Melanoma was the only cancer in this study to be
associated with low levels of anti-oxidant vitamins. A similar
result was obtained for -tocopherol in a case-control study of
melanoma carried out in Moscow (crude relative risk for highest
tertile of -tocopherol was 0.08, 95% CI 0.01-0.38; Zaridze et al.,
1992); risk was not reduced by high serum concentrations of
-carotene. As to nonmelanocytic skin cancer, in a hospital-based
case-control study covering 53 cases of BCC and 35 of SCC, high
intakes of vegetables were protective and cases had a significantly
lower mean level of -carotene than did controls (Kune et al.,
1992). It should be noted, however, that cases were on average, five
years older than controls. No evidence was found for a protective
effect of dietary carotenoids with vitamin A activity, vitamin C or

vitamin E in a study of diet and BCC in a cohort of US nurses
(Hunter et al., 1992).

    Immune-suppression

    UV has been shown to suppress immune functions in humans (see
Chapter 9). In addition there are a number of lines of evidence that
link immune suppression from other sources with skin cancer in
humans.

    As early as 1980 it was clear that renal transplant patients,
who receive long-term immunosuppressive therapy, had an increased
incidence of nonmelanocytic skin cancer (Kinlen et al., 1979;
Hardie et al., 1980). Among 290 transplant patients in Queensland,
Australia, it was estimated that the incidence of nonmelanocytic
skin cancer was 21 times that in the general population Hardie et
 al., 1980); the ratio of BCC to SCC was reversed from 4:1 in the
general population to 1:1.7 in the transplant patients suggesting
that the incidence of SCC was particularly increased in them.
Similar results were obtained in Canadian and Dutch series of
transplant patients (Gupta et al., 1986; Hartevelt et al., 1990)
In the Dutch study it was estimated that the incidence of SCC was
250 times higher than that in the general population and that of BCC
10 times higher.

    There is evidence to suggest that the nonmelanocytic skin
cancers occurring in renal transplant patients are caused by sun
exposure. First their site distribution is similar to that of all
nonmelanocytic skin cancers and strongly favours sun exposed sites
(Hartevelt et al., 1990). Second, all 5 nonmelanocytic skin
cancers found by Boyle et al. (1984) in 94 transplant patients
occurred in the 17 patients judged to have high sun exposure. In a
more thorough study based on 137 Dutch transplant patients, 20 of
whom had SCC, 7 BCC and 9 both types of cancer, Bouwes-Bavinck
(1992) found a relative risk for 20 000 or more cumulated hours of
sun exposure compared with 10 000 or less of 97.5 (95% CI 6.6-1444)
for SCC and 49.3 (2.8-878) for BCC thus suggesting that sun exposure
had a strong effect on development of the transplant related skin
cancers.

    The incidence of cutaneous melanoma has also been observed to
be increased in patients with renal transplants (relative risk 3.9,
95% CI 1.4-8.5; Hoover, 1977; Greene et al., 1981). All 14 renal
transplant patients with melanoma reported by Greene et al. (1981)
had fair complexions, light-coloured hair, light-coloured eyes and a
tendency to freckle thus suggesting that there may have been an
interaction between sun exposure and immune suppression in causing

their melanomas. The rapid appearance of new melanocytic naevi has
been reported in two renal transplant patients (Barker & MacDonald,
1988; McGregor *et al.,* 1991). Melanoma incidence is also increased
in patients with lymphohaematopoetic neoplasms which are associated

with immune suppression (Greene & Wilson, 1985; Tucker *et al.,*
1985b; Travis *et al.,* 1991, 1992) and has been reported to be
increased in patients with human immunodeficiency virus infection
(McGregor *et al.,* 1992; Reynolds *et al.,* 1993). Rapid appearance
of melanocytic naevi has also been reported in HIV infection (Duvic
 et al., 1989).

8.6 Conclusions

    UV exposure of the skin has both beneficial and harmful
effects. The beneficial effects include photochemical production of
vitamin D and widely believed but poorly documented effects on
general well-being. The harmful effects include sunburn,
phototoxicity, photoallergy, benign abnormalities of melanocytes
(freckles, melanocytic naevi and solar or senile lentigines) a range
of other chronic abnormalities resulting from UV injury to
keratinocytes, blood vessels and fibrous tissue, often described
together as "photoageing", skin cancer (melanoma and non-
melanocytic cancer) and possibly cancer of the lip.

    The indirect epidemiological evidence that sun exposure causes
cutaneous melanoma and non-melanocytic cancer is strong. Their
incidence is less in darker-skinned ethnic groups than in those with
lighter skins residing in the same geographic area and, within
populations that are reasonably homogeneous ethnically, risk of skin
cancer increases with decreasing pigmentation of the skin and
reduced ability to produce a protective tan. Albinos, who lack
cutaneous pigmentation, appear to have an increased risk of
non-melanocytic skin cancer but not melanoma. The anatomic site
distibution of SCC favours the head and neck and upper limbs, sites
that are more or less continuously exposed to the sun when outdoors.
This concentration is less pronounced for BCC and melanoma, but both
are rare on sites that are rarely exposed to the sun.

    Within countries covering an appreciable span of latitude, an
inverse relationship within latitude and incidence of both
non-melanocytic skin cancer and cutaneous melanoma has generally
been observed. The incidence of both cancers is substantially lower
in migrants from the United Kingdom (an area of low solar
irradiance) to Australia (an area of high solar irradiance) than it
is in persons of similar ethnic origin born in Australia. This
difference is not observed for BCC and melanoma in those who migrate
to Australia within the first ten years of life; this observation
may suggest that sun exposure in childhood is particularly important
in determining subsequent risk of skin cancer. Similar observations
have been made for melanoma in migrants to other countries with high
solar irradiance. Risk of melanoma has been shown to increase with
increasing lifetime average ambient solar irradiance at an
individual's places of residence.

    The direct epidemiological evidence linking sun exposure and
skin cancer is weaker. Estimated total sun exposure of individuals
has not been consistently associated with risk of either
non-melanocytic skin cancer or melanoma. Indicators of benign sun
damage to the skin, however, are positively associated with risk of
both types of skin cancer. Occupational sun exposure has been found
to be weakly associated with non-melanocytic skin cancer in a few
studies but not consistently associated, either positively or
negatively, with melanoma. Non-occupational or recreational sun
exposure is consistently and quite strongly associated with risk of
melanoma whereas there are insufficient data to draw a conclusion
regarding non-occuptional exposure and non-melanocytic skin cancer.
The same is substantially true of history of sunburn although a few
observations suggest that it is associated with non-melanocytic skin
cancer.

    Together, the indirect and direct evidence is sufficient to
conclude that sun exposure causes both melanoma and non- melanocytic
skin cancer.

    Use of sunlamps or sunbeds has not been consistently associated
with risk of non-melanocytic skin cancer in several rather poorly
conducted studies. There is stronger evidence that it may be
associated with risk of melanoma in a number of better studies but
possible confounding of use of sunlamps and sunbeds with sun
exposure has not been consistently controlled.

    Cancer of the lip is much more common in white than black
populations and is less frequent in migrants from areas of low
ambient solar irradiance to Australia and Israel than in those born
in these countries. It is associated with outdoor work but possible
confounding with tobacco and alcohol use has not been adequately
controlled in any study.

    There are no data in humans from which the action spectrum for
production of either non-melanocytic skin cancer or cutaneous
melanoma can be inferred directly.

    Problems in the quantitative measurement of the sun exposure of
individuals have prevented the determination, in humans, of the
relationship between individual dose of UV and risk of any form of
skin cancer. The observed geographical relationship between ambient
UV irradiance and incidence of skin cancers has been used to
estimate the quantitative relationship between ambient UV irradiance
and population risk of these cancers. Exponential or power

relationships have generally given an adequate fit to the data, but provide rather variable estimates of the proportional increase in incidence of skin cancer per unit proportional increase in biologically effective UV irradiance. The accuracy of these estimates is uncertain, particularly because of difficulties in the accurate measurement of skin cancer incidence and difficulties in

control of likely confounding with cutaneous sensitivity to the sun and sun-related behaviour.

A number of features of the epidemiology of melanoma suggest that infrequent or intermittent exposure of skin that is unadapted to sun exposure may be particularly important in its causation. This hypothesis is supported by the relatively strong evidence relating non-occupational (recreational) sun exposure and sunburn to melanoma. There is little evidence that pattern of sun exposure is important in the aetiology of non-melanocytic skin cancer but few directly relevant observations exist.

The much increased rates of all skin cancers in patients with xeroderma pigmentosum, who are deficient in the capacity to repair UV-induced DNA damage, suggest that direct UV damage of DNA may be a step in the causation of these cancers. This suggestion has been supported by observation of UV specific mutations of the p53 tumour suppressor gene in a proportion of patients with non-melanocytic skin cancer. No such evidence is available for melanoma. Oxidative and immune suppressant effects may also contribute to the capacity of UV to cause skin cancers.

9. HUMAN STUDIES: IMMUNE FUNCTION

9.1 Immune Function Assays

Several investigators have examined the effect of UV on contact hypersensitivity (CHS) responses to dinitrochlorobenzene (DNCB) or other contact sensitizers in humans (Hersey *et al.,* 1983a, 1983b; O'Dell *et al.,* 1980; Kalimo *et al.,* 1983; Halprin *et al.,* 1981; Friedmann *et al.,* 1989; Sjovall *et al.,* 1985; Yoshikawa *et al.,* 1990; Vermeer *et al.,* 1991; Cooper *et al.,* 1992). Some of these studies are inconclusive because they used patients with skin diseases or recent UV-exposure, had insufficient subjects for statistical analyses, or used subjective assessments of CHS. Hence only 3 of these studies are discussed here.

Yoshikawa *et al.* (1990) exposed human buttock skin to 4 daily UV doses of 1440 J m^{-2} using a high pressure mercury vapour lamp (290-320 nm).Immediately after the last exposure, the irradiated site was sensitized with 2000 μg DNCB. The inner surface of the forearm was challenged 30 days later with 50 μg DNCB and CHS was assessed. In this study 40-45% of healthy irradiated adults failed to develop CHS. They designated these subjects UVB-S and suggested that, as in mice, susceptibility to UV is genetically controlled. Among biopsy proven skin cancer patients a much higher percentage (92%) of UV-exposed individuals failed to developed CHS. The UVB-S phenotype appeared to be a risk factor for the development of skin cancer. Suppression of CHS was also demonstrated in 50% of black-skinned individuals indicating that melanin does not protect against the deleterious effects of UVB on the development of CHS (Vermeer *et al.,* 1991). Attempts to resensitize healthy UVB-S individuals through normal skin following primary sensitization to DNCB through irradiated skin were generally successful; however, 50% of skin cancer patients failed to respond to resensitization attempts suggesting that these patients developed immunological tolerance similar to that demonstrated in experimental animal models (Yoshikawa *et al.,* 1990; Vermeer *et al.,* 1991).

Cooper *et al.* (1992) exposed human buttock skin (using FS lamps) to 0.75 or 2 MEDs of UVB (1 MED = 291 J m^{-2} to 325 J m^{-2} depending on the individual) for 4 days and sensitized with 30 μg DNCB through irradiated skin immediately after the last exposure. Subjects were challenged 3 weeks later with 4 serial 2-fold dilutions of DNCB, the highest of which was 12.5 μg. In addition, some subjects were exposed to 4 MED (moderate sunburn) and sensitized 3 days later with DNCB. Analysis of overall individual responses revealed decreased frequencies of fully successful immunizations in all UVB exposed groups. Increasing doses of UVB resulted in a linear decrease in immunological responsiveness to DNCB. Only 5% of individuals exposed to 2 MED had strong positive responses as opposed to 73% of unexposed individuals. The rate of immunologic tolerance to DNCB (lasting up to 4 months) in the groups

that were initially sensitized on skin receiving erythemagenic doses of UVB was 31% compared to 7% in controls. Similar results were observed with UVA (320-340 nm) exposure (Cooper, 1993). The differences in the Cooper and Yoshikawa studies may have to do with different sensitization and challenge regimens, and differences in methods used to quantitate the CHS response. Also, Cooper controlled for diminished levels of CHS that occur in menstruating women except during midcycle (Oberhelman *et al.,* 1992) by sensitizing all female subjects 14 days after the onset of menses.

Despite differences in the 2 studies it appears that unresponsiveness following the application of a contact sensitizer on UV-exposed skin can be induced in some parts of humans following exposure to moderate levels of UV and that some individuals become immunologically tolerant to the sensitizer in a manner reminiscent of animal studies. Cooper *et al.* (1992) also demonstrated modulation (although not clear-cut suppression) of contact sensitivity to diphenylcyclopropenone (DPCP) in subjects exposed to

4 MED and sensitized 3 days later through unirradiated skin. A
similar effect was not observed with the 2 MED exposure regimen,
either because the dose was lower or the sensitization was
immediately following the last exposure. Hence the systemic effects
observed in mice may also occur in humans, although currently the
experimental data to support such effects are minimal.

     As in the mouse, UV treatment of human skin resulted in altered
antigen presentation. UV caused depletion of Langerhans (CD1a+DR+)
cells followed by an influx of CD1a⁻ DR+ macrophages that
preferentially activate CD4+ cells (suppressor-inducer) which, in
turn, induce maturation of CD-8+ suppressor T lymphocytes and
deregulate lymphocyte activation (Baadsgaard et al., 1990; Cooper
 et al., 1986). Rasanen et al. (1989) reported a 70-80%
suppression in the ability of epidermal cells exposed to 2000 J
m⁻² UVB in vivo to present PPD or HSV to lymphocytes in vitro.
In these studies recovery was observed 3 and 7 days post exposure.
The UV wavelengths responsible for induction of CD1a-DR+ cells were
found to lie predominantly within the UVB band and to a lesser
extent in the UVC band; UVA was a poor inducer of these
non-Langerhans cell antigen presenting cells (Baadsgaard et al.,
1987,1989). Hersey et al. (1983b) reported an increase in CD8+ T
cells and a decrease in CD4+ T cells in subjects exposed for 1
hour/day for 12 days to natural sunlight and a suppressor T cell
activity which lasted in many subjects for up to 2 weeks. Filtration
of solarium radiation through mylar prevented these changes
suggesting effects were due to UVB (Hersey et al., 1988). Hence in
humans as in mice, UVB appears to act by altering antigen
presentation in ways that favours suppressor cells.

     Robinson & Rademaker (1992) studied 61 patients with two or
more BCC for occurrence of a further BCC. Patients were counselled
to avoid sun exposure, however there was a clear distinction between

those who reduced their sun exposure and those who did not. The
numbers of new BCC occurring after 36 months was determined by
regular examination of all patients. Plasma lymphocyte
subpopulations were measured at 0, 6, 12 and 18 months. At 36 months
an index of sun exposure was developed from questions on sun-related
behaviour before and after entry to the study. All 35 patients with
high sun exposure had low T helper to T suppressor cell (CD4/CD8)
ratios. The mean number of BCCs occurring during follow-up was 5.5
in those with high sun exposure and low CD4/CD8 ratios, 2.2 in those
with low sun exposure and low CD4/CD8 ratios and 1.1 in those with
low sun exposure and high CD4/CD8 ratios. The difference between the
first and the third groups was statistically significant. While
there is total confounding between high sun exposure and low CD4/CD8
ratios in this study it is consistent with the possibility that the
effect of sun exposure on risk of recurrent BCC was mediated by way
of its effect on cell-mediated immunity.

     UV from solaria suppressed natural killer(NK) cell activity in
the blood of subjects exposed for 1 hr/day for 12 days and tested 1
and 7 days after exposure. NK activity returned to normal 21 days
post exposure. Filtration of UV through mylar did not affect this
response; hence effects on NK activity were attributed to UVA
(Hersey et al., 1983a; Hersey et al., 1988).

9.2 Susceptibility to Tumours, Infectious and Autoimmune

Diseases

     As previously indicated Yoshikawa et al. (1990) found that
suppression of contact sensitivity following UV exposure was more
common among skin cancer patients than in healthy subjects. In their
study only skin cancer patients developed an immunological
tolerance. They suggested that individuals who were phenotypically
sensitive to the immunosuppressive effects of UV were at greater
risk of skin cancer.

     Adverse effects of UV on 4 types of human infections have been
reported. Smallpox lesions were made larger by exposure to sunlight
(Finsen 1901). Lesions from Herpes Simplex Virus(HSV) types I and II
were reactivated by exposure to UV (Spruance, 1985; Klein, 1986).
Using the criteria established by Yoshikawa et al. (1990) for the
UVB-S phenotype, Taylor et al. (1993) reported that 66% of
individuals who had a strong history of HSV lip lesions provoked by
sun exposure were UVB-S as compared to 40-45% in the general
population and 92% in skin cancer patients (Yoshikawa et al.,
1990). Also, exposure of immunosuppressed patients to sunlight led
to an increased incidence of viral warts caused by papilloma virus,
presumably due to UVB exposure (Boyle et al., 1984; Dyall-Smith &
Varigos, 1985). Hence there is some indication that UV may
exacerbate certain infections in humans.

     Recent attention has been paid to the effects of UV on immune
response in patients with human immune deficiency virus (HIV)
because UV has been shown to activate HIV in vitro (reviewed by
Zmudzka & Beer, 1990). It has been suggested that UV exposure could
progress these patients to full blown AIDS by interfering with
protective immunity, since Th1 responses appear to be protective
against AIDS whereas Th2 responses are not (Shearer & Clerici,
1992). However, Warfel et al. (1993) found no difference in CD4+
cell counts in HIV patients before and after treatment with 50-60%
of their MED for dermatological disease. More research in this area
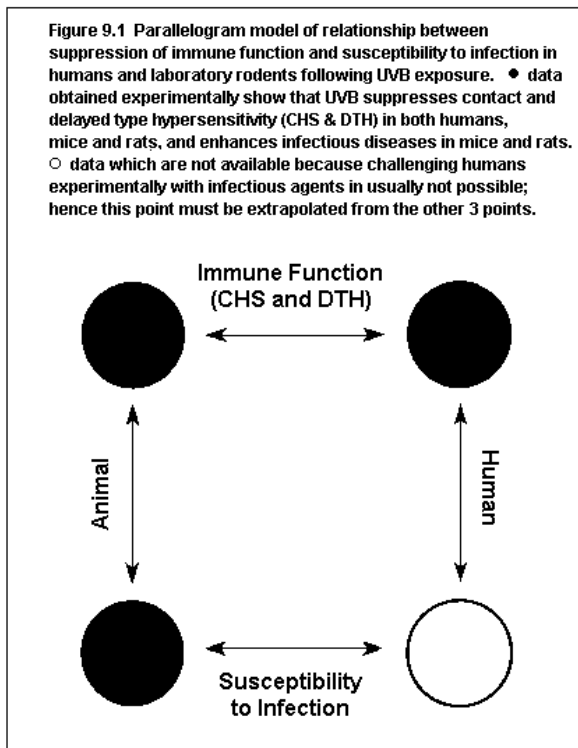is needed to resolve these issues.

     Finally, it has been known for some time that UV exposure
adversely affects the clinical course of systemic lupus

erythematosus, an autoimmune disease (Epstein *et al.,* 1965); however, the relationship of UV in this immune response is unclear.

9.3 Conclusions

The above studies suggest that UV exposures at environmental levels suppress immune responses in both rodents and man. In rodents this immune suppression results in enhanced susceptibility to certain infections with skin involvement as well as some systemic infections. The mechanisms associated with UV-induced immunosuppression in rodents and man are similar. Also, host defense mechanisms which provide protection against infectious agents are similar in rodents and man as shown in figure 9.1. It is therefore reasonable to assume that exposure to UV may enhance the risk of infection and decrease the effectiveness of vaccines in humans.

Additional research is needed to substantiate these assumptions. In particular, experimental studies are needed in rodents and man to access effects on immune function parameters in a fashion that allows quantitative comparisons between the two species. Results of experiments on rodents showing the effects of UV exposure on the susceptibility to various infections could be used to extrapolate the risk of infectious disease in humans. Ultimately epidemiological studies on the effects of UV exposure on susceptibility to infection and vaccine effectiveness are needed to validate this hypothesis.

Figure 9.1 Parallelogram model of relationship between suppression of immune function and susceptibility to infection in humans and laboratory rodents following UVB exposure. ● data obtained experimentally show that UVB suppresses contact and delayed type hypersensitivity (CHS & DTH) in both humans, mice and rats, and enhances infectious diseases in mice and rats. ○ data which are not available because challenging humans experimentally with infectious agents in usually not possible; hence this point must be extrapolated from the other 3 points.

10. HUMAN STUDIES: THE EYE

10.1 Introduction

Since the early part of this century ophthalmologists have suggested an association between sunlight exposure and UV and the development of cataracts and other ocular effects (Widmark 1889, 1901; Hess 1907; Martin 1912; Birch-Hirschfeld, 1914; Verhoeff and Bell, 1916; Duke-Elder, 1926b); however, only in the past twenty years have epidemiological studies provided a scientific link. UV is probably one of a number of factors associated with the development of cataract. Despite the number of animal and human studies, many questions remain as to the validity of interpretations of past data and the biological and physical factors that influence the outcome of UV exposure of the eye.

10.2 The Eye

The eyeball is deeply set in a bony orbital cavity, and the upper bony ridge provides not only protection from mechanical injury but also serves as a shield from overhead sky light. The upper and lower eyelids (figure 10.1) also provide considerable protection by serving as " *shutters*" against bright light. The eyeball consists of three layers of tissue: (a) an outer protective layer, the sclera and cornea; (b) a middle layer of blood vessels, pigment cells and muscle fibres called the uvea; and (c) an inner, light sensitive layer called the retina.

The sclera, the outer posterior layer, is a tough, thick, opaque tissue formed of collagen fibres. The cornea, the anterior transparent part of the eyeball, consists of multiple layers. The surface epithelium continues with the surface epithelium of the conjunctiva. The epithelial cells are known to be constantly

changing and the basal layer overlies the Bowman layer. The
outermost epithelial cells undergo rapid turnover, having a lifetime
at the surface of approximately 48 hours.

The main bulk of the cornea, the stroma, consists of highly
organized collagen fibres in a pattern that makes the cornea
transparent. The innermost layer, the endothelium, is a single layer
of an active ion pump (Na-K) that maintains the hydration state of
the stroma, an important factor for corneal transparency.

The middle layer of the eyeball consists of the iris
anteriorly, the ciliary body, and the choroid. The iris is a
diaphragm that adapts by changing the pupillary size according to
ambient light level. The iris is formed of mainly pigmented cells of
various densities, blood vessels and smooth muscle fibres that are
attached to the anterior part of the ciliary body. The smooth muscle
fibres form the sphincter and dilator of the pupil.

Figure 10.1 Schematic of the human eye
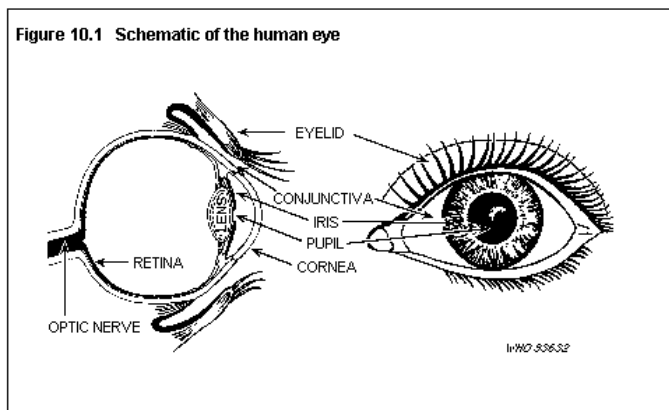
As part of the middle layer lining the sclera, the choroid
consists of a meshwork of blood vessels, nerves and pigment cells
that contribute to the nutrition of the retina and support the
function of the innermost layer, the retina, that contains the
photoreceptors and the neuronal network.

The lens, embryologically of ectodermal (skin) in origin,
consists of closely and orderly packed transparent elongated lens
cells that are enclosed in a capsule. New lens cells are constantly
formed at the so-called lens equator and old ones are displaced
towards the centre of the lens. The lens is suspended to the ciliary
body by fine ligaments. The lens shape can be changed by contraction
or relaxation of the ciliary muscles. This change provides a
focusing power to the eye that is called accommodation and is made
possible by the elasticity of the young lens. The lens is avascular
and obtains its nutrient from the aqueous fluid in front of it and
the vitreous body that fills the posterior cavity behind it.
Notably, the lens proteins cannot be renewed and therefore
accumulate lesions inflicted on them throughout life.

The photoreceptors, the rods and cones of the retina,
constitute the primary light receptor with rods functioning at low
light levels (scotopic vision) and cones operating at high light
levels (photopic vision). Thus the rod system subserves the function
of retinal sensitivity, whereas cones provide colour vision, high
resolution visual acuity and motion perception. The retinal pigment
epithelium is essential for the maintenance of photoreceptor
metabolism including, the transport, storage and regeneration of the
visual pigments.

Visible light (400-760 nm) incident upon the eye is strongly
refracted at the cornea, then transmitted through the aqueous humour
in the anterior chamber to the lens where it is refracted further.
After transmission through the vitreous gel-like structure, it
finally reaches the light-sensitive receptors in the retina. It is
these structures that are primarily damaged by UV and visible
radiations. The neuronal layers perform the complex task of
information processing. The primary visual signal is transformed and
ultimately transmitted to the visual cortex in the brain, thus
providing the image seen by the eye.

Most of the UV incident on the eye is absorbed in the tear
film, the cornea and the lens. The lens and the tissues in the
anterior part of the eye may however, be exposed to UV at
wavelengths above 295 nm and the retina is exposed to a fraction of
the incident UVA. Absorption of UV in the ocular media is given in
Fig 10.2 (Sliney & Wolbarsht, 1980). Boettner & Wolter (1962)
measured the transmission of direct forward scattering UV in the
cornea, aqueous humour, lens and vitreous humour from freshly
enucleated normal human eyes. The cornea absorbed all UV with
wavelengths <300 nm, while above 300 nm some UV was transmitted

through the cornea. About 60% of UV at 320 nm and 80% at 380 nm was
transmitted through the cornea. The aqueous humour transmitted most
incident UV (90% transmission at 400 nm) with no evidence of
scattering.

Recently Barker and Brainard (1993) quantified the change in UV
transmittance of the human lens with age. All of these studies
clearly show the steady decrease in UV transmittance of the lens

age. At birth there is a small window of transmission to the retina
at 320 nm. This window almost disappears by the second decade due to
an age-related yellowing of the human lens. As shown in Fig 10.3 the
lens absorption is strongest in the 340-380 nm band with somewhat
less absorption in the 310-320 nm range (Rosen, 1986; Barker and
Brainard 1993). The human lens is unique in that it contains a UVA
absorbing filter (O-beta of 3-hydroxykynurenine) which protects the
retina.

10.3 Study Design

This chapter reviews the epidemiological evidence for a causal
association between exposure to UV and development of specific eye
diseases which have at some point been linked with exposure to UV.
Two distinctive types of UV exposure assessments have been used in
the epidemiological studies. Some studies have related the
occurrence of eye disease to non-personal factors associated with
place of residence, such as meteorological data on average annual UV
dose or average annual hours of sunlight. Other studies have
obtained estimates of exposure at the individual level (e.g. hours
of sunshine exposure, lifetime exposure to UV) and related these to
disease occurrence.

Three types of epidemiological studies have been used to
investigate an association with UV exposure: geographical
correlation studies, cross-sectional studies, and case-control
studies. In the geographical correlation studies the prevalence of
eye disease in different areas has been related to non-personal
factors associated with place of residence. These studies are useful
for generating hypotheses but of limited value in testing a
particular hypothesis because observed correlations may result from
confounding by other factors which also vary geographically, and
because the level of exposure for persons with the disease is not
known.

Figure 10.2 Schematic of absorption of UV in the ocular media. Values represent the percent of UV incident upon the corneal surface that are absorbed by various layers. From Sliney & Wolbarscht (1980), based on data from Boettner & Wolter (1962)
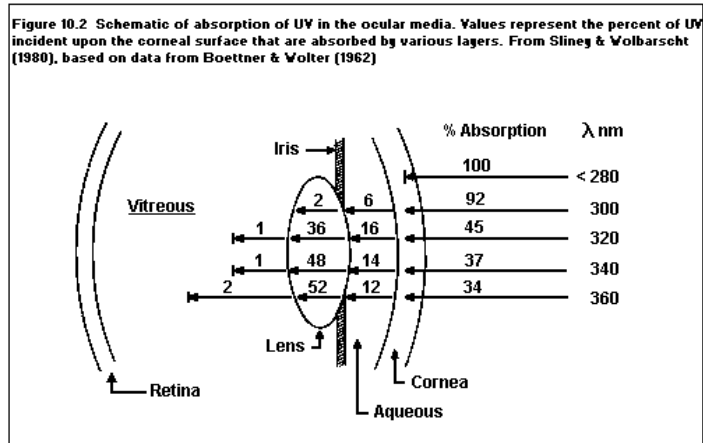
Figure 10.3 Special transmission of the human lens as a function of age (adapted from Barker & Brainard, 1993)
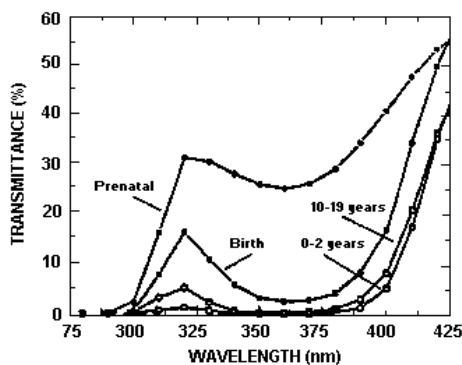
The second, and most common type of study design, has been the
cross-sectional study in which a population or occupational group is
surveyed and disease prevalence measured. Cross-sectional surveys
identify all persons with the disease, some of which are new cases
while other persons may have had the disease for a period of time.
Some cross-sectional studies have related non-personal factors
associated with place of residence to disease status. Other studies
have collected detailed information from each study participant on
personal exposure to UV or indices of exposure (e.g. hours of
exposure to sunshine, occupation) and related these exposures to
disease status.

The third type of study design has been the case-control study,
where differences in UV exposure between persons with the disease
and those without have been compared. Cases have usually been drawn
from a hospital or clinic. Controls have been drawn from other
hospital or clinic patients or from the general population and have
usually only included persons with good visual acuity, without the

disease of interest, and without a disease that is associated with
UV exposure. Some case-control studies have related disease status
to non-personal factors associated with place of residence while
others have used personal exposure information.

Data from both cross-sectional and case-control studies can be
useful in confirming a hypothesis, but have a number of limitations.
If there is an excess risk of death associated with the disease, as
has been suggested for cataract (Minassian *et al.,* 1992; Vitale
et al., 1992), both types of study will be biased towards the
survivors. In addition, disease status and prior exposure indices
are measured at the same time and it may not be possible to
differentiate between cause and effect, especially if the disease
has a long latency period.

10.4 Diseases of the External Eye

10.4.1 Photokeratitis and photoconjunctivitis

Cases of photokeratitis and photoconjunctivitis have occurred
between 0.5 and 24 hours after prolonged exposure to intense solar
radiation, often in highly reflective environments (Wittenberg,
1986). The most severe cases are usually manifested as snow
blindness, suggesting that UV is the cause of this condition.

The action spectrum for UV photokeratitis produced in the
rabbit was first measured by Cogan and Kinsey (1946). Pitts (1974,
1978) in a series of laboratory studies on humans estimated the mean
threshold of UVB (290-315 nm) for photokeratitis at 3500 J m^{-2}.
These laboratory data are supported by Blumthaler *et al.* (1987),
who estimated that the radiant exposures in clinically observed
cases of photokeratitis ranged from 1200 to 5600 J m^{-2}. It is
estimated that 100 to 200 seconds of direct, unattenuated exposure

to 295-315 nm solar radiation will result in photokeratitis (Sliney,
1987; Wittenberg, 1986). Blotting out the solar disc would remove
around 40% of the UV, still leaving a threshold of around 5.5
minutes. Sliney (1986) has estimated that the reflected levels of UV
from light sand should be sufficient to cause a threshold
photokeratitis within exposure periods of 6-8 hours centred around
midday, and within 1 hour for UV reflected from snow.

Experimental data shows photokeratitis can be induced in
animals by UVB exposure and that use of UVB absorbing contact lens
or chromophores can prevent UVB induced photokeratitis in laboratory
animals. Collectively, there is sufficient experimental and
epidemiological evidence that exposure to intense UVB radiation
causes photokeratitis and photoconjunctivitis.

10.4.2 Climatic droplet keratopathy

Climatic droplet keratopathy, among a variety of other names
(Gray *et al.,* 1992), is also known as spheroidal degeneration from
its histological appearance. It is a degenerative condition usually
affecting both eyes symmetrically, and restricted to the exposed
interpalpebral band of the cornea. This condition is of major
significance for vision in some parts of the world, reducing vision
to blindness levels in older people. For example, in Mongolia it has
been found in an initial survey to be the third cause of blindness
(Baasanhu *et al.,* in press).

Climatic droplet keratopathy occurs throughout the world, but
is more common in areas with snowfall persisting late into the
summer in the northern hemisphere, such as parts of northern Canada,
Siberia and Mongolia, and in areas of sand and desert in other
latitudes, including Somalia, the Arabian peninsula, Iran, and
Australia. It is also particularly common on sea coasts where there
is coral sand or the sand is impregnated with salt, such as the
islands of the Red Sea (Gray el al., 1992).

In a cross-sectional study of Australian aborigines Taylor
(1980a) found no correlation between the prevalence of climatic
droplet keratopathy and ambient UVB levels, although the condition
was more common among those working as stockmen. Johnson (1981)
reported a geographical correlation with the calculated flux of
reflected UV from snow and ice throughout the year in the eastern
coast of Newfoundland and Labrador and the eastern Arctic of Canada.

In a cross-sectional study of Chesapeake Bay waterman study
Taylor *et al.* (1989) examined the risk of climatic droplet
keratopathy with chronic UVB exposure. Although a positive
association was found (RR= 6.4, 95%CI=2.5-11.7) for those in the
highest quarter of exposure compared to those with the bottom
quarter, further analyses of this data (Taylor *et al.,* 1992)

showed the risk of climatic droplet keratopathy was also related to
UVA.

There is strong evidence that the corneal degeneration is due
to environmental factors. Circumstantial evidence exists that it is
caused by solar UV, mainly reflected from ground surfaces such as
snow and sand which are particularly reflective of UV.
Histologically, the material deposited in the superficial corneal
stroma as spheroidal droplets is most likely to be derived from a
mixture of altered plasma proteins, including fibrinogen, albumin,
and immunoglobulins (Johnson & Overall, 1978).

Other proposed aetiological agents such as low atmospheric
humidity, low temperature or high temperature have been excluded. It

is possible that particulate injury by wind-blown ice or snow or
sand particles may contribute to the development of the condition by
causing inflammation and therefore outpouring of additional plasma
proteins from the blood vessels of the limbs.

10.4.3 Pinguecula

Pinguecula is a fibro-fatty degeneration of the interpalpebral
conjunctiva. The pathological changes that occur in pinguecula are
similar to actinic elastosis of the skin, a condition thought to be
linked to sunlight exposure. This indirect evidence suggests that
exposure to sunlight may be a risk factor for pinguecula.

Geographical variation in the occurrence of pinguecula has been
reported, with higher prevalence in Arabs living near the Red Sea
than in Eskimos from Greenland or Caucasians in Copenhagen (Norn,
1982). Johnson et al. (1981) in a study of pinguecula in Labrador
found the size of pinguecula was correlated with the severity of
climatic droplet keratopathy. Taylor et al. (1989) in the study of
Chesapeake Bay watermen found a weak association for the presence or
absence of pinguecula with exposure to UVA and UVB. The relative
risk for the top quartile of exposure was 1.4 (95%CI=0.9-2.2), less
than for climatic droplet keratopathy or pterygium. Karai &
Horiguchi (1984) in a study of 191 Japanese welders found no
difference in the occurrence of pinguecula between welders and
controls.

It is concluded that there is currently insufficient
epidemiological or experimental data for an assessment of the risk
of pinguecula with exposure to UV.

10.4.4 Pterygium

Pterygium is a triangular shaped degeneration and hyperplastic
process in which the bulbar conjunctiva encroaches on the cornea.

A geographical association between variation in the occurrence
of pterygium and variation in sunlight exposure was first suggested
by Talbot (1948). Based on observation of pterygium in New Zealand
and South Pacific Islands Elliott (1961) suggested pterygium in
these locations resulted from UV exposure.

Studies of non-personal factors associated with place of
residence

In a study of pterygium patients in US Veterans Administration
hospitals during 1957-59 Darrell & Bachrach (1963) related mean
daily UV (319nm) levels to the ratio of pterygium to all hospital
discharges. A trend was found between UV level and pterygium ratio
for persons born in rural counties. A similar association with UV
level was seen for persons residing in a rural county at the time of
the hospital discharge. Cameron (1965) examined the global pattern
of pterygium and reported an inverse gradient with latitude. In a
study of Australian aborigines Taylor (1980a) found pterygium was
correlated with ambient UVB level and hours of sunshine at place of
residence. Data from Canada indicates that pterygium is also common
in arctic and sub-arctic environments (Johnson et al., 1981).
Moran & Hollows (1984) found a nonsignificant increase in the
prevalence of pterygium among Australian aborigines residing in
areas with higher ambient UV levels.

Studies with personal exposure measurements

Four studies have related occurrence of pterygium to personal
measurements. Karai & Horiguchi (1984) examined 191 Japanese welders
for the presence of pterygium. A trend of increasing risk of
pterygium was found with years of employment as a welder, an
indirect measure of cumulative occupational exposure to UV.

Booth (1985) undertook a hospital-base case-control study of
pterygium in Sydney. No difference between cases and controls was
found in subjective assessment of exposure to sunlight in work or
sport. However, a family history of pterygium was found to be a
strong risk factor.

Among Chesapeake Bay watermen, Taylor et al. (1989) found a
dose-response relationship between risk of pterygium and exposure to
UVA and UVB. The relative risk for the top quarter of UVB exposure
was 3.1 (95%CI=1.8-5.3) compared to the lowest quarter. However, it
is noted that pterygium was equally associated with ocular exposure
to UVA and visible light.

Mackenzie et al. (1992) undertook a hospital-based
case-control study of pterygium in Queensland. A strong
dose-response relationship was found with closeness of place of
residence to the equator, type of outdoor work environment (e.g.
sandy) and amount of time spend outdoors. The most striking finding

was the magnitude of risk associated with spending most of the time
outdoors was stronger when related to childhood exposure (RR=17.2,
95%CI=6.2-47.6) than to adult exposure (RR=5.7, 95%CI=3.1-10.6). The
risk associated with working at ages 20-29 in an outdoors
environment of mainly sand or concrete was associated with a
relative risk of 11.3 compared with indoor workers. Corneo (1993)
has suggested that the cornea is acting as a side on lens focusing
light and also UV across the anterior chamber to the nasal limbus.
This hypothesis may explain why pterygia usually commence on the
nasal side of the eye.

Evaluation of epidemiological evidence

While several geographical studies have reported an inverse trend with latitude, the common occurrence of pterygium in arctic and subarctic locations suggest that closeness to the equator does not fully explain the distribution of this disease.

The strength of the association with time spent outdoors reported by Mackenzie *et al.* (1992) suggests that the association may be causal. However, there is insufficient evidence to show that the observed association with UV exposure is not, in part, due to confounding. The findings from three of the studies lend support to a hypothesis that irritation by particulate matter is associated with pterygium. The Australian aborigines live in a dry, dusty environment and welders are occupationally exposed to a range of particles. Similarly, the Queensland study found highest risk among those who worked in sandy locations. The particulate matter hypothesis is also supported by a report (Dhir *et al.,* 1967) of higher prevalence of pterygium among Punjabi Indians working in sawmills (an indoor occupation) in New Delhi and British Columbia than Punjabi farmers (an outdoor occupation). Similar findings of increased risk of pterygium among sawmill workers in Thailand and Taiwan have been reported (Detels & Dhir, 1967). The evidence of possible confounding by particulate matter is inconsistent, with the Chesapeake Bay watermen study finding an association with sunlight exposure in a location that was neither hot, dry or dusty.

It is not possible, based on available epidemiological data, to assess the risk of pterygium with exposure to UV because of possible confounding of observed associations by exposure to particulate matter or other factors.

10.4.5 Hyperkeratosis, carcinoma-in-situ, and squamous cell
        carcinoma of the conjunctiva

These conditions probably form a gradation of development and cannot necessarily be distinguished clinically. Invasive squamous cell carcinoma is often said to arise from a pre-cancerous lesion. Epithelial dysplasia and carcinoma-in-situ look the same, and are sometimes keratinized and present as leucoplakia in which case the

term actinic keratosis may be applied (Naumann & Apple, 1986; Garner, 1989). The main argument for an actinic causation is that these tumours usually present in the exposed area of the eye between the lids (the interpalpebral fissure) and under conditions where they may be expected to be exposed to solar radiation.

Xeroderma pigmentosum is a recessively inherited syndrome characterized by clinical and cellular hypersensitivity to solar radiation and a defect in the capacity to repair UV-induced damage in DNA (Fitzpatrick, *et al.,* 1963). Among reports of 337 patients with xeroderma pigmentosum for whom ocular findings had been described, Kraemer *et al.* (1987) identified 88 ocular tumours of which 73 were specific to the corneal-scleral limbus (34), the cornea (24) or the conjunctiva (15). Of the non- melanomas for which histopathological type was specified, 28 were squamous cell carcinomas and 12 were basal cell carcinomas. Among 64 patients with ocular neoplasms whose age was stated, half the neoplasms had occurred before 11 years of age. While the eyelids are a site of preference for basal cell carcinoma, this tumour rarely, if ever, arises in the conjunctiva in otherwise normal individuals.

Squamous cell carcinoma of the conjunctiva is an uncommon tumour. Garner (1989) reviewed all cases of tumours at the limbus sent over a 40 year period for examination to the Institute of Ophthalmology, London. The total was only 636 tumours, of which 73 were squamous carcinomas. This amounts to less than 2 cases per year coming to the Pathology Laboratory, even though Moorfields Eye Hospital which the Laboratory serves, attracts patients from all over the country and from overseas.

Lee & Hirst (1992) attempted to provide population-based figures and estimate the incidence of these tumours in metropolitan Brisbane (latitude 30° south). They surveyed the histological records of all ocular surface tumours examined in the pathological laboratories over the previous 10 years, serving a population of more than 745,000 in 1989. There were 139 cases of which 79 were corneal epithelial dysplasia, 28 carcinomas-in-situ and 32 were squamous cell carcinomas. There was a strong male preponderance. The incidence ranged from 1 per 100,000 in 1980 to 2.8 per 100,000 in 1982. This is well below the rate for squamous cell carcinoma of the skin and melanoma of the skin in Queensland as a whole. On the other hand, it is a substantially higher rate than that recorded in London where the pathological laboratory referred to also covers a much larger population.

Squamous cell carcinoma of the conjunctiva has been reported to form a greater proportion of eye tumours in Africans living in areas close to the equator (Templeton, 1967) than in the south of Africa (Higginson & Oettlé, 1959), and much higher than in Baltimore (39°N). The incidence (0.3 per 100,000) in Uganda (0°) has been

reported to be twice that in Denmark (55°N) despite the potential underascertainment in Africa (Templeton, 1967).

It is extremely rare for a neoplasm to arise *de novo* in the corneal epithelium, where it may be called a corneal intra-epithelial neoplasm. Most such intra-epithelial sheets are connected at the corneo-scleral limbus to a conjunctival lesion, such as a papilloma or a leucoplakia over a pterygium or pinguecula (Waring *et al.,* 1984). The only available evidence for an UV aetiology is

the location of the lesion within the interpalpebral fissure, and
the fact that it may arise from a lesion which is itself associated
with UV. Three cases of corneal intra-epithelial neoplasia have been
recently reported in people aged 31 to 38 who wore contact lenses
and were considered to have had substantial exposure to artificial
and solar UV (Guex-Crosier & Herbort, 1993).

10.5 Diseases of the Lens

10.5.1 Cataract

     For the purpose of this review, a cataract is defined as an
opacity of the lens of the eye. The three major types of cataract
are cortical, nuclear and posterior subcapsular (PSC). When a lens
opacity interferes with vision, a clinically significant cataract is
present. If left untreated, cataract will often progress to
blindness. Cataract causes half of the world's blindness.

     Definitions of cataract and methods used to assess the presence
and severity of cataract have not been uniform in epidemiological
studies of cataract. Many studies include lens opacities that are
not necessarily accompanied by a decrease in visual acuity. Some
have combined all three major types of lens opacities into a single
"cataract" category, while others have investigated associations for
specific types of opacity. Methods of assessing the presence and
sometimes the severity of opacities range from reviews of existing
charts to clinical examinations using written definitions of
cataract, and the use of standardized grading systems that have been
found to be highly reliable.

     Occupational case series

     When cataracts result from occupational exposure to UV, it may
be difficult to differentiate between the contribution of
occupational and non-occupational factors to the development of the
disease. Lerman (1980) described the onset of lens opacities in
three persons who worked in a dental clinic and were exposed to UV
(300-400 nm) from a dental curing unit. The lens damage varied from
posterior subcapsular cataract in the dentist, who was reported to
have received the highest dose, to zonular type opacities in one of
the dental assistants. However, any retrospective reconstruction of

the actual ocular exposure has a large degree of uncertainty, and
the results from such an exercise must be interpreted with caution.

     Studies in which UV exposure was inferred from place of residence

     Selected studies of humans exposed to solar UV are presented in
tables 10.1 and 10.2. Studies were selected for inclusion in the
tables on the basis of the scientific quality of the published
report and the overall contribution of the paper to the evaluation
of the UV-cataract hypothesis. The tables do not include the
relative risks for other factors, which in some instances are higher
than for sunlight or UV exposure.

     Hiller et al. (1977) investigated sunlight and cataracts
using data from the large sources (blindness registries in 14 states
and the cross-sectional Health and Nutrition Examination Survey
(HANES) of 35 geographic areas of the US) and US Weather Bureau
geographical data on annual hours of sunlight in each geographical
area. Above the age of 65 the prevalence of cataract increased with
annual hours of sunlight, with the highest prevalence found in
locations with 3000+ annual hours of sunshine. At ages 45-64 there
was some evidence of an association with hours of sunshine but the
gradient was weaker. Below age 45 there was little association
between annual hours of sunshine and prevalence of cataract. In a
further analysis of HANES data Hiller et al. (1983) reported a
correlation between average daily UVB levels and prevalence of
cataract. Analysis of HANES data by type of cataract (Hiller et
 al., 1986) revealed UVB levels at location of residence were
associated with pure cortical cataract but not with pure nuclear or
posterior subcapsular cataract.

     The prevalence of cataract among Australian aborigines was
found to be correlated with annual ambient UVB level at place of
residence (Taylor et al., 1980b). Hollows & Moran (1981) found the
prevalence of cataract was highest among aborigines living in the
north of Australia, an area with high average daily UVB radiation.
Mao & Hu (1982) studied age related cataract in seven rural areas of
China and found the prevalence of cataract was correlated with
annual direct solar radiation.

     Residents of rural villages in Nepal had a prevalence of
cataract related in different zones of the country to average hours
of sunshine (Brilliant et al., 1983). The prevalence was higher in
the plains where there were 12 hours of direct sunshine compared to
the mountains with 7-9 hours per day. Factors such as use of glasses
and hats modify personal ocular exposure to UV and should be
assessed.

TABLE 10.1 SELECTED HUMAN CATARACT STUDIES WITH SUNLIGHT OR UV EXPOSURE BASED ON RESIDENCE

AUTHOR	POPULATION	MEASURE OF OUTCOME	MEASURE OF SUNLIGHT EXPOSURE	ASSOCIATIONS OBSERVED	COMMENTS
Hiller et al. (1977, 1983,	MRA: 9110 persons registered as blind	Blind from cataract, visual acuity (VA)	Average hours of sunlight ≤ 2400 vs	RR= 3.3 (age 65-74)	Adjusted for age and sex; blind registry data

1986)	in 14 US States; whites;	6/60	3000+		
	NHANES: 3580 persons; probability sample of US population;	Lens opacity and VA $\leq$ 6/7.5	Average hours of sunlight $\leq$ 2400 vs 3000+	RR= 2.7 (age 65.74)	Adjusted for age and sex
	NHANES data	Lens opacity and VA $\leq$ 6/9	Average daily UVB count in area of residency 6000 vs 2600	RR= 1.58 (age 45-74, p<.05)	Adjusted analysis
	NHANES data	Nuclear and cortical opacity	Average daily UVB count in area of residency 6000 vs 2600	RR= 3.6 for cortical opacity; no association with nuclear opacity	Adjusted analyses; pure opacity types only
Taylor (1980b)	Survey of 350 Australian Aborigines	Lens opacity with good vision, poor vision or blindness	Average daily sunlight hours in area of residence: 9.5+ vs $\leq$ 8	RR= 4.2 (95% CI=0.9-18.9[1]	Unadjusted for age or potential confounding factors
			Annual mean UVB radiation level for area of residence: 3000 vs 2000	RR= 1.8 (95%ci=0.9-3.4)[1] [1] 95%CI estimated from published data	
Hollows & Moran (1981)	Survey of 64,307 Aborigines and 41,254 non-Aborigines, Australia	Lens opacity and VA < 6/6	Average daily UVB count in 5 zones of Australia: 3000 vs 1000	Significant positive correlation between prevalence of lens opacity and UVB counts in Aborigines; no association in non-Aborigines	Wide age bands; unadjusted analyses

TABLE 10.1 (contd).

AUTHOR	POPULATION	MEASURE OF OUTCOME	MEASURE OF SUNLIGHT EXPOSURE	ASSOCIATIONS OBSERVED	COMMENTS
Brilliant et al. (1983)	Survey of 27,785 Nepalese; national probability sample; lifelong residents;	Lens opacities or aphakia	Average daily sunlight hours: 12 vs 712 vs 7-9	RR= 3.8 (p<.001)	Adjusted for age and sex; RR decreased with increasing altitude; sun blocked by mountains at high elevations
			12 vs 712 vs 7-9	RR= 2.6 (p<.005)	
Cruickshanks et al. (1993)	Cross-sectional survey of 4926 persons, Wisconsin, USA	Nuclear, cortical and PSC opacities	Average annual ambient UVB exposure	UVB exposure associated with cortical opacities in men (RR=1.36, 95%CI=1.02-1.79) but not women, not associated with nuclear or PSC opacities	Adjusted for other risk factors; measure of exposure represents average potential exposure at residency; also Table 9.2

TABLE 10.2 SELECTED HUMAN CATARACT STUDIES WITH INDIVIDUAL UV EXPOSURE ASSESSMENT

AUTHOR	POPULATION	MEASURE OF OUTCOME	MEASURE OF SUNLIGHT EXPOSURE	ASSOCIATIONS OBSERVED	COMMENTS
Collmann et al. (1988)	Clinic-based case control study of 113 cases and 168 controls, North Carolina, USA; whites	Nuclear, cortical and PSC opacities	Average annual sunlight exposure, based on residential history and amount of time spent in sun	No significant association with any type of opacity	Low power to detect association; matched on age and sex
Taylor et al. (1988)	Cross-sectional survey of 838 watermen, Maryland, USA	Nuclear and cortical opacities	Cumulative ocular exposure to UV since age 16, based on life history and ocular exposure model	Dose-response relationship in which a doubling of cumulative UVR exposure increased risk of cortical opacity by 1.60 (95%CI=1.01-2.64). RR= 3.30 (95%CI=0.90-9.97) for highest vs lowest quartile. No association between ocular exposure to UVR and nuclear opacity	High exposure study population; detailed ocular exposure model
Bochow et al. (1989)	Clinic-based case-control study of 168 cases and 168 controls, Maryland, USA	PSC cataract (surgical patients)	Cumulative ocular exposure since age 16, based on life history and exposure model	Increased levels of UVB exposure associated with increased risk of PSC cataract	Adjusted analyses; association present when adjusted for cortical cataract
Dolezal et al. (1989)	Clinic-based case-control study of 160 cases and 160 controls, Iowa, USA	Cataract (scheduled for surgery)	Lifetime sunlight exposure, based on life history, amount of time in sun and use of glasses and hat	No association between lifetime sunlight exposure and risk of cataract; use of head covering reduced risk of cataract in males (RR=0.48, 95%CI=0.25-0.94)	Only partially adjusted for potential confounding factors; crude index of exposure, low power

TABLE 10.2 (contd).

AUTHOR	POPULATION	MEASURE OF OUTCOME	MEASURE OF SUNLIGHT EXPOSURE	ASSOCIATIONS OBSERVED	COMMENTS
Italian-Am. study (1991)	Clinical-based case-control study of	Nuclear, cortical, PSC and	Work location in the sunlight; leisure time in	Cortical and mixed opacities associated with work location in	Adjusted for other risk factors;

	1008 cases and 469 controls, Italy	mixed opacities	the sunlight; use of glasses and hat	sunlight (RR=1.75, 95%CI=1.15-2.65), leisure time in sunlight (RR=1.45, 95%CI=1.09-1.93). Cortical, PSC and mixed opacities associated with use of a hat in summer (RR=1.80, 95%CI=1.17-2.47). No association between sun exposure indices and nuclear opacities	crude indices of exposure; also Table 9.1
Leske et al. (1991)	Clinical-based case-control study of 945 cases and 435 controls, Massachusetts, USA	Nuclear, cortical and PSC mixed opacities	Work in sunlight; leisure time in sun; residence and travel to areas of high sun exposure, use of hat and sunglasses	Work in sunlight significantly reduced risk of nuclear opacity (RR=0.61, 95%CI=0.37-0.99); no significant associations between exposure and cortical or PSC opacities	Analyses adjusted for other risk factor
Cruikshanks et al. (1993)	Cross-sectional survey of 4926 persons, Wisconsin, USA	Nuclear, cortical and PSC opacities	Leisure and work time outside; use of glasses and hat	No associations with cortical opacities; reduced risk of nuclear and PSC opacities amount men for outdoor leisure time in winter; use of hats and sunglasses significantly increased risk of PSC opacity in women	Adjusted for other factors; crude indices of exposure; also Table 9.1

Age and sex adjusted prevalence for all types of cataract in persons aged 40 years and older was found to be 60% greater in Tibet than in Beijing (14.6% versus 9.1%, p>0.001) (Hu *et al.,* 1989). The authors suggested a relationship with higher UV at the higher altitudes of Tibet, but confounding factors could not be excluded and prevalences were higher in women than men.

Studies with personal exposure measurements

A number of studies have collected information from each study participant and estimated personal exposure to either sunlight or UV. Factors such as use of glasses and hats should be assessed. The characteristics of selected studies are outlined in Table 10.2.

In a cross-sectional study of cataract in the Punjab related prevalence of cataract to work environment Chatterjee *et al.* (1982) found a suggestion of lower cataract incidence among men whose main work location was outdoors (RR=0.7, 95%CI=0.5-1.1).

Collman *et al.* (1988) examined lifetime exposure to sunlight in a clinic-based case-control study of cortical, nuclear or PSC. Lifetime exposure to sunlight was estimated from intensity of solar radiation in area of residence, years of residence and average amount of time spent outdoors during daylight hours. A non-significant risk (RR=1.1) of cataract was found for the highest category of lifetime exposure to sunlight.

Personal exposure history and ambient UVB data were combined to estimate an individual's lifetime annual ocular exposure to UVB after age 15 in a cross-sectional study of Chesapeake Bay watermen (Taylor *et al.,* 1988). This included information on occupational and leisure exposures, type of work surfaces, seasons, and use of head wear and eyewear. A moderate association with a trend of increasing risk with exposure to UVB was seen for cortical cataract, with a RR of 3.3 (95%CI=0.9-10.0) for the top quarter of exposure relative to the bottom quarter. A nonsignificant association was also found between exposure to UVA (320 -340 nm) and prevalence of cortical cataract. Little evidence was found for an association between UVA or UVB exposure and nuclear cataract. It is noted that UVA and UVB exposures were highly correlated and that the study would not have been able to differentiate between the effects of UVA and UVB. Further analyses suggested a significant difference between the cumulative lifetime ocular exposure among cases of cortical cataract compared to non- cataract controls. No threshold or latency period was observed.

In a clinic-based study of PSC cataracts in Maryland, cases were persons who underwent PSC extraction in an ophthalmic practice (Bochow *et al.,* 1989). Controls, matched on age, sex, and type of referral were chosen from other patients on the appointment book of

the same ophthalmic practice who did not have a PSC cataract or a previous cataract extraction. Annual and cumulative ocular UVB exposures were estimated for each individual using the same method as the studies of Chesapeake Bay watermen. Thirty-nine percent of cases had a pure PSC cataract, the remaining 61% had mixed PSC and other cataracts. Almost half the controls had a non PSC cataract (nuclear, cortical or other lens opacity). UVB exposure was significantly associated with PSC cataracts. Both the average cumulative exposure and average annual exposure were higher in cases than controls, after adjusting for steroid use, eye colour, education, diabetes and presence of cortical cataracts.

In a hospital-based study of cataract patients in Iowa Dolezal *et al.* (1989) found little evidence of an association between individual lifetime sunlight exposure and cataract. Mohan *et al.* (1989) in a similar study of cataract in New Delhi examined a range of environmental factors, including occupation. An increase in cloud cover was significantly associated (RR=0.8, 95%CI=0.7-0.9) with cataract when adjusted for each of the other environmental variables. The study did not quantify individual lifetime exposure to sunlight or UV.

In a study of cataract patients in a Massachussetts hospital, Leske *et al.* (1991) investigated occupational exposure to sunshine. No association was found for PSC cataract (RR=1.3, 95%CI=0.7-2.3), cortical cataract (RR=0.9, 95%CI=0.6-1.3), or mixed cataract (RR=0.8, 95%CI=0.6-1.1) among those with at least 2 hours of exposure to bright sunshine per day for at least 2 months. The risk of nuclear cataract was reduced (RR=0.5, 95%CI=0.3-0.9).

A hospital-based study from Italy (Italian-American Cataract Study Group, 1991) found an excess of pure cortical and mixed cataract (RR=1.8, 95%CI=1.2-2.6) and a nonsignificant deficit of nuclear (RR=0.6) and PSC cataract (RR=0.8) among those with a work location in the sunlight. Leisure time spent in the sunlight was associated with an excess of cortical and mixed cataract (RR=1.4, 95%CI=1.1-1.9) and a nonsignificant deficit of posterior subcapsular cataract (RR=0.6).

In an Indian clinic-based study of cataract and history of severe diarrhoeal diseases Bhatnagar *et al.* (1991) found an elevated risk of cataract (RR=2.1, 95%CI=1.2-3.6) for outdoor occupations compare with indoor occupations. However Zaunuddin & Saski (1991) found no relationship between hours of exposure to sunshine and prevalence of nuclear or cortical cataract in Sumatra (0° latitude). In Beaver Dam, Wisconsin, Cruickshanks *et al.* (1993) found no association between average annual exposure to UVB and cortical, PSC or nuclear cataract. Wong *et al.* (1993) surveyed fishermen in Hong Kong. A sun exposure score was calculated based on daily sunlight exposure, and protection from use of a canopy, hat, and glasses. The highest grades of cataract of all types considered

together were more common in subjects with the highest sun exposure scores, but none of these associations was significant at the 5% level. A population-based case-control study (Shibati *et al.,* 1993) reported an increased risk of cortical cataract among men aged 40-50 years who spent 5 or more hours per day outdoors compared with those who spent less time outdoors (RR = 6.89; 95%CI = 1.22-39).

Evaluation of epidemiological evidence

An association has been demonstrated between prevalence of cataract and residence in areas at low latitudes, with long hours of sunlight or high ambient UV radiance in several studies undertaken in different parts of the world. However, in each study, the observed association may be confounded by other possibly causal factors. Certain of the earlier studies did not classify the lens opacities into types of cataract.

Cortical cataract was examined separately in four studies. Only one study assessed individual exposure. Taylor *et al.* (1988) found a dose-response relationship with exposure to UVB radiation. The relative risk for the highest exposure category was three times that for the lowest exposure category. It is unlikely that the exposure assessment was able to distinguish between UVA and UVB exposure. The other two used simple measures of sun-related behaviour. Leske *et al.* (1991) found no association between exposure to bright sunshine and cortical cataract, while in the Italian-American Cataract Study (1991), a work location in the sunlight was related to cortical and mixed cataract. The Italian study also found an association between leisure time outdoors and cortical and mixed cataract. The other two studies showed non-significant trends in opposite directions. More recently, Cruickshanks *et al.* (1993) found annual UVB exposure was associated with cortical opacities among men, but no association was found for women.

Four studies report risk estimates for posterior subcapsular (PSC) cataracts. Bochow *et al.* (1989) measured individual exposure and found PSC cataract patients had higher annual and cumulative exposures to UVB than controls, even after allowing for the effects of several other factors. The other two studies used simple measures of sun-related behaviour and showed non-significant trends in opposite directions. Leske *et al.* (1991) found elevated risk for pure PSC cataract patients compared to controls. However, the Italian-American Cataract Study (1991) reported reduced risk for pure PSC cataract patients with a work location in the sunlight or who spent leisure time in the sunlight. Cruickshanks *et al.* (1993) found no association between annual UVB exposure and risk of PSC cataract.

Five studies provide risk estimates separately for nuclear cataracts. These studies are consistent in showing no association between UV exposure and nuclear cataract (Taylor *et al.,* 1988;

Dolezal *et al.,* 1989; Leske *et al.,* 1991; The Italian-American Cataract Study, 1991; and Cruickshanks *et al.,* 1993). Collectively these studies are consistent in showing no association between UV exposure and nuclear cataract.

All of the published epidemiological studies of UV and cataract have been challenged by the enormous difficulty of determining ocular exposure in different climates. As noted previously, the cornea and lens are seldom directly exposed to light rays from much of the sky; hence the sunlight scattered from the ground and the horizon determine the actual accumulated UV dose.

These studies clearly demonstrate that UV is at least one aetiologic factor in cataractogenesis. However, extrapolation of strong associations found in a mid-latitude population where no serious nutritional problems are present (e.g. Taylor, *et al.,* 1988) to a tropical population in less developed regions, may not be

valid, since the contribution of UV relative to other factors such
as malnutrition and dehydration may be far more important.

10.5.2 Exfoliation syndrome

     The exfoliation syndrome (pseudoexfoliation of lens capsule)
consists of abnormal material deposited on or arising from various
parts of the anterior eye. This condition was originally described
from Finland by Lindberg (1917). In the Nordic countries it
contributes to a high proportion of glaucoma in the older
population. This appears as a round area in the centre of the
anterior lens capsule, corresponding to normal pupil size, on which
bluish-grey flakes are deposited. This is surrounded by a clear
zone, which in turn is surrounded by a peripheral band of
involvement as well. On the border of the pupil it looks like
"dandruff". Similar material is trapped in the pores of the
trabecula meshwork and may be seen on the ciliary processes, on the
zonulas, surrounding the conjunctival vessels and in retro-orbital
tissues. It is a basement membrane material, akin to amyloid in some
respects, although many histochemical studies do not support this
identification.

     The prevalence varies enormously from country to country, and
even within countries. The highest prevalence was found in the
Navajo Indians of New Mexico, in which 38% were over 60 years of
age. At the other extreme, only 2 cases have ever been recorded in
Eskimos, and these were two Greenlanders, possibly of mixed
ancestry, aged over 70 years (Ostenfeld-Åkerblom, 1988). The average
prevalence in central Europe is around 2% on the basis of figures
from several authors (Forsius, 1988).

     The possibility of environmental factors was proposed by Taylor
(1979) based on observations of exfoliation in Australian

aborigines. The distribution of exfoliation was linked to annual
global radiation and to climatic droplet keratopathy.

     Exfoliation syndrome sometimes occurs in other areas of high
UV, and high prevalence of climatic keratopathy. Examples include
Somalia, Djibouti and Saudi Arabia. There is, however, considerable
evidence to suggest that UV is not the main factor associated with
the development of exfoliation. The geographic distribution does not
consistently correspond with that of climatic keratopathy. There may
be wide differences in prevalence of exfoliation syndrome at similar
latitudes. For example, it is frequent in parts of East Africa, but
rare in West Africa. Similarly it may be seen at high prevalence in
the Lapps of Finland and Sweden, but not in Eskimos at the same
latitude. The prevalence may vary within the same country. A total
of 4,042 patients aged over 50 were examined in clinics in 6 areas
in different parts of France over a 2 week period. The prevalence
was high in Brittany (20.6% in those over 60 years) and extremely
rare in Picardy at a similar latitude (Colin et al., 1985).
Exfoliation is usually more frequent in females than males. It is
found in parts of the eye, such as the ciliary body and in the
orbit, remote from the influence of light. Forsius (1988) has
reviewed the evidence for genetic aetiology for the condition.

     The present conclusion is that environment, at least in the
form of UV, is not the primary cause. There is not a consistent
direct relationship with solar radiation. There is at least a major
racial or genetic predisposition, but it is possible that light or
some other environmental factor activates or induces the development
of the exfoliation syndrome in those who are genetically
predisposed.

10.5.3 Anterior lens capsule

     In 1989 a previously unrecorded condition was reported from
Somalia (Johnson et al., 1989). This consisted of alterations of
the pupillary area of the anterior capsule of the lens. The first
stage appeared to be an opalescence of the capsule, which then
became a plateau-shaped elevation above the surrounding contour of
the anterior lens. In its most developed form it was a bagging of
the anterior lens capsule and contents through the pupil, appearing
like a hernia. This condition was invariably associated with
climatic droplet keratopathy, but not necessarily with cataract. In
fact, there appeared to be an inverse relation with cataract.

     The absolute association with climatic keratopathy suggests
that it also may be due to excessive UV exposure. Attempts to secure
histology on extracted lenses with this condition were difficult
because the lens capsule so frequently tore from the rest of the
lens as it was extracted by the cryoprobe. The capsules examined
showed thinning and splitting of the layers, and death of many of
the nuclei of the epithelial cells. However, there were no controls

from the same geographical and ethnic area of the same ages for
comparison.

10.6 Diseases of the Choroid and Retina

     Among adults, only extremely small amounts of UVA and UVB at
wavelengths below 380 nm reach the retina, because of the very
strong absorption by the cornea and lens. Less than 1% of radiation
below 340 nm and 2% of radiation between 340 and 360 nm reaches the
retina (Barker and Brainard, 1993). Even in early childhood the
highest spectral transmittance reaches about 4% in the UVB and is
generally of the order of 1%. However, because of the biological
activity of the shorter wavelengths of UVB, the biological
importance of the small amount of this radiation that does reach the

retina cannot be completely neglected. As children age, UV is
increasingly absorbed by the cornea and lens, and the proportion
reaching the retina decreases. This suggests firstly, that exposure
to UV during childhood may be of more importance than exposure to UV
during adult life, and secondly, that exposure to longer wavelength
radiation (e.g. visible light) may be of more importance in
adulthood.

10.6.1 Uveal melanoma

     Exposure to solar radiation is considered to be causally
associated with the development of cutaneous malignant melanoma
(IARC, 1993). There is a possibility that exposure to UV may also
cause melanoma of the uveal tract. There is no separate ICD code for
intra-ocular melanoma, so descriptive studies have generally been
based on cancer of the eye (ICD-9 190), of which it has been
estimated that 80% are intra-ocular melanomas (Osterlind, 1987). In
the case-control studies cases of uveal-tract melanomas were
confirmed histologically, but also included tumours of iris and
ciliary body with those of the choroid.

     The incidence of cancer of the eye is higher among white than
black or Asian populations residing at the same latitude. For
example, in US whites the incidence rates are 0.7 per 100 000 person
years in males and 0.6 in females compared with 0.2 in both sexes in
blacks (Parkin et al., 1992). Among people of European ancestry,
risk of ocular melanoma was observed to be least in those of
southern European ethnic origin; for example, in comparison with an
RR of 1.0 in those of southern European origin, the RR in people of
northern European origin was 6.5 (95% CI 1.9-22.4; Seddon et al.,
1990). Risk of ocular melanoma was observed to be increased in those
with light eye colour, with RRs of 1.7 to 2.1 (Gallagher et al.,
1985; Tucker et al., 1985c; Holly et al., 1990), but not when
ethnicity was taken into account (Seddon et al., 1990). Kraemer
(1987) found five cases of ocular melanoma among reports of 337
patients with xeroderma pigmentosum for whom ocular findings had

been described. The defect in this condition is failure to repair
DNA after damage by UV.

     There is no evident latitude gradient in incidence of ocular
melanoma in white populations of the northern hemisphere or
Australia (IARC, 1992) and, within the USA, its risks in those born
in southern parts of the country, where ambient solar radiation is
highest, has variously been reported to be more (Tucker et al.,
1985c), less (Seddon et al., 1990) or the same (Schwartz & Weiss,
1988; Mack & Floderus, 1991) as that in those born elsewhere in the
country. Similarly Gallagher et al. (1985) in Canada found no
association with latitude of residence.

     Two studies have examined place of birth and risk of uveal
melanoma, but the findings are inconsistent. Tucker et al. (1985)
found an excess of cases were born south of latitude 40°N, whereas
Seddon et al. (1990) found a deficit.

     Indicators of personal sun exposure have been inconsistently
associated with risk of cancer of the eye or ocular melanoma. A
small rural excess in incidence of cancer of the eye has been
reported (Doll, 1991). Two descriptive studies reported an
association with farming (Saftlas et al., 1987; Gallagher, 1988)
but this was not found in several other such studies (Milham, 1983;
Office of Population, Censuses and Surveys, 1986; Vågerö et al.,
1990) or two case-control studies of ocular melanoma (Gallagher et
al., 1985; Seddon et al., 1990). Some high exposure activities
such as gardening (RR 1.6, 95% CI 0.7-1.6) and taking sunny
vacations (RR 1.5, 95% CI 1.0-2.3, for highest category) were
significantly associated with increased risks of ocular melanoma in
one case-control study (Tucker et al., 1985c) but no similar
associations with personal sun exposure at work in leisure time, or
in vacation were found in three other studies (Gallagher et al.,
1985; Holly et al., 1990; Seddon et al., 1990). Indeed,
Gallagher et al., (1985) found an elevated risk for government
workers, a predominantly indoor managerial group. The lack of use of
protective eyewear (sunglasses, visors, headgear) was associated
with an increased risk of ocular melanoma in one study (Tucker et
al., 1985c) with an RR for infrequent or rare use of 1.6 (95% CI
1.2-2.2). Weak evidence of a similar effect was found by Seddon et
al. (1990).

     No statistically significant association has been observed
between ocular melanoma and a personal history of skin cancer in
several studies of cancer registry or other data (Osterlind et al.,
1985; Tucker et al., 1985a; Holly et al., 1991; Lischko et al.,
1989; Turner et al., 1989).

     There is evidence of associations between exposure to sunlamps
and some other artificial sources of UV and risk of ocular melanoma
in the three case-control studies in which they have been examined.

Tucker et al. (1985c) found a relative risk of 2.1 (95% CI
0.3-17.9) for frequent use of sunlamps compared with no use (p=0.10
for trend over four categories of use); Holly et al. (1990) found
a relative risk of 3.7 (95% CI 1.6-8.7) for ever having an exposure
to "artificial UV or black light" and with welding burn, sunburn to
eyelids, or snow-blindness, RR 7.2 (95% CI 2.5-20.6); and Seddon et
al. (1990) found a relative risk of 3.4 (95% CI 1.1-10.3) for
frequent or occasional use of sunlamps compared with never used. In
one of these studies, there was also a strong association with
employment as a welder (RR 10.9, 95% CI 2.1-56.5; Tucker et al.,
1985c). No similar association was found by Seddon et al. (1990)

but an increased risk in welders (RR 8.3, 95% CI 2.5-27.1) was found
in an occupational study of French Canadians (Siemiatycki, 1991).

Overall, the epidemiological studies do not provide convincing
evidence of an association between exposure to solar UV and uveal
melanoma. None of the studies has developed a practical assessment
of individual cumulative ocular exposure to UVB. They have all used
various simple estimates of sun-related behaviour.

On the other hand, the use of a sunlamp, an artificial source
of UV, was significantly associated with uveal melanoma in the two
case-control studies that examined their use. Another study found
elevated risk of uveal melanoma with exposure to UV or black lights.
Collectively, these studies suggest frequent use of a sunlamp may be
associated with a 2-4 fold increase in risk of developing uveal
melanoma. Sunlamp use can produce over five-fold more DNA damage per
unit of erythema than the sun (Nachtwey & Rundel, 1981).

The large number of ocular melanomas in xeroderma pigmentosum
patients also means that exposure to UV cannot be ruled out as a
causative factor.

10.6.2 Age-related macular degeneration

Age-related macular degeneration (AMD) is one of the leading
causes of blindness in the industrialized world. Visual loss can
occur because of the development of geographic atrophy (loss of the
outer retinal segments and retinal pigment epithelium), retinal
pigment epithelial detachment or sub-retinal neovascularization
(exudative AMD). Prior to visual loss AMD is characterized by the
presence of drusen (lipofuscin and other material deposited between
the retinal pigment epithelial cells and Bruch's membrane and
appearing as yellow-white nodules with distinct and indistinct edges
on retinal examination).

There is evidence for association of AMD with UV exposure.
Photochemical retinal damage can occur from prolonged exposure to
high intensity light. Whether such damage is directly related to AMD
is unknown. Although aged Rhesus monkeys have drusenoid deposits, no
good experimental animal models for AMD currently exist.

In a case control study, Hyman et al. (1983) found no
association of AMD and light exposure based on residential history.
They also found no association of AMD to occupational light
exposure.

In studies based on individual exposure data; the results are
equivocal. The initial evaluation of the association of AMD and UV
exposure in the cross-sectional study of Chesapeake Bay watermen
revealed no statistically significant association (West et al.,
1989). However, a reanalysis based on the small number of cases of
AMD with exudative disease or geographic atrophy suggested an
association with 20 year exposure to blue light but not UVA or UVB
(Taylor, 1992).

The Beaver Dam Eye Study found an association of late stage AMD
(exudative AMD or geographic atrophy) and summer leisure time
outdoors (RR=2.2 CI=1.1-4.2). It was also suggested that an
association existed in men only between early stage AMD and summer
leisure time outdoors. The magnitude of the risk estimates were
unchanged after adjusting for numerous possible confounding factors
(Cruickshanks et.al. 1993).

It can be concluded that there are very limited data
demonstrating an association of AMD with UV exposure. The finding of
an association with blue light exposure is consistent with the
wavelengths of visible light reaching the retina and needs further
investigation.

10.7 Conclusion

The causal links between UVB exposure and various ocular
conditions were evaluated on the basis of the following definitions:

 Sufficient evidence for a causal association indicates that
positive associations have been observed between human exposure to
UV and the effect in which chance, bias and confounding could be
ruled out with reasonable confidence.

 Limited evidence for a causal association indicates that positive
associations have been observed between exposure to UV and the
effect for which a causal interpretation is considered to be
credible, but chance, bias or confounding could not be ruled out
with reasonable confidence.

 Inadequate evidence for a causal association indicates that the
available studies are of insufficient quality, consistency, or
statistical power to permit a conclusion regarding the presence or
absence of a causal association between UV and the effect, or no
data were available.

 Evidence for lack of causal association indicates that there are
several adequate studies covering the range of exposure that humans
are known to encounter which are consistent in not showing a
positive association between UV and the effect.

There is sufficient evidence to link photokeratitis to acute
ocular exposure to UVB.

Sufficient evidence exists to link the production of cortical

and PSC cataracts to UVB exposure in animals. There is limited
evidence to link cortical and PSC cataract in humans to chronic
ocular exposure to UVB. Inadequate evidence is available to link PSC
cataract in humans to chronic UVB exposure. Insufficient data have
been collected upon which to evaluate the risk of cataract
associated with childhood exposure to UVB. Half the world's
35-million blind people are blind because of cataract. The
proportion of cataract that results from UVB exposure is unknown,
but may be as high as 20%.

There is limited evidence to link sunlight exposure of the eye
to the development of pterygium. It is unclear whether the observed
association is specific for UV. The contribution from other
environmental factors remains unclear.

There is limited evidence to associate climatic droplet
keratopathy with UV exposure and insufficient to link pinguecular
and cancers of the anterior ocular structures. Insufficient evidence
exists to link uveal melanoma to ocular exposure to solar UV
radiation. However, several epidemiological studies have suggested
that the use of sunbeds (an artificial source of UV) is associated
with uveal melanoma.

There is inadequate evidence of an association between ocular
UV exposure and acute solar retinitis, age-related macular
degeneration, acceleration of pigmentary retinopathies and
exfoliation syndrome.

11. EFFECTS ON PLANT AND AQUATIC ECOSYSTEMS

11.1 Introduction

Human populations may be affected by direct and indirect
consequences of increased solar UVB on aquatic food webs. Because
more than 30% of the world's animal protein for human consumption
comes from the sea (in many developing countries this percentage is
even larger), a substantial decrease in biomass production would
diminish fishery resources in the face of growing world populations.
Reductions of leaf area, fresh and dry weight, lipid content and
photosynthetic activity were typically found in UVB sensitive plant
species. Additionally, alterations of leaf surface, epicuticular
waxes, diffusion of water vapour through the stomata have been
reported. For previous comprehensive publications see Caldwell *et
al.* (1989), Wellmann (1991) and SCOPE/UNEP (1993).

11.2 Effects on Terrestrial Plants

11.2.1 UV penetration into the leaf

UVB has a direct effect on photosynthesis. Reductions in
photosynthesis often accompany changes in leaf pigmentation,
anatomy, and leaf thickness. After exposure to enhanced UVB, the
internal light regime of leaves was altered (Bornman & Vogelmann,
1991). In a recent study, *Brassica campestris* (origin: northern
latitudes) was subjected to 6.3 kJ m^{-2} day^{-1} of UVB and
responded by increasing leaf thickness by 45% and UVB screening
pigments by 21% relative to controls (Bornman & Vogelmann, 1991).
Chlorophyll content (per leaf area) and photosynthetic activity
decreased while scattered light within the leaves of UV-treated
plants increased. Since the distribution of photosynthetically
active radiation was altered at different depths within leaves after
UV, these changes can also be expected to have an indirect effect on
photosynthetic capacity.

In a study on a group of 22 diverse plant species (including
herbaceous and woody dicotyledons, grasses and conifers), widely
varying UVB penetration was found. For instance, epidermal
transmittance of the herbaceous dicotyledons ranged from 18% to 41%
with penetration up to 140 μm, while conifer needles excluded a
large percentage of the incident UVB. Penetration of UVB into leaves
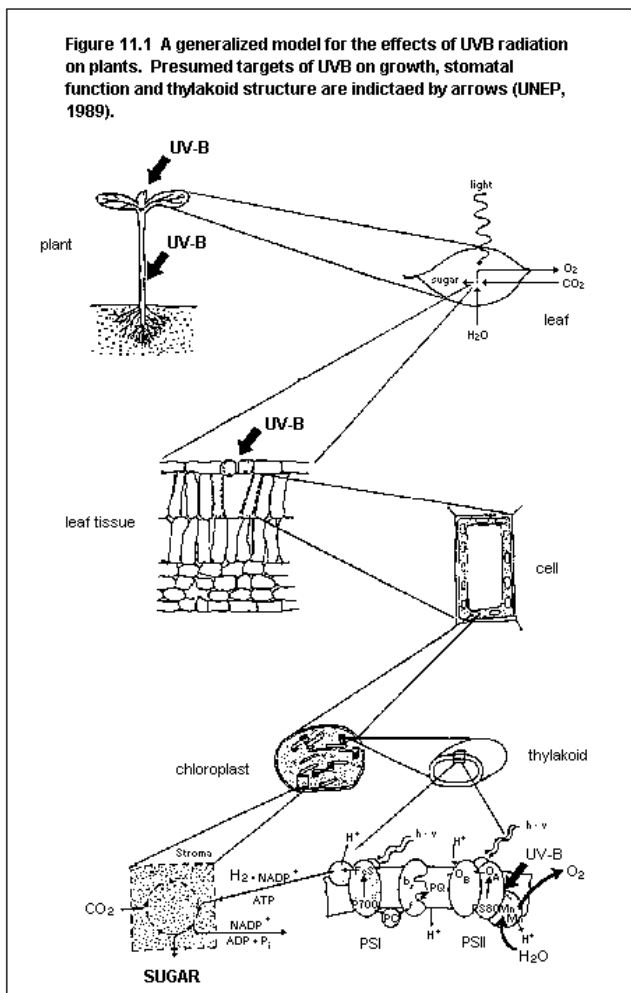
of the woody dicotyledons and grasses was in between that of the
herbaceous dicotyledons and conifers (UNEP 1989).

11.2.2 Changes in growth

The growth of many plant species is reduced by enhanced levels
of UVB. The main components of plants affected by UVB are shown in
figure 11.1 (UNEP 1989). The ozone filter technique was used to
simulate a relative solar UVB enhancement of 20% by providing 54.4
kJ m^{-2} day^{-1} (unweighted) or 5.1 kJ m^{-2} day^{-1} of
biologically effective radiation (UVB_{BE}) through one cuvette and
45.3 kJ m^{-2} day^{-1} (unweighted) or 3.6 kJ m^{-2} day^{-1} UVB_{BE}
through the other cuvette (Tevini et al., 1991b). These were average
values measured from May 1990 to August 1990 and are equivalent to
an ozone depletion of approximately 10%. Plant height, leaf area,
and the dry weight of sunflower, corn, and rye seedlings were
significantly reduced, while oat seedling remained almost unaffected
(Tevini *et al., 1991b*). The reduction of hypocotyl growth of
sunflower seedlings under artificial UVB irradiation is associated
with a UV dependent destruction of the growth regulator
indole-3-acetic acid (IAA) and the formation of growth inhibiting
IAA photoproducts. The inhibition of elongation in UV-irradiated
sunflower seedlings might also be due to the action of peroxidases
working as IAA-oxidase, causing a decrease in cell wall
extensibility of the hypocotyl epidermis (Ros, 1990). Shading of
shoot apex was shown to reduce UVB induced reduction in growth of
Vigna seedlings (Kulandaivelu *et al.,* 1993).

11.2.3 Effects on plant function

     When high UVB irradiances were used in combination with low
levels of white light, such as commonly found in growth chambers,
effects on photosynthesis were generally deleterious. However, even
in the presence of higher levels of white light in green houses and
in the field, reductions in photosynthesis of up to 17% were
reported in the UVB sensitive soybean cultivar Essex when supplied
with UVB equivalent to an 18% ozone depletion (Murali & Teramura,
1987). Solar UVB also reduced net photosynthesis in sunflower
seedlings by about 15% when a 12% ozone depletion was simulated by
using the ozone filter technique (Tevini *et al.,* 1991c). One
reason for the reduction in overall photosynthesis might be due to
stomatal closure by enhanced UVB.

Figure 11.1 A generalized model for the effects of UVB radiation
on plants. Presumed targets of UVB on growth, stomatal
function and thylakoid structure are indictaed by arrows (UNEP,
1989).

     Recent studies reveal the effects of UVB radiation on tropical
plants. Rice is among the most important tropical crops in the
world. Sixteen rice (*Oryza sativa L.*) cultivars from several
different geographical regions when grown for 12 weeks in
greenhouses with supplemental levels of UVB exposure equivalent to
20% ozone depletion over the equator (15.7 kJ m^{-2} day^{-1} UVB$_{BE}$)
showed alterations in biomass, morphology, and photosynthesis.
Approximately one-third of all cultivars tested showed a
statistically significant decrease in total biomass with increased
UVB exposure. Photosynthetic capacity declined for some cultivars,
but only a weak relationship existed between changes in
photosynthesis and biomass with increasing UVB exposure. In one of
the rice cultivars tested, total biomass significantly increased by
20% when grown under enhanced levels of UVB exposure. Therefore,
despite the fact that the effects of UVB are generally damaging, in
some cases, it has been reported to have a stimulating effect. Such
positive growth effects are presently not easily explainable.
Results from this experiment indicate that 1) a number of rice
cultivars are sensitive to increases in UVB exposure; 2) the
diversity exhibited by rice in response to increased levels of UVB
suggests that selective breeding might be successfully used to
develop UVB tolerant rice cultivars. Other preliminary screening
studies on rice seedlings also corroborate these observations
(Coronel *et al.,* 1990).

     In a three year field study (Sullivan & Teramura, 1991),
photosynthetic capacity was generally reduced in loblolly pine trees
exposed to supplemental levels of UVB simulating a 16% and 25% ozone
depletion (11.5 and 13.6 kJ m^{-2} UVB$_{BE}$). Absolute reductions
varied from 0 to 40% between the seed sources and with needle age.
For example, photosynthesis was significantly reduced by up to 40%
in needles which had been exposed to UVB for an entire season, but

only 19% on recently expanded needles. These reductions, however,
were only transient in some plants because they could not be
detected following the dormant winter period. This suggests that UVB
repair mechanisms may exist. Measurements of chlorophyll
fluorescence and the photosynthetic response to light indicated that
the quantum yield was significantly reduced in some cases by direct
effects on photosystem II. No significant effects were observed on
stomatal conductance of transpiration, and chlorophyll
concentrations were not generally altered by UVB exposure.

   In vitro studies, using isolated chloroplasts, indicate that
UVB-induced damage to photochemical reactions is greater in C_3
plants (*Dolichos lab lab, Phaseolus mungo,* and *Triticum vulgare)*
than in C_4 (*Amaranthus gangeticus, Zea mays,* and *Pennisetum
typhoides)*. Such differences are associated with the polypeptide
composition of the thylakoids (Kulandaivelu *et al.,* 1993).

   Studies in growth chambers with the ozone filter for
attenuating solar UVB report significant reductions in net

photosynthesis (measured under saturating light conditions) on a
leaf area and whole plant basis in sunflower seedlings, when grown
for three weeks at a daily maximum temperature of 28°C or 32°C under
a 20% higher UVB level compared to controls (5.1 kJ m^{-2} day^{-1}
UVB_{BE} vs. 3.6 kJ m^{-2} day^{-1}). These represent average values
from May 1990 to August 1990 and are equivalent to approximately a
10% ozone depletion. In contrast, net photosynthesis was lower in
maize seedlings only during the earliest stages of development at
both temperatures (Tevini *et al.,* 1991c).

11.2.4 Species competition

   Enhanced UVB exposure can cause changes in the growth of plants
without necessarily decreasing plant production. Such changes
include reduced leaf length, increased branching, and increased
number of leaves (Barnes *et al.,* 1990). These changes seem to be
general among different crop and weed species. Both graminoid and
broad-leaf species respond in this fashion, with graminoids
generally more responsive. Although these growth form changes do not
lead to changes in the production of monocultures, in mixed species
these alterations can lead to a change in the balance of competition
for light.

   Multi-year field studies had shown that the balance of
competition between wheat and wild oat (a common weed) began to
favour wheat when mixtures of these species were subjected to
increased UVB irradiation (Barnes *et al.,* 1988). In a recent study
involving canopy light microclimate assessments and a detailed
canopy radiation interception model, it was shown that the shift in
growth-form of the two species was sufficient to quantitatively
explain the change in the competitive balance (Ryel *et al.,* 1990).
Thus, in many cases where plants are not necessarily depressed in
overall growth by increased UVB exposure, changes in growth-form can
have ecologically meaningful consequences. The direction of
competitive balance changes are not easily predicted at present.
However, altered competitive balance also has important implications
for mixed-crop agriculture and species composition of
nonagricultural ecosystems.

11.2.5 Plant diseases

   Certain diseases may become more severe in plants exposed to
enhanced UVB levels. Sugar beet (*Beta vulgaris)* plants infected
with *Cercospora beticola,* and receiving 6.9 kJ m^{-2} day^{-1}
UVB_{BE}, showed large reductions in leaf chlorophyll content, and
fresh and dry weight of total biomass. In another study, three
cucumber (*cucumis sativus)* cultivars were exposed to a daily UVB
dose of 11.6 kJ m^{-2} UVB_{BE} in a greenhouse before and/or after
infection with *Colletotrichum lagenarium* or *Cladosporium
cucumerinum,* and analyzed for disease development (Orth *et al.,*
1990). Two of the three cultivars were disease resistant and the

other was disease susceptible. Pre-infection treatment with UVB led
to greater disease development in the susceptible cultivar and in
one of the disease resistant cultivars. Post-infection treatment did
not alter disease development. The increased disease development in
UVB irradiated plants was found only on the cotyledons and not on
true leaves, suggesting that the effects of UVB on disease
development in cucumber vary according to the cultivar, timing of
UVB exposure, and tissue age.

11.2.6 UV-protection systems

   Epidermal pigments

   UVB induces flavonoid production (Wellmann, 1971), and may
regulate the synthesis of UV protective pigments (Braun & Tevini,
1991). In a study using two important crops (rye and oat),
UV-fluence and wavelength dependent accumulation of isovitexin
derivatives in the epidermal layer of rye seedlings prevented damage
to chloroplast functions. In contrast, photosynthetic function was
low without the accumulation of screening pigments (Tevini *et al.,*
1991a). Because the epidermal layer of oat seedlings already
accumulates large amounts of UV-absorbing pigments during early
development, the photosynthetic apparatus is better protected than
rye seedlings against UVB (Braun, 1991). This inherently higher
flavonoid production occurs even in absence of UVB irradiation, and
appears to be constitutive in nature. UVB induction of flavonoids

was demonstrated in two species of columbines, *Aquilegia caerulea,* growing in alpine environments, and *Aquilegia canadensis,* which grows at lower elevations (Larson *et al.,* 1990). In both species, flavonoid content increased upon UVB irradiation, even though the alpine species accumulated higher amounts in the UVB-free controls when compared to *A canadensis* after UVB irradiation. This demonstrates that plants which are already genetically adapted to higher UVB environments can further increase their adaptation capacity.

   Photorepair

   A second protective mechanism in plants is photoreactivation. The UV-induced production of DNA pyrimidine dimers can be repaired by DNA photolysase. This enzyme was shown to increase with UVB irradiation in *Arabidopsis* (Pang & Hays, 1991) but also by visible light via phytochrome in bean seedlings (Langer & Wellmann, 1990). This inducibility means that *de novo* synthesis of DNA photolysase itself is a target for UV damage. Thus, the repair capacity of the cell may be reduced in the presence of increasing UVB (Wellmann, 1991).

11.3 Effects on Aquatic Ecosystems

   Aquatic ecosystems contribute more biomass (104 Gt a^{-1}) than all terrestrial ecosystems (100 Gt a^{-1}) combined. Recent work on UVB effects has concentrated on inhibition mechanisms and field studies in the subpolar waters of Antarctica, because of its high biomass production and the occurrence of the ozone hole over this region.

   Phytoplankton organisms orient within the water column using external factors. Mobility and orientation mechanisms are impaired by UVB exposure. Most organisms do not possess UVB receptors, and so cannot avoid deleterious effects of enhanced UVB that produces higher intensities deeper into the water column. New action spectra indicate that, in addition to DNA, other targets absorb UVB including proteins of the photoreceptor and photosynthetic apparatus. The inability of phytoplankton to adjust their position within the water column causes massive inhibition of photosynthesis. In only a few cases have UVB inducible screening pigments been identified.

11.3.1 Effects on phytoplankton

   Recent UVB aquatic research has concentrated on phytoplankton and the Antarctic ecosystem. As shown in figure 11.2, phytoplankton is at the base of the aquatic food chain/trophic structure and serves as food for primary consumers (e.g., larvae of fish and shrimp), which in turn are consumed by secondary and tertiary consumers (e.g. fish). The production of phytoplankton has been estimated at about 6 x 10^{14} kg (UNEP, 1989). A loss of 10% would far exceed the gross national product of all countries in the world, assuming any reasonable price for biomass on the market. table 11.1 gives the estimated annual biomass production for plankton and fish.

Table 11.1 Estimated annual biomass production at different levels in marine food web and possible loss after 10% decrease at the phytoplankton level (adapted from UNEP 1989 report)

Type	Annual Production (in million tonnes)	10% loss
Phytoplankton	600,000	60,000
Zooplankton	60,000	6,000
Small fish	6,000	600
Large fish	600	60

Figure 11.2 Example of the biological food web in a marine ecosystem, which starts with the primary producers; the biomass they produce in utilized by the primary consumers, which in turn serve as food input for the next level in the food web (UNEP, 1989).
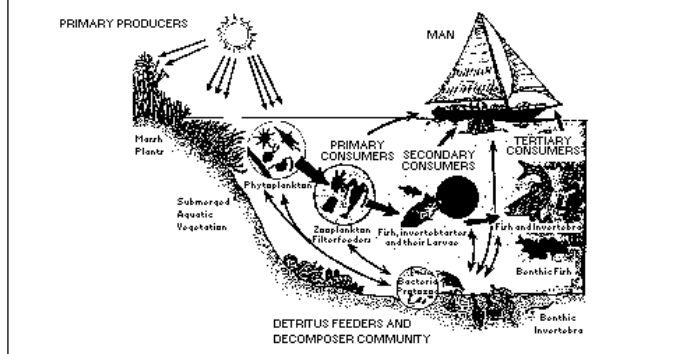
   Concentrations of phytoplankton in subpolar waters may be 103 to 104 times greater than concentrations of phytoplankton found in tropical and subtropical seas (Jeffery & Humphrey, 1975). Any significant increase in UVB could well diminish growth and productivity of phytoplankton, subsequently affecting all higher trophic levels in the aquatic food web. Therefore, it is not surprising that a majority of recent research has looked at the

effects of increased UVB exposure in Antarctic waters. Ongoing research activities include investigations of both direct (physiological and behavioural) and indirect (trophic implications) effects.

Phytoplankton dwell in the top layers of the water column (the photic zone) because of their requirement for solar energy (Ignatiades, 1990). Their position within the column is maintained by precise orientation strategies using light, gravity and other external factors as guides. Phytoplankton in the photic zone would be exposed to any increase in solar UV. Most phytoplankton organisms do not possess UVB photoreceptors to guide them away from harmful UV, a situation similar to humans. Previous work demonstrated that mobility/orientation mechanisms in response to light are impaired by solar UV (Häder & Worrest, 1991; Baker & Smith, 1982). The ability of phytoplankton to adjust their position within the water column, in response to constantly changing conditions, may even be affected at ambient UVB levels. Although ambient UVB fluxes may cause damage to some species of phytoplankton, it should be emphasized that there are uncertainties regarding the magnitude of these effects. These included problems of extrapolating laboratory findings to the open sea and the nearly complete absence of data on long-term effects and ecosystem responses. Likewise, there is a need to investigate adaptation mechanisms. Before effects of exposure to solar UVB can be predicted, information is required on seasonal abundances and vertical distributions of marine organisms, vertical mixing, and the penetration of UVB into appropriate water columns.

In their natural habitats, organisms are exposed to a wide range of UVB intensities. This radiation has been shown to affect growth, photosynthesis, nitrogen incorporation, and enzyme activity (Döhler & Alt, 1989; Döhler, 1990).

11.3.2 UV increase and primary biomass production

Recent results indicate that orientation mechanisms responsive to both light and gravity are affected by solar UV in a number of ecologically significant phytoplankton groups (Häder & Lui, 1991). Action spectra inhibitory effects are different from the DNA absorption spectrum and the action spectra calculated for higher plants, suggesting that UV exposure affects these organisms by a different mechanism. Proteins essential for specific functions such as orientation and photosynthesis are the primary targets of UVB.

Biochemical analyses conducted to reveal the molecular targets of UVB inhibition show that specific photoreceptor proteins are degraded. Simultaneously photosynthetic pigments (responsible for converting solar energy) are bleached and destroyed by radiation (UNEP, 1989). The results of these biochemical studies are further supported by spectroscopic investigations showing losses in pigmentation.

In order to evaluate the effects of enhanced UV, the vertical movement of natural phytoplankton was analyzed in 3m Plexiglas columns (Eggersdorfer & Häder, 1991). Most organisms moved to the surface during daytime hours, although some species avoided periods of intense UV during the midday hours by moving slightly down in the water column. However, this avoidance response is not sufficient to protect organisms under conditions of increased UVB irradiation (UNEP, 1989).

The UVB irradiance in Antarctic waters significantly increased during the occurrence of the ozone hole (Bidigare, 1989; Lubin *et al.,* 1989; Karentz & Lutze, 1990). However changes in marine productivity accompanying UV flux changes have not been determined. Recent measurements show that UVB penetrates 65 meters deep into clear Antarctic waters (UNEP 1991). Consequently, measurements of photosynthetic biomass production in Antarctic waters under the ozone hole show a pronounced decrease in productivity by up to 25% (Holm-Hansen, 1990).

Field studies indicate that photosynthesis is impaired first, followed by decreases in protein concentration and changes in pigment composition. As a result, a dramatic decrease in photosynthetic oxygen production can be measured after exposure to solar radiation (Smith *et al.,* 1980). Other spectral bands, such as UVA and visible radiation, may contribute to photosynthetic inhibition (Smith *et al.,* 1980). Likewise, photosynthetic inhibition has been detected in macroalgae at their natural depth (Bittersmann *et al.,* 1988; Nultsch *et al.,* 1990).

In contrast to higher plants only a few photoplanktons produce UV absorbing substances (Carretto *et al.,* 1990; Karentz *et al.,* 1991b). However, all of these mycosporine-like amino acids have maximal absorption in the UVA range and only secondary peaks in the UVB. It is not clear whether the production of these potentially screening substances can be induced by exposing organisms to UV (Raven, 1991). One exception is cyanobacteria where a UVB inducible pigment has been found within the slime sheath surrounding the organisms, which absorbs up to 88% of the incident UVB (Garcia-Pichel and Castenholz, 1991).

11.4 Conclusion

Field and laboratory experiments on plant responses to increased UVB radiation underscore the concern for agriculture, forestry and natural ecosystems as the stratospheric ozone level is depleted.

Growth and photosynthesis of certain crop plants can be

inhibited even under ambient levels of UVB radiation. Certain environmental factors, both biotic (e.g. plant diseases and competition with other plants) and abiotic (e.g. carbon dioxide, temperature, heavy metals, and water availability) can alter UVB effects in plants. This increases the difficulty in making any quantitative predictions. Plants in temperate regions and certain tropical species were found to be adversely affected by enhanced UVB radiation.

Marine ecosystem which provides the primary food for human consumption (in some countries) has been shown to be more sensitive to UVB than terrestrial plants. One consequence of loss in phytoplankton is reduced biomass production which would be propagated throughout the whole food web. The marine phytoplankton is a major absorber of atmospheric carbon dioxide. Any reduction in this population would decrease the uptake of carbon dioxide and so augment the greenhouse effect.

12. HEALTH HAZARD ASSESSMENT

12.1 Introduction

For the vast majority of people, the sun is the single largest source of exposure to UV. In some cases solar exposure will be elective such as from sunbathing, in others it will be adventitious as a result of outdoor recreational and/or occupational activity. Exposure may also occur from artificial sources of UV, either deliberately for example during medical treatment or the use of a sunbed for cosmetic purposes.

The health risks associated with exposure to UV include those of both acute and chronic effects and will vary according to the nature of the exposure. Factors important in assessing such risks include: the biologically-effective irradiance of the UV incident on the person exposed; the duration and frequency of occurrence of exposures; and the individual sensitivity of the person to UV as determined by genetic and other factors.

International guidelines on protection against UV given in chapter 13 are based on available scientific data (IRPA/INIRC, 1991). The guidelines define occupational exposure limits (ELs) below which it is expected that nearly all people may be repeatedly exposed without adverse effects. The Els are intended to be used to evaluate potentially hazardous exposures from, for example, solar radiation, arcs, gas and vapour discharges, fluorescent lamps and incandescent sources. The Els are generally below levels which are often used for the UV exposure of patients required as part of medical treatment and below levels associated with sunbed exposure. IRPA/INIRC recommend that, where they are to be incorporated in regulations, the ELs should be considered as absolute limits for the eye, but only as advisory for the skin. This is because of the wide range of susceptibility to skin injury depending on skin type. The values were developed by considering lightly pigmented populations, with greatest sensitivity to sunburn and non- melanocytic skin cancer. In recommending similar limits, Threshold Limit Values (TLVs), the American Conference of Governmental Industrial Hygienists (ACGIH 1993) indicate that conditioned, tanned, individuals can tolerate skin exposure in excess of the exposure limits without sunburn effects, but that conditioning may not protect individuals against skin cancer. ELs are not intended to apply to exposure of pathologically photosensitive individuals, to people concomitantly exposed to photosensitising agents or to neonates.

The threshold for adverse acute effects may be exceeded in certain people without exceeding the exposure limit. The risk of skin cancer increases with cumulative exposure over time. Therefore, it is recommended that all exposures should be reduced as far as is reasonably practicable.

An estimate of the risk of cumulative exposure to UV can be expressed in terms of the cumulative incidence (I) of non-melanoma skin cancer in the form of the equation (Schothorst *et al.*, 1985; Diffey 1988).

$$I = \text{gamma } A \; H^{\beta} \; a^{alpha} \qquad\qquad 12.1$$

where I is the total number of cases per 100,000 of the population in the age group up to age 'a' years:

H is the annual carcinogenic-effective radiant exposure at the skin surface:

A is the fraction of the body surface area exposed:

gamma, ß and alpha are numerical constants reflecting the genetic susceptibility of the exposed population, the biological amplification factor and the age dependence of the cumulative incidence respectively.

The above equation applies only to situations where the annual effective exposure remains constant year by year. This will not be the case, for example, for workers whose job may result in additional occupational exposure during their working lives (Diffey 1988). In these circumstances the cumulative incidence I can be represented by the equation (Slaper *et al.*, 1986).

$$I = \text{gamma } A \; H_e^{\beta} \; a^{alpha} \qquad\qquad 12.2$$

where H_e is given by

$$H_e = H + H^o(a-a_s)/a$$

H is the annual effective radiant exposure of solar UV:

a_s is the age at which the occupational exposure began:

H^o is the annual effective radiant exposure from occupational exposure.

In the following sections estimates of personal exposures likely to result from different situations are considered and, where the availability of data permits, examples of estimates of quantitative risk are provided. The exposure situations include elective exposure to solar UV, from medical treatment and from the use of sunbeds, as well as adventitious exposure resulting from solar radiation and from artificial sources of UV.

12.2 Elective Exposures

12.2.1 Medical exposure

UV is used in medicine for both the diagnosis and treatment of disease. The highest and most extensive medical exposures to UV result from phototherapy and photochemotherapy.

Medical treatment using UV carries the risk of acute side effects and long term risks of chronic effects, in particular skin cancer. The acute side effects of UVB phototherapy exposure include; reddening, swelling, blistering and desquamation of the skin. The acute effects following PUVA treatment include itching, skin pain and nausea (Green *et al.,* 1992).

Chronic effects include those on both the eyes and the skin. However, the eyes of patients are generally well protected during PUVA treatment and only one case of PUVA induced cataract in humans appears to have been reported (Cyrlin 1980). Structural changes in the skin, akin to those characteristic of long term damage resulting from solar radiation exposure, have been observed as a result of both UVB and PUVA phototherapy.

The risk of skin cancer from ultraviolet phototherapy has been reviewed by Green *et al.* (1992). They conclude that data on the association between UVB phototherapy and skin cancer are very poor. Only one case control study has been reported and no correlation was found between UVB phototherapy and skin cancer in 85 patients who had received UVB phototherapy for up to 25 years. The association between PUVA treatment and skin cancer in psoriasis patients has been reported in ten studies. However, only one study (Stern *et al.,* 1979) indicated that PUVA acted as an independent carcinogen, the risk of developing skin cancer being 6-12 times that of a population survey. The results of other studies point to PUVA acting in the role of a co-carcinogen, other factors involved being a family history of skin cancer and treatment with antipsoriatic medication. Comparisons and interpretations of data from US and European studies have been complicated by differences in the exposure regimens used.

12.2.2 Phototherapy of seasonal affective disorder (SAD)

Typical treatment consists of sitting in front of a panel of fluorescent lamps and exposing the face, with the eyes open, to an illuminance of about 2500 lux for 2 to 6 hours per day during the winter months. This is equivalent to a daily erythemally-effective radiant exposure of up to 40 J m^{-2} (Diffey 1993). An annual cumulative exposure of up to 24 MEDs results, which, if continued for several decades is estimated to result in a risk of non-melanoma skin cancer of about 1.5, compared with someone (typical indoor worker) minimally exposed.

12.2.3 Sunbeds

Among lightly pigmented people, a suntanned skin is unfortunately still socially desirable. The establishment of the 'suntanning industry' has enabled the acquisition of a 'suntan' irrespective of the availability of solar radiation. Suntanning is caused by UV and as with exposure to the sun, there are attendant risks in using sunbeds.

Adverse health effects of sunbed use include acute effects on the skin, longer term structural damage of the skin and increased risk of skin cancer (Roza *et al.,* 1989). Provided that appropriate protective eyewear is worn, adverse health effects on the eyes will be avoided. The extent to which adverse, but relatively transient skin effects occur is demonstrated by the results of a survey of the use of sunbeds in the United Kingdom (Diffey 1986). Questionnaire replies from over 1000 sunbed users indicated that the incidence of acute adverse effects was substantial; 28% of users complained of itching and about 8% developed a skin rash or had felt nauseous at some time during or immediately after exposure. The incidence of such effects was higher among women taking oral contraceptives than in women who were not. No conclusion could be drawn about other medications as few individuals were taking them. The survey also revealed that 50% of sunbed users in the United Kingdom are female and aged between 16 and 30 years. 43% of users had skin types I and II, the most sensitive to the adverse effects of UV and the ones least likely to tan well.

Structural damage to human skin from exposure to UVA, such as demonstrated experimentally in mice (Kligman *et al.,* 1987, Bissett *et al.,* 1989) might be expected in people as the result of excessive use of sunbeds. Increased skin fragility and blistering (Farr *et al.,* 1988; Murphy 1989) and atypical melanocytic lesions (Jones *et al.,* 1987) have been observed in people who have used UVA sunbeds excessively. In some people, photodermatosis and polymorphic light eruption, is readily caused by exposure to UVA radiation from a sunbed (Rivers *et al.,* 1989). Certain photo-aggravated dermatoses, such as lupus erythematosus, are exacerbated by the use of UVA sunbeds (Stern and Docken 1986). The use of certain medications such as antihypertensives and antibiotics (Hawk 1984) and topical application of certain products, including perfumes, body lotions, etc., may produce a photosensitising effect on exposure to a sunbed.

Some localised skin and systemic changes in immunological reactions result from exposure to UV and, of particular relevance to sunbeds, from exposure to UVA. There is also evidence that exposure to UV can accelerate the growth of human viruses (e.g. Otani and Mori 1987, Perna *et al.,* 1987), including human immunodeficiency virus (HIV) (Zmudzka and Beer 1990). At present, the significance of

these observations with respect to the health of people exposed to UV from sunbeds is unclear.

The risk of non-melanocytic skin cancer in northern Europeans who sunbathe and who use sunbeds has been estimated by Diffey (1987) using a mathematical model of skin cancer incidence that makes allowance for childhood, occupational and recreational solar radiation exposure. The model takes into account the fractions of total skin surface area that might normally be exposed during everyday activities and the larger fraction, normally unexposed, but exposed during sunbathing and sunbed use. The annual effective radiant exposures resulting from different activities and exposure scenarios used as the basis for risk calculations are expressed as representative minimal erythemal doses (MEDs) in table 12.1.

Table 12.1 Representative annual minimal erythemal doses (MEDs) for various exposure scenarios in northern Europeans (Diffey, 1987, 1993a).

Scenario	Annual MEDs
Outdoor worker	270
Indoor worker (including weekend exposure)	90
Sunbathing holiday in Mediterranean area for 2 week period in summer	50-100
UVA sunbed (low pressure fluorescent lamps, 30 x 30 minute sessions *	20

*   Recommended maximum number of sessions per year (IRPA/INIRC, 1991a) with estimated exposure of 0.7 MED per session (Diffey, 1987).

Diffey (1987) concluded that the increased risk of non-melanocytic skin cancer associated with the use of a UVA sunbed for 10 sessions per year is negligible. However, frequent use of a sunbed, for example once per week from the age of 20 years will result in an estimated doubling of the risk of non-melanocytic skin cancer by age 45 years.

Several studies have reported increased risks of cutaneous melanoma in users of sunlamps and sunbeds (IARC 1992).

12.2.4 Sunbathing

A significant contribution to the risk of non-melanocytic skin cancer that results from sunbathing (Diffey, 1987). In these calculations it was assumed that the subjects were indoor workers who began sunbathing at age 20 years, and that their annual exposure up to age 16 years is one half that of an outdoor worker. An indoor worker who does not sunbathe is estimated to have a 2-3% risk of non-melanoma skin cancer by age 70. Annual two week vacations spent sunbathing at Mediterranean latitudes (approx. 40°N) will increase this risk by a factor of about 5. Sunbathing for four weeks annually is estimated to result in a 10-20 fold increase in cumulative risk compared with non-sunbathers. It should be stressed that sunbathing during vacation periods was assumed to take place for nearly the whole day on every day of vacation. This is unlikely to be the case for most holiday makers and so the estimated risk factors for most people taking holidays in a sunny climate are likely to be one-third to one-half of those given.

12.3 Adventitious Exposures

12.3.1 Outdoor exposures

Studies using personal dosimeters to monitor exposure of individuals to UV have shown that, on average the carcinogenic-effective UV exposure (excluding vacation exposure) of outdoor workers is about 3 times that of indoor workers (Holman *et*

al., 1983; Larko and Diffey 1983; Schothorst *et al.,* 1985).

Assuming that up to the age of 16, indoor and outdoor workers receive the same carcinogenic-effective radiant exposure and that both receive equivalent vacation exposures, the relative risk for non-melanoma skin cancer for outdoor workers is estimated to be 3.7 times that for indoor workers (Diffey 1987). However, recent population studies have found only small differences in skin cancer incidence between outdoor and indoor workers (see chapter 8).

Armstrong & Kricker (1994) have estimated the proportion of cutaneous malignant melanomas that is caused by sun exposure. The estimated proportions varied from 0.97 in males and 0.96 in females in Queensland, Australia, when the incidence on the whole body was compared with the incidence on unexposed sites, to 0.68 when the incidence in people born in Australia was compared with that in migrants to Australia from areas of lower sun exposure. A comparison of whites and blacks in the US in which the incidence in blacks was taken as the incidence in unexposed whites, gave estimates of 0.96 in males and 0.92 in females. It was estimated that some 59,000 (65%) of about 92,000 malignant melanomas worldwide in 1985 were caused by sun exposure.

12.3.2 Artificial sources

General public exposure

Exposure of the general public to potentially hazardous levels of UV from artificial sources is unlikely. However, an area that merits note is the increased use of tungsten halogen lamps for lighting. Very high filament temperatures combined with quartz envelopes results in the emission of significantly higher levels of UV compared with conventional incandescent lamps (Césarini & Muel, 1989; McKinlay *et al.,* 1989). For many applications of such lamps the presence of a glass filter effectively attenuates the potentially harmful UV. However, for some others, and particularly when such lamps are incorporated in desk-top luminaires, no protective filter is present, and significantly high levels of erythemally effective UV have been measured. However, for lamps of similar design and having nominally the same power, there is a wide range of emitted levels of UV, (for example, between 2 and 56 mW m^{-2} effective, in the beam of the lamp at 30 cm distance)

Occupational exposure

Sources that emit UV are used for a wide range of applications in the workplace. High intensity discharge sources should be, and often are, contained in interlocked enclosures thus obviating hazardous exposure of people. Hazard evaluation surveys generally consist of measurements of the effective exposure levels of UV and comparison with recommended guidelines on limiting exposure. This approach addresses the adverse acute effects of exposure, but very few risk assessments have been carried out in relation to chronic effects. The risk of non-melanocytic skin cancer for any occupational situation can be calculated using multivariant analysis, provided the effective exposures related to the occupation are known. However, although data on levels of exposure exist for some occupational situations there is generally a paucity of such data. Where estimates of skin cancer risk have been made, they have related to specific occupational exposure situations (Diffey 1988, 1989) or broadly with respect to general (fluorescent) lighting (Lytle *et al.,* 1993).

Examples where occupational exposure to UV from artificial sources may occur include; electric arc plasma welding, the drying and curing of inks, resins, plastics and paints; printing, graphics arts, copying (using photographic processes) and photography, photoetching, projector lamps operation, medicine, scientific laboratory work, tanning and salon work and UV associated with general lighting fluorescent lamps and desk-top and other luminaires incorporating tungsten halogen lamps.

Welders are likely to be the largest occupational group with potential exposure to UV (IARC 1992). The UV effective irradiance

levels around an operating welding arc can exceed recommended exposure guideline levels by several orders of magnitude, and the occurrence of acute effects of exposure, photokeratitis and erythema, is common (Eriksen 1987).

Many industrial photoprocesses use high intensity discharge lamps that emit copious quantities of UV. However, most of these sources are effectively shielded and interlocked to prevent human exposure. Some sources emit leakage radiation and, under these circumstances, a detailed measurement survey is required to assess the degree of hazard.

Medical physiotherapists involved in the phototherapy of patients are occupationally exposed to UV and an analysis of probable risk has been published (Diffey 1988). During a working life of 40 years, the additional risk of non-melanoma skin cancer for a member of this group is estimated to be around 25% compared with that for non-exposed workers.

General lighting

Low pressure mercury vapour fluorescent lamps are ubiquitous in the workplace and the home and concern has been expressed regarding the potential role of the UV they emit in the aetiology of malignant

melanoma. Epidemiological data on exposure to general lighting
fluorescent lamps and malignant melanoma are few and inconsistent.
IRPA/INIRC (1991) concluded that UV exposure from indoor fluorescent
lighting should not be considered as a malignant melanoma risk.

The exposure levels associated with the use of general lighting
fluorescent lamps have been measured in a number of studies (Cole
et al., 1986; McKinlay & Whillock, 1987; Muel et al., 1988 and
Lytle et al., 1993). Exposure data vary considerably depending on
the types of lamps examined and the exposure conditions considered.
A recent study (Lytle et al., 1993) serves to illustrate estimates
of the risk associated with long term exposure to unfiltered general
lighting fluorescent lamps used in the United States. It was
estimated that 50 years exposure to typical unfiltered levels of UV
from fluorescent lamps added approximately 4% (1.6 - 12%) to any
risks associated with exposure to solar UV.

13.   INTERNATIONAL GUIDELINES ON EXPOSURE TO ULTRAVIOLET RADIATION

A number of national and international organizations have
promulgated guidelines or standards on exposure to UV. Most are
based upon the same basic criteria of ACGIH (1993) and IRPA/INIRC
(1991).

The basic exposure limit (EL) for both general public and
occupational exposure to UV incident on the skin or eye is 30 J
m^{-2} effective), when the spectral irradiance E_{lambda} at the eye
or skin surface is mathematically weighted with the hazard relative
spectral effectiveness factor S_{lambda} from 180 nm to 400 nm. This
is given as follows:

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

where:

E_{eff} = effective irradiance W m^{-2}

E_{lambda} = spectral irradiance from measurements in W m^{-2}
nm^{-1}

S_{lambda} = relative spectral effectiveness factor (unit-less)

$Delta_{lambda}$ = bandwidth of the calculation or measurement in
nm

At 270 nm in the UVC range, S_{lambda} is 1.0, but at 360 nm in
the centre of the UVA range, its value falls to 0.00013, and
continues to fall for longer wavelengths.

For the UVA, the total radiant exposure incident on the
unprotected eye should not exceed 10^4 J m^{-2} (1 J cm^{-2}) within
an 8 h period. The total 8 h radiant exposure incident on the
unprotected skin should not exceed the values in table 13.1.

The radiant UV exposure incident upon the unprotected skin or
eye within an 8-hour period should not exceed the values given in
table 13.1. The limits apply to sources whose emissions are measured
with an instrument having a cosine response detector oriented
perpendicular to the most directly exposed surfaces of the body when
assessing skin exposure and along (or parallel to) the line(s) of
sight when assessing ocular exposure. Although no measurement
averaging aperture is recommended, 1 mm is commonly used.

Table 13.1   International UV exposure limits and spectral weighting
             factor (IRPA/INIRC, 1991)

Wavelength[a] (nm)	EL (J m^{-2})	EL (mJ cm^{-2})	Relative Spectral Effectiveness S_{lamda}
180	2,500	250	0.012
190	1,600	160	0.019
200	1,000	100	0.030
205	590	59	0.051
210	400	40	0.075
215	320	32	0.095
220	250	25	0.120
225	200	20	0.150
230	160	16	0.190
235	130	13	0.240
240	100	20	0.300
245	83	8.3	0.360
250	70	7.0	0.430
254[b]	60	6.0	0.500
255	58	5.8	0.520
260	46	4.6	0.650
265	37	3.7	0.810
270	30	3.0	1.000
275	31	3.1	0.960
280[b]	34	3.4	0.880
285	39	3.9	0.770
290	47	4.7	0.640
295	56	5.6	0.540
297[b]	65	6.5	0.460
300	100	10	0.300
303[b]	250	25	0.190

305	500	50	0.060
308	1,200	120	0.026
310	2,000	200	0.015
313[b]	5,000	500	0.006
315	1.0×10^4	1.0×10^3	0.003
316	1.3×10^4	1.3×10^3	0.0024
317	1.5×10^4	1.5×10^3	0.0020
318	1.9×10^4	1.9×10^3	0.0016
319	2.5×10^4	2.5×10^3	0.0012
320	2.9×10^4	2.9×10^3	0.0010
322	4.5×10^4	4.5×10^3	0.00067
323	5.6×10^4	5.6×10^3	0.00054
325	6.0×10^4	6.0×10^3	0.00050
328	6.8×10^4	6.8×10^3	0.00044
330	7.3×10^4	7.3×10^3	0.00041
333	8.1×10^4	8.1×10^3	0.00037
335	8.8×10^4	8.8×10^3	0.00034
340	1.1×10^5	1.1×10^4	0.00028

Table 13.1 (contd).

Wavelength[a] (nm)	EL (J m^{-2})	EL (mJ cm^{-2})	Relative Spectral Effectiveness S_{lamda}
345	1.3×10^5	1.3×10^4	0.00024
350	1.5×10^5	1.5×10^4	0.00020
355	1.9×10^5	1.9×10^4	0.00016
360	2.3×10^5	2.3×10^4	0.00013
365[b]	2.7×10^5	2.7×10^4	0.00011
370	3.2×10^5	3.2×10^4	0.000093
375	3.9×10^5	3.9×10^4	0.000077
380	4.7×10^5	4.7×10^4	0.000064
385	5.7×10^5	5.7×10^4	0.000053
390	6.8×10^5	6.8×10^4	0.000044
395	8.3×10^5	8.3×10^4	0.000036
400	1.0×10^6	1.0×10^5	0.000030

[a] Wavelengths chosen are representative; other values should be
     interpolated at intermediate wavelengths.
[b] Emission lines of a mercury discharge spectrum.

     The permissible exposure duration, t_{max}, for exposure (in
seconds) to UV is calculated by:

$$t_{max} = 30/ \ E_{eff} \ (W \ m^{-2})$$

     Examples are provided in table 13.2.

Table 13.2 Limiting UV exposure durations based on exposure limits
(IRPA/INIRC, 1991)

Duration of exposure per day	Effective irradiance	
	E_{eff} (W m^{-2})	E_{eff} (μW cm^{-2})
8 hours	0.001	0.1
4 hours	0.002	0.2
2 hours	0.004	0.4
1 hour	0.008	0.8
30 minutes	0.017	1.7
15 minutes	0.033	3.3
10 minutes	0.05	5

     The EL's were developed considering lightly pigmented
populations with greatest sensitivity and predisposition to adverse
health effects from exposure to UV. The limits apply to UV exposure
of the working population, but with some precaution also apply to
the general public. However, some rare, highly photosensitive

individuals exist who may react adversely to exposure at these
levels. These individuals are normally aware of their heightened
sensitivity. Likewise, if individuals are concomitantly exposed to
photosensitizing agents, an enhanced reaction can take place. Many
individuals who are exposed to photosensitizing agents (ingested or
externally applied chemicals, e.g., in cosmetics, foods, drugs,
industrial chemicals, etc.) may not be aware of their heightened
sensitivity. Lightly pigmented individuals conditioned by previous
UV exposure (leading to tanning and hyperplasia) and heavily
pigmented individuals can tolerate skin exposure in excess of the
EL's without erythemal effects. However, repeated tanning may
increase the risk of accelerated skin aging and even skin cancer.
Such risks should be understood prior to the use of UV for medical
phototherapy or cosmetic exposures.

14. PROTECTIVE MEASURES

14.1 Introduction

     It is widely accepted by scientific and medical authorities
throughout the world that UV is potentially carcinogenic and capable

of producing other undesirable health effects. It is sensible
therefore to take steps to minimise UV exposure. Many risks in life
are completely beyond our control such as contracting a rare
disease. However, risks to health associated with exposure to UV
from both natural and artificial sources can be substantially
reduced by taking appropriate control measures.

        Since UV exposure occurs externally, simple measures can be
taken to reduce the exposures received. A high degree of protection
can be afforded by protective clothing (including hats), UV
protective eyewear (welding helmets, face shields, goggles,
sunglasses, spectacles etc.) and by sunscreens for exposed skin.
However, the degree of protection afforded can be reduced by
ingestion of photosensitizing drugs or photoallergic/phototoxic
reactions produced by chemicals or cosmetics in contact with the
skin. Thus, education is also an important control measure.

14.2 Education

        Concern about high incidences of skin cancer and eye damage
have led to national educational campaigns in some countries to
encourage people to protect themselves against excessive UV exposure
from the sun and in the workplace. Educational programmes directed
at both the workforce and the public are intended to create an
awareness of the adverse health effects that can result from
overexposure to UV.

        Presently, in several different countries around the world,
daily environmental UV levels are supplied to the general public in
the form of UV indices. Their provision is intended to educate the
public on the basic climatology of UV, increase awareness of the
hazards of UV and provide information necessary to plan protection.
In a report commissioned to investigate Canadian attitudes to
Environment Canada's UV index (Environment Canada, 1993), it was
found that 73% of Canadians were aware of the UV index, 91% believed
UV affected human health, and most important, 59% of respondents who
were aware of the UV index had changed their sun exposure habits.

        Different countries have adopted their own national UV indices.
Unfortunately, they are not all compatible. Clearly, international
uniformity would help to prevent confusion.

        Educational programmes aim to produce a change in knowledge and
attitudes, then a change in behaviour and eventually a reduction in
the incidence and mortality rates of skin cancer. A survey of

sunscreen use on beaches in Brisbane, Australia found about 70% of
females and males applied sunscreen. Half of the sunscreens provided
the maximum protection (SPF 15+) and almost 90% used a waterproof
formulation. However, the sunscreen was not applied over the entire
body with over half neglecting ears and lower limbs (Pincus *et al.,*
1991). Survey results show that sunburn is still occurring; in a
randomly selected group of adults in Melbourne, Australia 16%
reported sunburn over a summer weekend (Hill *et al.,* 1992). With
regard to skin cancers it is still too early to evaluate the
effectiveness of current educational/publicity campaigns.

        With respect to changes in behaviour, there is good reason to
avoid exposure to the midday sun since it has been estimated that up
to one third of the day's erythemally effective UV is received
within the period one hour before noon to one hour after noon. Shade
is a useful method of protection but its value should not be
over-estimated, as one may be exposed to a quarter or more of the
total solar UV while shaded from direct sunlight, depending on the
prevailing exposure conditions.

14.3 Protection Factors

        The concept of a protection factor is useful when attempting to
quantify the UV protection that items such as sunscreens, clothing
and eyewear can provide (Gies *et al.,* 1992). To determine the
protection factor, the following procedure is conducted. An
effective dose (ED) of UV to the unprotected skin or eye is
calculated by summing the incident solar spectral power over the
wavelength range 280 to 400 nm. In order to determine the effective
dose (ED_m) for the skin or eye when it is protected, the
calculation is repeated with the spectral transmission of the
protection item as an additional weighting. The protection factor
(PF) is then defined as the ratio of ED to ED_m and is given by the
following equation:

$$PF = \frac{ED}{ED_m} = \frac{\Sigma E_{lambda} . S_{lambda} . \Delta \, lambda}{\Sigma E_{lambda} . S_{lambda} . T_{lambda} . \Delta \, lambda}$$

where:

E_{lambda} = spectral irradiance (W m^{-2} nm^{-1}) at wavelength lambda

S_{lambda} = relative spectral effectiveness

T_{lambda} = spectral transmission of protective item at
        wavelength lambda

Delta lambda = wavelength interval or bandwidth (nm)

lambda = wavelength (nm)

The inclusion of the spectral effectiveness function in the
calculation ensures that sufficient weighting is given to the
biologically effective wavelengths below 315 nm. A description of
how the protection factors for fabrics, eyewear and sunscreens are
determined is given in Roy and Gies (1993) and CIE (1991).

14.4 Clothing

Use of protective clothing provides one of the simplest means
of reducing UV exposure. Hats have been shown to afford protection,
to various degrees, to the forehead, scalp, ears and most of the
neck. Their protective properties have been studied by Diffey and
Cheeseman (1992). In this study hats were classified into four
categories, small brim, medium brim, large brim and peaked cap. The
protection afforded to different anatomical sites on the head and
neck is shown in table 14.1.

Table 14.1 Sun protection for various anatomical sites on the head
and neck provided by different types of hat (Diffey & Cheeseman,
1992).

Style of hat	Forehead	Nose	Cheek	Chin	Back of neck
		Typical sun protection factor *			
Small brim < 2.5 cm	15	1.5	1	1	1
Medium brim 2.5-7.5 cm	>20	3	2	1	1
Large brim >7.5 cm	>20	7	3	1.2	5
Peaked cap	>20	5	1.5	1	1

* In this table 'sun protection factor' is defined as the reciprocal
  of the fraction of UV exposure recorded relative to that of the
  unprotected head.

The degree of protection provided by clothing depends on the
penetration of UV through materials and this can vary considerably.
Fabrics which are visibly opaque tend to be more highly absorbent of
UV, but the structure or weave of a material is the most important
factor in determining its protective value. Colour and thickness are
a poor guide to UV protection. The transmission properties of some
fabrics commonly used in the manufacture of clothing for everyday

wear are given in table 14.2 (Welsh and Diffey 1981). Here the
protection factor is an estimate of the protection afforded against
biologically effective solar radiation. A high protection factor is
associated with a tightly woven material. UV is transmitted and
scattered through the interstices of the material itself rather than
penetrating the fabric.

Gies *et al.* (1992) have recently extended the concept of
protection factor (PF) to fabrics and proposed the Ultraviolet
Protection Factor (UPF). The UPF scheme, as shown in table 14.3, is
designed to give the general public information on the amount of UV
protection available from fabrics and clothing and is now in use in
Australia. UPF is analogous to SPF and a fabric of UPF 10 would, in
principle, provide a similar level of protection as a sunscreen of
SPF 10.

Table 14.2 UVB transmission properties of common fabrics
        (from Welsh & Diffey 1981)

Fabric	Structure	Colour	Thickness (mm)	% of incident UV transmitted	Protection factor
Nylon-tricel	Woven	Black	0.1	0.15	750
Nylon-viscose jacquard	Woven	Black	0.2	0.20	500
Nylon	Woven	White	0.1	1.7	55
Nylon-terylene mixture	Knitted	Blue	0.2	11	9
Nylon-acetate jersey	Knitted	Pink	0.2	24	4
Polyester-slub viscose	Woven	Pink	0.5	9	14
Polyester-printed lawn	Woven	Red	0.2	7	11
Polyester-jersey	Knitted	Fawn	0.3	7	14
Polyester-jersey	Knitted	Cream	0.4	5	19
Polyester-jersey	Knitted	Black	0.3	8	12
Polyester-jersey	Knitted	Orange	0.3	5	23
Polyester-jersey	Knitted	Turquoise	0.5	16	6
Polyester-jersey	Knitted	Brown	0.7	1.6	68
Polyester-jersey	Knitted	Black	0.5	4.4	23
Polyester-brushed jersey	Knitted	Blue	0.4	5.2	19
Polyester-brushed jersey	Knitted	Green	0.4	6.0	16
Polyester-bouclette	Knitted	Orange	0.4	3.0	33
Polyester-bouclette	Knitted	Purple	0.4	2.0	51
Cotton-needlecord	Woven	Brown	0.5	< 0.1	> 1000
Cotton-denim	Woven	Blue	0.5	< 0.1	> 1000
Cotton-printed	Woven	Brown	0.3	< 0.1	>1000
Cotton-printed	Woven	Cream	0.3	2.7	36
Wool-jersey	Knitted	Fawn	0.7	0.7	150

Table 14.3   Summary of the ultraviolet protection
             factor scheme for fabrics

| Ultraviolet protection factor UPF	Mean % UV transmission	Protection category
UPF 40+	less than 2.5	Maximum protection 40+
UPF 30 to 39	3.3 to 2.5	Very high protection
UPF 20 to 29	5.0 to 3.3	High protection

     Whether a material is wet or dry is important in relation to
its UV transmission properties. The spectral transmittances of some
cotton and polyester-cotton samples are shown in figure 14.1.
Measurements show that the variation of UPF for wet and dry fabrics
is consistent for cotton, all examples showing a decrease in UPF
when wet (Gies *et al.,* 1992). The variation in UPFs between wet
and dry was less consistent for polyester- cotton than for the
cotton, some UPFs increasing for wet fabric, while others decreased.

14.5 Sunscreens

     Sunscreens are physical and chemical topical preparations which
attenuate the transmission of solar UV into the skin by absorption,
reflection or scattering. Physical sunscreens (sunblocks), for
example zinc oxide, titanium dioxide or red ferric oxide, function
by reflecting and scattering and provide protection against a broad
spectrum of UV and visible wavelengths. They are normally nontoxic
and have few known adverse effects. Sunscreens based on chemical
absorbers contain one or more colourless UV-absorbing ingredients
which generally absorb UVB radiation more strongly that UVA.
Para-aminobenzoic acid (PABA) and its derivatives, salicylates,
cinnamates and camphor derivatives primarily absorb UVB and transmit
UVA; benzophenones essentially absorb UV of wavelengths of less than
360 nm. The use of solely UVA absorbers (di-benzoyl-methane) is
allowed in only certain countries. These chemicals are all based on
benzene (Moseley 1988).

     The application of any sunscreen normally changes the spectrum
of UV that reaches the target cells. Although most sunscreens are
designed to attenuate UV, some contain additives such as bergamot
oil (containing 5-methoxypsoralen) to enhance pigmentation and
photoprotection (Young *et al.,* 1991). The role of such
preparations remains controversial.

Figure 14.1 Percentage transmissions of wet and dry samples of cotton and polyester fabrics (from Gies et al., 1992).
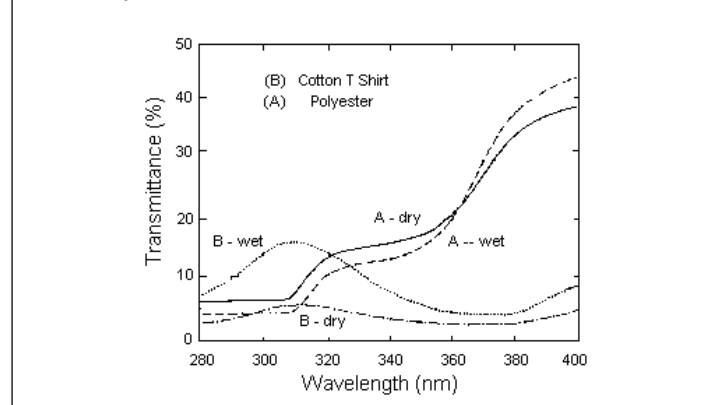
     The generally accepted parameter for evaluating the efficacy of
sunscreen preparations is the sun protection factor (SPF), which is
defined as the ratio of the least amount of UV required to produce
minimal erythema after application of a standard quantity of the
sunscreen to the skin to that required to produce the same erythema
without sunscreen application. Several countries have published
recommendations for the efficacy testing of propriety sunscreens,
e.g. the US Food and Drug Administration (1978) and CIE (1991).

     Many factors influence SPF values; particularly important are
the spectral power distribution of the source used for SPF testing
and a clear definition of the end-point used for assessment (Urbach,
1989). Variations in these factors can lead to considerable
differences in measured SPF values for the same product.

     SPF values generally reflect the degree of protection against
solar UVB radiation, but their protective capacity against UVA must
also be defined. Several in-vivo and in-vitro methods have been
proposed for defining protection against UVA but there is currently
no international consensus on which is the most appropriate.
However, this issue is currently being considered by a technical
committee of the CIE.

     Correctly used, sunscreens are effective in preventing sunburn.
Actual SPF values depend critically on the thickness of the
application and on other factors such as absorption into the skin,
sweating and contact with water (for example while swimming).

     If sun exposure causes skin cancer, it would be expected that

the use of efficient sunscreens would prevent skin cancer. In animal
experiments, sunscreens with a SPF of as low as 4 have been shown to
be effective in preventing or delaying the onset of UV-induced skin
tumours and cancers (Forbes et al., 1989). There is, at present,
neither direct epidemiological nor laboratory evidence to suggest
that they prevent melanoma or basal cell carcinoma. The few studies
conducted to date suggest either no effect or a causal rather than a
protective effect. For example, Holman et al. (1986) found a
relative risk of melanoma of 1.06 (95% confidence interval
0.71-1.57) with 1-9 years use of sunscreens and 1.15 (95% confidence
interval 0.78-1.68) with 10+ years of use relative to "never use". A
statistically significant positive association of "often or very
often" use of sun protection agents with melanoma (relative risk
1.8, 95% confidence interval 1.5-3.8) was found by Beitner et al.
(1990). In their cohort study of basal cell carcinoma in US nurses,
Hunter et al. (1990) found a higher risk in those who spent 8+
hours per week outside and used sunscreen than in those who spent
the same time outside but did not use sunscreen.

     These results cannot be taken at face value. First, there is
likely to be negative confounding of the use of sunscreens with
cutaneous sun sensitivity, people with highly sun sensitive skins

are likely to use sunscreens more than people with less sensitive
skin. Second, there is good evidence that the epidemiological
studies have identified an enthusiastic suntanning population using
sunscreens with minimal SPF to promote their suntan. Third, it is
likely that people adopt or increase their use of sunscreens after
their first skin cancer has been diagnosed, or their attention is
drawn to their personal risk in some other way (for example,
diagnosis of a solar keratosis). Thus present users of sunscreens
are likely to be enriched with people at higher than average risk of
skin cancer. While adjustment for confounding with skin sensitivity
has been carried out in some studies (Holman et al. 1986, Hunter
 et al. 1990), this third issue has not been addressed in any
published analysis. Fourth, relatively little information is
available on the mutagenic and carcinogenic potential of various
sunscreens. The US National Cancer Institute (1989) recommended the
following six compounds to be evaluated for chronic testing in
rodents by the US National Toxicology Program: cinoxate;
2-ethylhexyl 2-cyno-3,3-diphenyl-acrylate; 2-ethylhexyl
para-methoxycinnamate; homosalate; methyl anthranilate; and
oxybenzone. Neither epidemiological nor long term mammalian
carcinogenicity data are available on these compounds. The results
of in-vitro studies were assessed as either negative or inconsistent
among systems or among batches of a compound (because of
impurities). 2-ethylhexyl para-methoxycinnamate was implicated as a
potential tumour initiator in one study in which hairless mice were
painted with the compound over a nine-week period and subsequently
treated with the tumour promoter, croton oil (Gallagher et al.,
1984a). Subsequent work by Reeve et al. (1985), however, failed to
confirm these results, and Forbes et al. (1989) found no evidence
of tumour initiation by the compound in an initiation-promotion
experiment in mice.

     Sunscreens have been strongly promoted by the medical community
such as in the United States, Canada, Australia, and Scandinavian
countries. However, incidence rates of melanoma have risen steeply
in recent decades, even after the introduction of sunscreens (Lee
1989, Jensen and Bolander 1980, Magnus 1977, 1986; Gallagher et
 al., 1986). The use of high SPF sunscreens is recommended by WHO
and by the International Union Against Cancer (UICC) as a supportive
part of a sun avoidance programme rather than its main thrust (Marks
& Hill, 1992).

     Both UVA and UVB have been shown to mutate DNA and cause skin
cancers in animals (Staberg et al., 1983). UVA penetrates deeper
into the skin than UVB and because of the energy distribution of
sunlight and filtering by the outermost layers of the skin,
melanocytes receive up to 70 photons of UVA for every photon of UVB.
Sunscreens effectively block solar UVB. UVB is the normal stimulus
for accommodation of the skin such as thickening and increased
pigmentation.

     Sunscreens suppress normal warnings of overexposure such as
erythema and sunburn and allow excessive exposure to wavelengths of
sunlight they do not block. Due to lack of these natural signs
sunscreens create a false sense of security and individuals tend to
stay in sun longer. In view of these behavioural changes which
increases individuals UVA exposure it has been suggested that,
because of the rising incidence of melanoma, UVA may be associated
with its occurrence (Garland et al., 1992). While a recent study
(Setlow et al., 1993) in fish reported melanoma induction by UVA,
the role of UVA in the causation of human malignant melanoma has yet
to be established.

     Trans-urocanic acid, a natural compound of the stratum corneum
which absorbs UVB and is used as an additive in some commercial
sunscreen products, increased the yield of solar-simulated UV
induced tumours in hairless mice (Reeve et al., 1989). The
significance of this finding for human exposure has not been
evaluated.

     Reports on sunscreen protection against UV induced
immunosuppression have been equivocal. Fisher et al. (1989)
reported no protection of hairless mice against UV-induced systemic
immunosuppression following application of Padimate 0 (a PABA ester
and UVB absorber) or oxybenzone (a UVB/UVA absorber) with sun
protection factors (SPF) of 6 or 15. Similarly SPF 15
octy-N-dimethyl-p-aminobenzoate (o-PABA) had no effect on UV-induced

systemic immunosuppression; nor was susceptibility to UV-induced
tumours altered in hairless mice (Reeve *et al.,* 1991). In this
study however, 2-ethylhexyl-p-methoxycinnamate (2-EHMC, SPF-15) was
fully protective. Morison (1984) also reported protection of mice
with PABA against both immunosuppression and susceptibility to UV-
induced tumours. In recent studies (Wolf *et al.,* 1993a, b),
sunscreens with SPFs of 4-6, including o-PABA, 2-EHMC, and
benzophenone all provided protection of mice against UV- induced
local and systemic immunosuppression, although they were less
effective in preventing systemic effects. Finally, in a human study,
a sunscreen containing 8% octyl dimethyl PABA, 2% 2-hydroxy-
4methoxybenzophenone, and 2% methoxydibenzoyl methane (SPF 15) did
not protect against effects of solarium exposure on NK activity,
recall antigen skin tests and immunoglobulin production *in vitro*
in mitogen stimulated cultures (Hersey *et al.,* 1987).

    While further studies are still needed to clarify concerns
raised about the ingredients and protectiveness of sunscreens, broad
spectrum sunscreens which absorb both UVA and UVB with an SPF of at
least 15 are still recommended as an effective means of personal
protection against UV exposure.

14.6 Tanning Devices

    Our modern lifestyle has suggested that having a tan is
synonymous with good health. The increasing popularity of this
symbol of health status and the inability to suntan during
non-summer months, has led to the growth of an artificial tanning
industry using sunlamps or sunbeds (combination of fluorescent
lamp-shaped sunlamps into a bed). The dangers of excessive exposure
to UV have been described earlier in this document. They range from
mild erythema to severe burns of the skin from acute exposure, to
skin cancer and skin ageing from long-term exposure. When eyes are
exposed, damage can occur to the cornea, lens and retina, depending
on the UV wavelength.

    The first generation of sunlamps emitted primarily UVB and, if
used correctly, were efficient tanning agents. Unfortunately, they
also tended to cause a painful 'sunburn' and other undesirable
side-effects. UVA lamps are now used and these, it is claimed, tan
safely without burning. However, as the carcinogenesis action
spectrum extends into the longer UVA spectral region, exposure to
these lamps is not without risk.

    Recommendations regarding the use of sunbeds

    Following a thorough review of this topic, the IRPA/INIRC
(1991a) issued recommendations on the use of sunlamps or sunbeds for
cosmetic purposes as follows:

    General

    The use of sunbeds for cosmetic purposes is not recommended.

    Specific

(1) People with skin types I and II should not use sunbeds. They
     are likely to be disappointed with the results of the
     exposures, they have higher susceptibility to sunburn and have
     a higher risk of developing skin cancer.

(2) Any person with a large number of nevi (moles), a tendency to
     freckle, a history of severe sunburn especially in childhood,
     or a family history of malignant melanoma should not use a
     sunbed.

(3) Any person taking a medicine that is known to be photoactive
     should not use a sunbed. If in doubt, they should seek the
     advice of a physician.

(4) Any person who already has extensive skin "sunlight" damage, or
     who has had premalignant or malignant skin lesions, should not
     use sunbeds.

(5) Any person who has a skin disease should seek the advice of a
     physician before using a sunbed.

(6) Children should not use sunbeds.

(7) Sunbeds should not be used if perfumes, body lotions or sprays
     have been applied that day.

(8) Because the sensitivities of individuals vary greatly, it is
     advisable to limit the duration of the first session to about
     one-half of a regular session in order to establish the user's
     skin response. If following the first session any adverse
     reaction occurs, further use of the sunbed is not recommended.

(9) Regular exposure should not exceed two sessions per week with a
     maximum of 30 sessions per year or 30 minimum erythemal doses
     (MEDs) per year, whichever is the smaller erythemally effective
     exposure. An occasional break from the regularity of exposure
     is advisable.

(10) With respect to recommendation (9), the manufacturer of the
     sunbed should supply a schedule of exposure and recommended
     maximum exposure durations based on the emission
     characteristics of the sunbed.

(11) Appropriate protective eyewear should be provided by the

manufacturer and should always be worn when using a sunbed.

(12) When the sunbed is being provided for use by a commercial
     operator, it is the responsibility of the operator to provide
     the person intending the use the sunbed with the appropriate
     information as summarized in recommendations (1) to (11) above.

14.7 Occupational Protection

Occupational exposure to UV should be kept to a minimum. Some
UV sources emit a considerable amount of visible radiation, and in
this case, the natural aversion response is evoked, so there is
little chance of accidental over-exposure of the eyes. On the other
hand, artificial sources emitting short wavelength UV radiation
exist where accidental exposure is quite likely. While working
outdoors, skin and eye protection should be used. Exposure outdoors
during the periods of 2 hours either side of noon should be avoided.

Where UV levels, compared with the ELs and erythemal dose, are
such as to constitute a hazard, protection against hazardous
exposure may be achieved by a combination of engineering control

measures; administrative control measures and personal protection.
For artificial sources, wherever possible, priority should be given
to engineering and administrative controls to reduce the requirement
for personal protection.

   Engineering controls

The principal and most effective engineering control measures
are those intended to contain the radiation. Wherever possible UV
from artificial sources should be contained within a sealed housing.
If observation windows are required they should be made of suitably
absorbent materials such as certain grades of acrylic and window
glass. Where the exposure process is required to take place external
to the source housing a screened area should be set aside where it
may be carried out; an example of this is arc welding where screens
must be provided to prevent exposure of people not involved with the
welding process. Any such screened area should be subject to
administrative control measures and persons working in the area
should be adequately protected from UV as described below. Where a
source of UV is normally enclosed during use but to which access is
required, for example for maintenance, the housing should be fitted
with safety interlocks. If anyone needs to gain access to the source
while it is energized, the interlock should immediately switch off
the power to the lamps and should not be able to be re-energized
until the interlocks are re-engaged Many such sources are used for a
variety of drying and curing purposes, particularly in the printing
industry and all should be subject to strict engineering controls.

   Administrative control measures

The principal administrative control measures are those that
limit access to the source and provide information directed at
making people aware of potential hazards associated with it. Access
to an area where equipment emits UV should be limited to those
persons directly concerned with its use. All persons concerned with
the use of such equipment should be made aware of this and should be
informed of the potential hazards. Appropriate hazard warning signs
should be used to indicate the presence of UV and whenever possible
warning lights may be used to show that equipment is energized. The
user of a UV emitting source should keep as far from the source as
possible. At large distances (greater than twice the greatest
dimensions of the source) the irradiance (W m^{-2}) falls off as the
square of the distance from the source. Closer to the source
irradiance falls off approximately linearly with distance. Exposures
should be kept to a minimum and the EL's recommended by IRPA/INIRC
(1991) given in chapter 13 should not be exceeded. Particular care
should be taken to prevent exposure of persons taking
photosensitising medications or concomitantly exposed to
photosensitisers in the environment.

   Personal protection

The most effective way to protect the skin from UV is to cover
it. In indoor occupational situations, the areas of the body most at
risk are the face (and eyes) and neck, the forearms and the backs of
the hands. The face can be protected by a shield and this should
also provide eye protection. The arms should be covered by clothing
with a low UVB transmission; in general materials that are visibly
opaque are suitable (see section 14.4). Hands can be protected by
wearing gloves. Face shields, goggles or safety spectacles which
absorb UV should be worn where there is a potential eye hazard.

A range of suitable protective eyewear is commercially
available (see figure 14.2). Welders should be protected by a helmet
fitted with appropriate absorption filters. Some high pressure lamps
are potential explosion hazards and the eyes and face should be
protected against flying fragments of glass. Particular care should
be taken to protect the eyes, face and hands when such lamps are
being removed or replaced. The risk to outdoor workers such as
agricultural workers, labourers, construction workers, fishermen etc
from solar radiation exposure can be minimized by wearing
appropriate tightly woven clothing, and most importantly a brimmed
hat to reduce face and neck exposure. Sunscreens can be applied to
exposed skin to reduce exposure further (see section 14.5).

   Hazards from ozone

The absorption of short wavelength UV by oxygen in the air forms ozone, a powerful oxidising agent. The American Conference of Governmental Hygienists has published a threshold limit value for ozone exposure, 0.1 ppm, (ACGIH, 1993), and concentrations above this value should be avoided.

Levels of ozone may be reduced by providing adequate ventilation in the area in which the source is located. Very intense sources emitting short wavelength UVB, for example, high pressure linear and compact mercury and xenon lamps will normally require an extraction system to remove ozone.

14.8 Protection in Medicine and Dentistry

Protection of both patients and staff must be considered. When a patient is being exposed to UV for clinical purposes, sites not intended to be treated should be covered and the eyes protected.

In medical care, chlorpromazine and thioridazine are phenothiazine derivatives which are widely used as psychosedatives. As well as producing photosensitivity as a side-effect in some patients, these drugs may induce a similar type of reaction in hospital staff. Contact dermatitis may occur in staff handling phenothiazines or fouled laundry since metabolites of chlorpromazine

are phototoxic (Moseley 1988). To avoid contamination, staff should wear protective clothing.

Problems may also occur in dentistry, both for patients and staff. The mouth is lined with a relatively thin squamous epithelium and so there may be considerable penetration of UV to underlying cells. Patients and staff with systemic lupus erythematous (SLE) have been reported to be at risk from lights used in dentistry (Moseley 1988). Both operating lamps and sources used to polymerise resins have been found to cause damage. In one case, a dentist, who was a known SLE sufferer, experienced a facial eruption after using a visible-light resin-curing source on a patient. Evidently, special care is required when lights are used on patients and a known history of SLE would be contraindicated for UV or visible light polymerisation.

14.9 Nutrition

Nutrition can provide the body with essential antioxidants and these molecules are distributed throughout the body. At the cellular level, they enter a number of endogenous photoprotective systems to control photochemical processes (Roberts *et al.,* 1991). Quenchers which can negate specific reactive intermediates may be important as a defence mechanism against UV insult to the eye. Glutathione, due to the low energy of the SH (thiol) bond (65 kcal) is an efficient free-radical scavenger and singlet oxygen quencher. Ascorbic acid quenches free radical and superoxide reactions. alpha-Tocopherol quenches both singlet oxygen and free radicals. There are also various antioxidant enzymes present in the eye. Exogenous scavengers and quenchers may be able to prevent UV damage by interrupting transient intermediates which cause ocular damage. An approach is to increase the known endogenous quenchers, (antioxidants) ascorbic acid, alpha-tocopherol and ß-carotene in the diet (Roberts *et al.,* 1991).

14.10 Additional Protective Agents

Although it has been known that glutathione is a particularly effective quencher of excited state transients in the eye, until now there has been no success in increasing this endogenous sulphydryl compound in ocular tissues. There have recently been found (Roberts *et al.,* 1991) a promising group of compounds, phosphorylated sulphydryls, which pass the blood retinal and blood ocular barrier, and appear to mimic the protective effect of the endogenous thiol glutathione. This offers a possible way of protecting the eye and other tissues from UV induced damage.

Protection from UV damage was reported in mice maintained on a diet supplemented with either carnosine (ß alanylhistidine), an antioxidant known to have immunopotentiating properties (Reeve *et al.,* 1993) or retinal palmitate in combination with canthaxanthin,

a carotenoid (Gensler, 1989). Some protection was also afforded by retinal palmitate alone. Protection has been shown in healthy humans receiving a daily supplement of ß-carotene (Fuller *et al.,* 1992).

14.11 Eye Protection

In industry there are many sources capable of causing acute eye injury within a short exposure time, while in the natural environment acute injury is likely to occur mostly in situations where solar UV is reflected onto the eye, such as from snow while skiing. A variety of eye protection is available with various degrees of protection appropriate to their intended use (see figure 14.2). Those intended for industrial use include, welding helmets (additionally providing protection from intense visible and infrared radiation and face protection), face shields, goggles and UV absorbing spectacles. For use in the outdoor environment, they include (ski) goggles for extreme exposure conditions and sunglasses.

The appropriateness and selection of protective eyewear is dependent on the:

(1) intensity and spectral emission characteristics of the UV

source,

(2) behavioural pattern of people near UV sources (distance and time are important),

(3) transmission properties of the protective eyewear material, and

(4) design of the frame of the eyewear to prevent exposure of the eye from direct unabsorbed UV.

In industrial exposure situations the degree of ocular hazard can be assessed by measurement and comparison with recommended limits for exposure (IRPA/INIRC, 1991) (see Chapter 13). Welders and nearby workers should routinely wear appropriate eye and face protection. For protection against other less intense sources of UV in the workplace tightly fitting goggles or spectacles with side shields may be appropriate, but consideration should also be given to the need for additional face protection. In general, protective eyewear provided for industrial use should fit snugly to the face, thus ensuring that there are no gaps through which UV can directly reach the eye and should have adequate mechanical construction to prevent physical injury.

For outdoor workers and the general public, the most hazardous source of UV exposure is the sun. Adequately designed (ski) goggles afford protection against exposure to solar UV at high altitudes and on snow, but for most other exposure conditions, good UV absorbing sunglasses are an adequate means of eye protection.

Transmission of UV through sunglasses varies considerably (Wester 1987, Gies *et al.,* 1992), yet consumers are provided with little information about the protection afforded by them. Some countries have drafted standards limiting UV transmission through sunglasses and Gies *et al.* (1990a) have proposed a UV eye protection factor (EPF) for sunglasses similar to the one developed for fabrics and sunscreens.
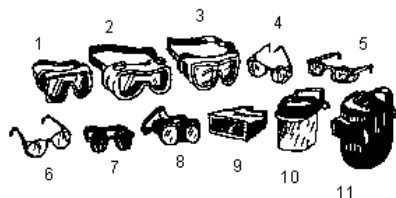
15. FUTURE RESEARCH

15.1 Introduction

At the United Nations Conference on the Environment and Development (UNCED) in 1992 it was declared under Agenda 21 that there should be activities on the effects of UV. Specifically:

(i) Undertake as a matter of urgency, research on the effects on human health of increasing UV reaching the earth's surface as a consequence of depletion of the stratospheric ozone layer;

(ii) On the basis of the outcome of this research, consider taking appropriate remedial measures to mitigate the above mentioned effects on human beings.

This report gives a thorough review of the health hazards of UV exposure. However, although it is known that the burden of UV-related diseases on human populations is high, the exact nature and extent of these diseases is still largely unknown.

There is great uncertainty about future trends in atmospheric ozone. For example the Antarctic holes and large depletions of ozone that have occurred recently were not predicted in any of the ozone depletion models. While agreements have been reached to reduce releases of CFCs into the environment, and this will have future benefit on the ozone layer, there is uncertainty about the extent of ozone depletion caused by chemical pollutants. What is apparent is that decreased ozone levels will persist for many years to come and the corresponding increases in UV intensities will result in more significant adverse health effects on all populations of the world for many decades to come (WMO 1993).

The health effects of UV are not restricted to fair skinned populations. UV exposure is thought to cause diseases of the eye and suppression of the immune system in all populations of the world. UV induced immune suppression may have adverse consequences on infectious disease immunization programmes, particularly in areas where the UV intensities are high. The possibility that UV will cause progression of various diseases such as for HIV positive patients still has to be elucidated. Many such important issues need to be resolved as a matter of urgency.

The WHO Task Group reviewing this monograph strongly supported action and coordination of UV research at the international level. In particular the Task Group supported the concept of the International Research Programme on Health, Solar UV Radiation and Environmental Change (INTERSUN). INTERSUN is a collaborative effort between WHO, the United Nations Environment Programme (UNEP) and the International Agency on Cancer Research (IARC). The group recognised specific research needs in areas of exposure assessment, terrestrial

plants, aquatic ecosystems, and human health effects related to the
skin, immune system and eye. Some of these could be accomplished
under the umbrella of INTERSUN, and some, at least initially, would
require more basic laboratory research to be undertaken.

15.2 INTERSUN

The objectives and approach of INTERSUN are: to accurately
evaluate the quantitative relationship between solar UV at the
surface of the earth and human health effects; develop reliable
predictions of health consequences of changes in UV; provide
baseline estimates of the occurrence of health effects of UV in
representative populations around the world; and develop practical
ways of monitoring change in these effects over time in relation to
environmental and behavioural change.

It is intended to establish field research centres covering a
range of latitudes in both hemispheres in which will be measured:
ground level UV irradiance; incidence of non-melanocytic skin
cancer; incidence and mortality of malignant melanoma; immune
function; biological markers of UV exposure and its' early
carcinogenic effects; constitutional sensitivity to sun exposure;
and present and past sun-related behaviour. In addition, in these
centres there will be undertaken case-control or cross-sectional
studies of relationships between skin cancers, cataract and immune
response and constitutional sensitivity to the sun, lifetime
exposure to the sun, and biological markers of UV exposure and early
carcinogenic effects. Surveys should be repeated at 5-yearly
intervals to allow trends in population measurements to be
established.

Data collected at such centres would be used

-    to describe quantitatively the relationship between ground
     level solar UV irradiance and the incidence of skin cancers and
     other health effects (particularly eye damage and effects on
     the immune system) of UV exposure in human populations.

-    to estimate the change in occurrence of health effects of UV
     radiation that would result from change in ground level solar
     UV irradiance due to environmental change.

-    to increase understanding of the relationship between personal
     risk of health effects of UV radiation and constitutional
     sensitivity to the sun and sun-related behaviour.

-    to develop and validate appropriate ways of monitoring human
     exposure to UV and the occurrence of associated health effects.

-    to develop a network of centres monitoring trends in ground
     level solar UV irradiance, sun exposure of populations, and the
     occurrence of health effects of UV radiation.

-    to interpret these trends, as far as is possible, in relation
     to environmental change, changes in human behaviour, and the
     implementation of public policies aimed at ameliorating
     environmental change or human exposure to solar UV radiation.

-    to provide a basis for development and evaluation of
     interventions to reduce the occurrence of adverse health
     effects of solar UV radiation.

In line with the above objectives and the gaps in knowledge
needed to be filled to make a satisfactory health risk assessment,
the following recommendations for future research are provided.

15.3 Solar and Personal UV Monitoring

The quantification of health detriment to an individual or to a
population requires the assessment of exposure of the individual or
the average exposure of a member of the exposed population. In
interpreting epidemiological data the exposures of the groups
comprising the study populations must be known. The requirements
here are precise measurement data of the environment occupied by the
exposed individuals combined with data on their exposure habits,
derived from representative personal exposure measurements, skin
damage or from questionnaires.

15.3.1 Solar monitoring

1.   A comprehensive network of spectral and broad band monitoring
     stations is needed worldwide giving quality ground measurements
     of surface UV, to assess the effects of enhanced UVA and UVB
     radiation on exposed populations, and to document the impact of
     stratospheric ozone depletion on ambient UV. A long-term data
     record is important.

2.   Quality and convenient monitoring data are needed as input to
     models and for model validation. Current models need to be
     further modified to account for cloud cover, gaseous pollutants
     and aerosols.

3.   Common calibration and audit procedures should be developed and
     implemented for national and international monitoring
     programmes.

4.   Monitoring activities should be coordinated with the efforts of
     other groups on a national and international scale. Close
     coordination is needed for inter-comparison studies and quality

control/quality assurance efforts.

5.   There is a need for global monitoring of UV radiation, with
     particular attention to long-term instrument stability and
     representative geographical deployment

15.3.2 Personal monitoring

     Population studies using personal UV monitoring devices are
needed to determine the fraction of the daily natural UV dose
received by persons at risk. The daily amount of UV received by
human skin varies greatly with occupation, behaviour, and local
climatic and environmental conditions. Little is known about these
factors and this seriously interferes with the interpretation of
existing data on the relationship between UV and the development of
skin cancer and of chronic skin and eye damage. Thus, the
development of personal UV monitoring devices is important.

     Small passive personal UV dosimeters or monitoring devices
should be further developed and used to provide data on personal
exposures. Biomarkers for UV exposure and skin cancer risk should be
further developed, e.g. UV-induced mutations in p53 tumour
suppressor genes. Such biomarkers might constitute a person's own
"built in" UV risk monitoring device.

     For some people, artificial sources of UV represents a
significant component of their exposure. Occupational exposures and
elective exposures such as from cosmetic sunbeds are important in
this respect. Measurement studies are required in these areas.

     Standardized monitoring of exposure to the sun in at risk
populations, particularly children, should be evaluated as a guide
to public health action to control melanoma.

15.4 Terrestrial Plants

     Particular attention must be given to the impact on food
production in the developing world and to development of crop
varieties resistant to higher levels of UV radiation.

     Substantial research is needed to describe and evaluate the
effects of enhanced UV on plants, specifically in the following
areas:

1.   Field validations on crop plants should be extended to
     determine whether UV affects yield in other agriculturally
     important plants.

2.   Studies should be initiated to determine the impacts on
     ecosystems. Little is known of the effects of UV in other
     ecosystems such as forests, where 80% of net primary production
     is currently stored.

3.   It is important to study natural plants because they serve in
     supplying new drugs, medicines and other natural products. They
     also act as a reservoir of genetic diversity for modern crop
     breeding programmes.

4.   Studies are needed to elucidate how UVB effects are modified by
     additional factors such as carbon dioxide, temperature, water
     and nutrient stress, heavy metals, diseases, and pests.

5.   Of increasing interest are man-made air pollutants such as
     sulphur dioxide and nitrogen oxides, which are known to have
     damaging effects on crops and forests. Attention should be
     focused on whether the negative effects of these air pollutants
     may be aggravated by UV radiation.

6.   The manner and magnitude of adaptation to increased UV,
     especially UVB, such as by increased screening pigments or
     enhanced DNA damage repair capacity, need to be investigated
     both as adaption capacity of individual plants and as
     genetically based changes in plant populations. The latter also
     provides a basis for plant breeding interventions for
     agricultural and tree species.

15.5 Aquatic Ecosystems

     Current data suggest that predicted increases in UV, especially
UVB radiation could have important negative effects in the marine
environment. However, uncertainties regarding the magnitude of these
effects remain large, including problems of extrapolating laboratory
findings to the open sea, and the almost complete absence of data on
long-term effects on ecosystems. Additional information is needed in
several areas before more reliable assessments of risk are possible.
Research is needed to:

1.   Determine accurate and appropriate biological action spectra
     for selected endpoints of key marine species.

2.   Produce dose-response data on a greater variety of ecologically
     important primary producers than is now available, as well as
     data for key higher organisms within the food web.

3.   Determine long-term effects for embryos or larvae exposed to
     UVB radiation. Is the survival of the adult population (or
     their offspring) affected?

4.   Determine effects of enhanced UV on major ecosystems, including
     the Antarctic ecosystems.

5. Obtain data on the mechanisms of damage and ranges of possible
    adaptation or genetic selection in response to increased UVB
    radiation.

6. Relate UVB penetration into the water column and through ice
    both in laboratory and field research to determine effects on
    phytoplankton and zooplankton.

7. Develop biomarkers to monitor current levels of UV damage in
    phytoplankton and zooplankton.

15.6 Human Health

15.6.1 Skin

To a substantial degree, answers are still required to the
following questions regarding the relationship between sun exposure
and both melanoma and non-melanocytic skin cancer. Research is
needed to determine:

1. The quantitative relationship between radiant exposure and
    incidence of these cancers; and in particular the shape of the
    exposure-response relationship.

2. How the effect of sun exposure is modified by: age at exposure,
    time since last exposure and pattern of exposure, particularly
    whether a particular dose is received intermittently or
    more-or-less continuously.

3. Biomarkers of UV exposure or early effects in the skin, e.g.
    UV-induced mutations for UV exposure and skin cancer risk.

4. The importance of UVA in causing skin cancers, both relative to
    UVB and comparatively between melanoma and non-melanocytic
    cancer.

5. The importance of indirect (e.g. oxidative) as opposed to
    direct UV damage in causing these cancers.

6. The contribution of sun exposure to the aetiology of these
    cancers in dark-skinned populations and how, in general,
    cutaneous sensitivity modifies both quantitatively and
    qualitatively the relationship between sun exposure and skin
    cancer.

7. If the associations of red hair and freckling with skin cancer
    are explained by effects of skin pigmentation or sensitivity to
    the sun or mediated by other susceptibility mechanisms.

8. If pigmentary characteristics or cutaneous sun sensitivity
    explain most of the ethnic variation in skin cancer incidence
    or are there other ethnically related susceptibility
    characteristics.

9. Whether the relationships between sun exposure and BCC and SCC
    are the same.

10. The role of UV-induced mutations of critical genes in causing
    melanoma.

11. The role of sun exposure in causing cancer of the lip. An
    epidemiological study is required with adequate control of
    potential confounding with alcohol and tobacco use.

12. The relationship between use of sunlamps and sunbeds
    (artificial tanning) and both melanoma and non-melanocytic skin
    cancer. Adequate control of likely confounding with sun
    exposure is required.

13. The effects of the interaction between UVB and the rest of the
    solar spectrum in relation to DNA repair, malignant
    transformation, and skin tumour development.

14. Additional animal models, particularly for the study of the
    experimental induction of malignant melanoma. Further, an
    action spectrum for induction of melanoma should be developed
    in *M. domestica* to see if the apparent response of UVA
    exposure observed in hybrid fish can be confirmed.

15.6.2 Immune System

Suppression of immune functions results from UV exposure of
humans. The following studies are needed to adequately assess the
consequent risk to human health.

1. Studies to determine whether systemic effects occur in humans
    as a result of UV exposure.

2. Establish immunological biomarkers that could identify persons
    who are susceptible to specific long-term UV-induced immune
    suppression, e.g. to infectious agents.

3. Human and rodent studies are needed to determine the
    relationship between UV exposure and susceptibility to
    infection and vaccine effectiveness, and quantitative
    comparison of the relative sensitivities of mice and humans.

4. Studies of the effects of UVB on immune function in human skin
    of all types to determine if all skin types show the same

quality and quantity of effects.

5. Studies to examine whether currently available sunscreens
   provide adequate protection and whether dietary supplements are
   protective. Specifically:

   a) Protective effects for immunosuppression;

   b) Systemic toxicity based on penetration of organic
       chemicals in sunscreens;

   c) Carcinogenicity assays.

6. Studies of the spectral effectiveness of UV in producing immune
   function defects and enhanced susceptibility to disease.

7. Research to determine the role of UVB exposure in
   immediate-type hypersensitivity (allergic) reactions as well as
   specific antibody responses, particularly as it relates to
   impact on incidence and severity of asthma.

8. Research on the effects of UV on the development of autoimmune
   disease and on underlying mechanisms.

9. Studies on systemic effects caused by release of cytokines
   within the epidermis and blood stream.

15.6.3 Eye

     Two issues underscore the need for undertaking studies of
health risks of UV exposure of the eye on a priority basis. First,
there is evidence of the depletion of the ozone layer and the
reported consequent increase in ambient UV which will impact on many
eye diseases. Second, the overall ageing of the population worldwide
would further compound the magnitude of the cataract and other eye
problems.

1. There is a need for well-conducted epidemiological studies to
   be undertaken to define the strength of the association between
   UVA and UVB exposure with cataract and other eye conditions,
   including climatic droplet keratopathy and pterygium, at both
   the individual and community levels. Ideally, this should be
   undertaken in a variety of locations. Careful attention needs
   to be given to quantifying, for each study participant, ocular
   exposure to UV and exposure to other possible risk factors that
   may confound observed associations.

2. Techniques need to be refined for measuring the proportion of
   UV of different wavelengths incident upon the human cornea and
   lens, and how these are affected by the behavioural response to
   avoid direct exposure to bright sunlight, and by different
   ground surfaces.

3. Studies should be conducted to provide data on the quantitative
   relationship between exposure to UV and cataract and other
   lesions of the anterior eye. In relation to this there is an

   urgent need to establish an internationally agreed system for
   grading the type and severity of cataract.

4. Investigations of the role of personal solar exposure in
   causing ocular melanoma, including the protective effect of
   ocular devices.

5. The relationship between sunlamp or sunbed exposure and
   malignant melanoma of the eye needs to be evaluated.

6. The relative efficacy of different protective devices, headwear
   and eye wear needs to be determined.

7. Techniques need to be defined for measuring the proportion of
   UV of different wavelengths penetrating the human cornea and
   lens in the intact eye, in view of possible retinal effects.

8. The action spectra for chronic exposure leading to ocular
   damage needs to be determined in primates and other animals.
   This includes action spectra for cataract formation, pterygium,
   climatic droplet keratopathy, and macular changes in aphakic
   animals.

9. Risks to aphakic people and those with intraocular lens
   implants for retinal changes, mainly from UVA and short
   wavelengths in the visible part of the spectrum, need to be
   determined.

15.7 Laboratory Studies

     Little is known about the mechanisms of interaction of UV and
environmental chemical agents on biological systems. Many widely
distributed natural or artificial chemicals (pesticides,
halocarbons, etc.) can be altered by UV, resulting in photoproducts
that may be less or more biologically effective than the parent
compound. Furthermore, many chemicals can be activated by UV *in
situ* in biological systems and this activation may elicit a
biological effect which neither the chemical nor the radiation alone
exhibits (Psoralens). An international registry of agents that
interact with light to cause adverse health effects would speed
identification of such agents.

     Much of the information on the chemical and biological effects

of UV comes from experiments using UVC (particularly 254 nm)
radiation not found in sunlight reaching the earth's surface. There
are studies showing direct and indirect effects on cells and
cellular constituents of UVB, UVA, and visible light that differ
considerably from those of UVC. Thus, the chemical and biological
effects of the wavelengths of UV found in sunlight should be
studied. There is evidence that visible light can, under different
conditions, either help cells to repair UV-induced damage or can

potentiate the detrimental effects of UV. Thus, to better understand
the effects of sunlight on humans and the environment, experiments
should be performed using natural sunlight or artificial lamps with
well-known continuous spectra.

Cellular and molecular studies needed include:

1. Extension of relevant biological action spectra to the
    UVA/visible wavelengths, as well as interactions between UVA
    and UVB radiation. Crucial spectra required include:

    -   pre-mutagenic lesions

    -   gene activation

    -   activation of viruses specially HIV (activation of DNA
        binding, promoter activity, viral replication)

2. Determination of the free radical/oxidative component of UVB
    and UVA radiation effects. Determine the reactive intermediates
    involved.

3. Determination of adaptation responses in human cells.

4. Determination of endogenous cellular antioxidant defences in
    eye tissue and skin.

5. Elucidation of DNA repair pathways in humans using the advanced
    technology available for analyses of gene and function.

6. Identification of key endogenous and exogenous sensitizers.

7. Studies to examine the effect of UV on the balance between Th1
    and Th2 cells.

15.8 Education

It is essential to educate the general population and workers
concerning the profound importance of sunlight and the possibilities
of either UV deprivation or of acute and chronic UV injury. It is
also important to overcome the lack of respect for the possible
adverse effects on health from overexposure to sunlight, simply
because sunlight is ubiquitous, and the concept that, if something
is natural, it must be totally beneficial and safe. In this context
there is a need to standardize a UV exposure index that can be used
as part of health information/education campaigns.

15.9 Administration

An international panel composed of key national experts, with
its secretariat at WHO, should be formed with the following terms of
reference:

(i)   to identify gaps in knowledge and set research priorities
       needed for a better health risk assessment of exposure to UV

(ii)   to evaluate and monitor progress of research

(iii) to establish mechanisms for funding research and initiate
       projects where crucial gaps in knowledge have been identified

(iii) to facilitate international cooperation on UV monitoring
       efforts, including instrumentation intercomparisons,
       calibration standardization and uniform analysis of data, and

(iv)   to facilitate international cooperation in measurement of
       human UV exposure, monitoring of trends in occurrence of UV
       health effects, and epidemiological studies of the
       relationship between UV exposure and health effects

(v)   to provide a database of research projects to facilitate
       cooperation between researchers and institutions involved in
       research.

16. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

16.1 United Nations Environment Programme

UNEP has undertaken a number of reviews on the environmental
effects of increased UV intensities resulting from ozone depletion
(1989, 1991, 1992). Their findings on each issue are summarized
below:

16.1.1 Ozone

Significant global scale decreases in total ozone have occurred
over the past ten years. All other factors being constant, there is
no scientific doubt that decreases in total ozone will increase UVB
radiation at ground level. Tropospheric ozone and aerosols may have
masked the consequences of stratospheric ozone depletion for UVB in
some industrialized regions. There are no reliable estimates of the

direction or magnitude of effects of any cloud cover trends on UVB.
Efforts to improve local and regional air quality may bring to light
the increases in UVB associated with the depletion of stratospheric
ozone.

16.1.2 Human health

The induction of immunosuppression by UVB has now been
demonstrated in humans, not only those of light pigmentation, but
also deeply pigmented individuals. This places all of the world's
populations at risk of the potential adverse impacts of UVB on the
immune system, including possible increases in the incidence or
severity of infectious disease.

An increased number of adverse ocular effects have been
associated with exposure to UV. These include age-related
nearsightedness, deformation of the lens capsule, and nuclear
cataract (a form of cataract which previous information excluded
from consideration). These effects appear to be independent of
pigmentation. Estimates of risk would increase slightly if one were
to include nuclear cataract among the forms of cataract increasing
with ozone depletion. It is now predicted that, all other things
being equal, a sustained 10% decrease in ozone will be associated
with between 1.6 and 1.75 million additional cases of cataract per
year world-wide.

Recent information on the relationship of nonmelanoma skin
cancer to UV exposures confirms previous findings and has allowed
refinement of the carcinogenic action spectrum. Incorporation of
this new information into the risk estimation process has led to
slightly lower predictions. It is now predicted that a sustained 10%
decrease in ozone will be associated with 26% increase in
non-melanoma skin cancer. All other things remaining constant, this

would mean an increase in excess of 300,000 cases per year
world-wide.

16.2 International Agency for Research on Cancer

The carcinogenicity of ultraviolet has been evaluated by IARC
(1992, 1993). IARC concluded that "There is sufficient evidence in
humans for the carcinogenicity of solar radiation. Solar radiation
causes cutaneous melanoma and nonmelanocytic skin cancer". With
respect to other potential sources of UV, IARC has concluded that
there is limited evidence for the carcinogenicity of exposure to
fluorescent lighting and there is inadequate evidence for the
carcinogenicity of other artificial sources of UV. Readers are
referred to these excellent monographs for more details -much of
which has been incorporated in this text.

16.3 World Health Organization

WHO and its Regional Office for Europe have completed reviews
on the health effects of ultraviolet (WHO, 1979, 1989). They
concluded that all people are exposed to UV from sunlight, and the
risk to health varies with geographical, genetic and other factors.
Similar risks are involved in the increasing exposure of people to
UV from artificial sources, such as those used for suntanning, in
phototherapy and in industrial processes. The biological effects of
a single exposure differ significantly from the effects of repeated
and cumulative exposures. Both types of risk increase markedly with
excessive exposure.

Most observed biological effects of UVB are extremely
detrimental to living organisms. Much less is known about the
biological effects of UVA. It can augment the biological effects of
UVB, and doses of UVA, which alone do not show any biological
effects, can in the presence of certain chemical agents, result in
injury to tissues (phototoxicity, photoallergy, enhancement of
photocarcinogenesis).

All those who work out of doors are potentially at risk of
overexposure, the consequences of which may be both acute and
long-term effects. The fashion of exposing a large part of the body
to sunlight has during recent years increased the exposure of the
skin, resulting in quite high UV doses. This is true not only for
outdoor work but is now also normal during leisure periods, as
exemplified by the holiday exodus of a large part of the population
of the northern European countries to the Mediterranean coast.

16.4 International Commission on Non-Ionizing Radiation Protection

Through its predecessor committee IRPA/INIRC the ICNIRP was
involved in the publication of the original review of the health
effects of UV (WHO/UNEP/IRPA, 1979). It has recommended

international guidelines on limits (IRPA/INIRC, 1991) as shown in
Chapter 13. It has also recommended against the use of sunlamps for
cosmetic purposes (IRPA/INIRC, 1991a). A review of the studies on
fluorescent lighting with reference to UV levels has suggested that
they do not seem to be associated with an increased risk of
malignant melanoma (IRPA/INIRC, 1991).

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See Also:
    Toxicological Abbreviations
    Ultraviolet radiation (EHC 14, 1979)