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Solar radiation and human health

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Abstract
The Sun has played a major role in the development of life on Earth. In Western culture, people are warned against Sun exposure because of its adverse effects: erythema, photoimmunosuppression, photoageing, photocarcinogenesis, cataracts and photokeratitis. However, Sun exposure is also beneficial, since moderate doses give beneficial physiological effects: vitamin D synthesis, reduction of blood pressure and mental health. Shortage of Sun exposure may be even more dangerous to human health than excessive exposure. Avoiding Sun exposure leads to vitamin D deficiency which is associated not only with rickets and osteomalacia, but also with increased risk of cardiovascular disease, multiple sclerosis, rheumatoid arthritis, diabetes, influenza, many types of cancer and adverse pregnancy outcomes. Solar radiation induces nitric oxide release in tissue and immediate pigment darkening which certainly play important roles, although these are still unknown. Action spectra relevant for health are described. We will also review what is known about spectral and intensity variations of terrestrial solar radiation as well as its penetration through the atmosphere and into human skin and tissue.

(Some figures in this article are in colour only in the electronic version)

This article was invited by G T Gillies.

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Abbreviations

1,25(OH)$_2$D	1,25-dihydroxyvitamin D_3 or calcitriol: the hormonally active form of vitamin D
5MTHF	5-methyltetrahydrofolate: the major natural and the most biologically active form of water-soluble B vitamin (folate)
7-DHC	7-dehydrocholesterol or provitamin D: the precursor of vitamin D
25(OH)D	25-hydroxycholecalciferol, 25-hydroxyvitamin D or calcidiol: the circulating form of vitamin D in the blood which is routinely used to diagnose vitamin D deficiency
ADHD	attention deficit hyperactivity disorder: a neurobehavioural developmental disorder
AP-1	activator protein-1: a nuclear transcription factor, which regulates the transcription of various genes essential for cell proliferation, differentiation and apoptosis
BCC	basal cell carcinoma: the first most common type of skin cancer
CCMs	chemistry-climate models: commonly used to simulate the past and future development of Earth's ozone layer
CIE	Commission Internationale de l'Eclairage (International Commission on Illumination): the international authority on light and lighting, colour and vision, photobiology and image technology
CMF	cloud modification factor: describes cloud effects on the transfer of radiation and is defined as the ratio between the irradiance under the cloudy sky and the irradiance for the same atmosphere but for cloud-free conditions
CMM	cutaneous malignant melanoma: the third and most deadly type of skin cancer
CR	circadian rhythm: a daily rhythmic activity cycle, based on 24 h intervals
CVD	cardiovascular diseases: the class of diseases that involve the heart or blood vessels
DBP	vitamin D-binding protein: the major carrier of vitamin D and its metabolites
DHICA	5,6-dihydroxyindole-2-carboxylic acid: a precursor of eumelanin
DP	delayed pigmentation: occurs a few days after UVB exposure due to melanin synthesis and remains for weeks
DPS	differential path length spectroscopy: a method of reflectance spectroscopy used to measure the optical properties of optically turbid media (tissue)

DU	Dobson unit: used to express ozone amounts in the atmosphere. One Dobson unit corresponds to a layer of 0.001 cm of pure ozone at standard atmospheric pressure and temperature
EUV radiation	extreme ultraviolet (10–121 nm) radiation
FAD	flavin adenine dinucleotide: a redox cofactor involved in several important reactions in metabolism
FMN	flavin mononucleotide or riboflavin 5′-phosphate: a coenzyme for a number of oxidative enzymes
GABA	γ-aminobutyric acid: a neurotransmitter in the central nervous system, essential for brain metabolism
GCM	general circulation model: a statistical model to explain, describe and predict global weather patterns under various conditions
GPU	graphical processing unit: a specialized microprocessor that offloads and accelerates graphics obtained from the central processor
Gyr	billion years ago
Hb	deoxygenized form of haemoglobin or deoxyhaemoglobin (without bound oxygen)
HbO_2	oxygenated form of haemoglobin or oxyhaemoglobin
HPA axis	hypothalamic–pituitary–adrenal axis: a complex set of interactions between the hypothalamus, the pituitary gland and the adrenal or suprarenal glands which helps in regulating temperature, digestion, immune system, mood, controls reaction to stress, trauma and injury
ipRGCs	intrinsically photosensitive retinal ganglion cells or melanopsin-containing ganglion cells: mediate non-image-forming visual functions such as pupillary light reflex and circadian photoentrainment
IPD	immediate pigment darkening: a transitory darkening of the skin observed during UVA and visible light exposure which decays within few hours
IR	insulin receptor
IU	International units: an internationally accepted amount of a substance
MED	minimal erythema dose: the minimum amount of UVB that produces redness (erythema, sunburn) 24 h after exposure
mtDNA	mitochondrial DNA: the DNA of the mitochondrion
MMP	matrix metalloproteinases: a family of extracellular zinc-dependent neutral endopeptidases collectively capable of processing and degrading various extracellular matrix proteins
MS	multiple sclerosis: a nervous system disease that affects the brain and spinal cord
NHANES III	Third National Health and Nutrition Examination Survey: a programme of studies designed to assess the health and nutritional status of adults and children in the USA in 1988–1994
NO	nitric oxide: a free radical
NOS	nitric oxide synthases: a family of enzymes that catalyse the production of nitric oxide
OCT	optical coherence tomography: an optical imaging modality for biomedical research and clinical medicine that produces high-resolution cross-sectional images of the internal microstructure of living tissue
OMI	ozone monitoring instrument: instrument onboard NASA's Aura satellite for measurements of atmospheric ozone, i.e. the ozone amount in a vertical column from the Earth's surface to the 'top' of the atmosphere
PUVA	a combination of psoralen and UVA radiation that is used to treat many different skin conditions
PTH	parathyroid hormone: a protein hormone released by the parathyroid gland which is the most important regulator of the body's calcium and phosphorus levels
RAF	radiation amplification factor: describes the relation between the sensitivity of the UVB intensity to changes in total ozone
RCT	randomized controlled trial: an experimental design used for testing the effectiveness of a new medication or a new therapeutic procedure where individuals are assigned randomly to a treatment group (experimental therapy) and a control group (placebo or standard therapy) and the outcomes are compared
REM	rapid eye movement: the stage of sleep characterized by rapid saccadic movements of the eyes
ROS	reactive oxygen species: chemically reactive molecules containing oxygen (hydrogen peroxide, superoxide anion, hydroxyl radical, singlet oxygen, etc)
RTE	radiative transfer equation: a monochromatic equation to calculate radiance in a single layer of the Earth's atmosphere
SAD	seasonal affective disorders or winter depression: a mood disorder in which people experience depressive symptoms in the winter
SCC	squamous cell carcinoma, the second most common type of skin cancer

SCN	suprachiasmatic nuclei: the 'master clock' of the central nervous system, which generates a circadian rhythm of neuronal and hormonal activities, and regulates many different body functions over a 24 h period
SCUP	Skin Cancer Utrecht–Philadelphia
SORCE	Solar Radiation and Climate Experiment: a NASA-sponsored satellite mission which provides state-of-the-art measurements of incoming x-ray, ultraviolet, visible, near-infrared and total solar radiation
SZA	solar zenith angle
TGF-β	transforming growth factor-β: a protein that controls proliferation, cellular differentiation and other functions in most cells
TOMS	Total Ozone Mapping Spectrometer: a satellite instrument onboard various satellites for measurements of atmospheric ozone, i.e. the ozone amount in a vertical column from the Earth's surface to the 'top' of the atmosphere
TSI	total solar irradiance integrated over all wavelengths
UARS	Upper Atmosphere Research Satellite: an orbital observatory whose mission is to study the Earth's atmosphere
UCA	urocanic acid: a major epidermal chromophore that undergoes *trans* (*trans*-UCA) to *cis* (*cis*-UCA) isomerization after UV irradiation
UV radiation	ultraviolet (10–400 nm) radiation
UVA radiation	ultraviolet A (315–400 nm) radiation
UVB radiation	ultraviolet B (280–315 nm) radiation
UVC radiation	ultraviolet C (200–280 nm) radiation
VDR	vitamin D receptor: a receptor binding vitamin D in cells, essential for the functioning of 1,25-dihydroxyvitamin D_3
XMRV	xenotropic murine leukaemia virus-related virus: a gammaretrovirus

1. Introduction

For several years solar radiation and human health has been one of the hottest topics worldwide within the field of photobiophysics. Physicists, biologists and medical doctors join forces to attack the problems from different angles. The reason for the sharpened focus on the topic is, no doubt, that numerous positive health effects of Sun exposure have recently been revealed (figure 1). Thus, the earlier one-eyed focusing on skin cancer is now balanced by considerations of positive effects. Delineation of these effects, looking for common causes and balancing them against the risks will be important research fields in coming years. Furthermore, there is a strongly increasing interest in solar radiation and health among nonexperts, so the new knowledge is rapidly diffusing into the public. A couple of years ago we started to invite some prominent scientists of high international reputation to submit updated reviews on different aspects of the topic, from solar physics to photomedicine. The result is the present review. The field is exponentially expanding, so the review has been continuously updated.

Solar radiation has played the main role in the primordial synthesis of biomolecules and evolution of life on the Earth. Ultraviolet (UV) radiation-induced mutations have expedited the process. Practically all energy on the Earth is provided by solar radiation.

From the time when the conditions on the Earth made development of life possible, the solar radiation reaching the surface of the Earth has changed, both with respect to intensity and spectrum. Such changes will continue to occur and will determine the conditions for life and its destiny in the future. Human health is a minor thing in this context, but of great importance for us.

In order to predict the future of life on the Earth, knowledge of the history of solar radiation and its biological impact is of great value. The changes in the atmosphere and the penetration of solar radiation through it are a part of this story.

Solar radiation has two major ways of interacting with humans: via eyes and via skin. The penetration of radiation down into and through the skin will be discussed in section 3.

Action spectroscopy is the main tool for physicists in the study of the biological effects of solar radiation. Such spectra are mandatory for the identification of chromophores for biological effects, such as carcinogenesis, pigmentation, vitamin D biosynthesis, immune effects and circadian rhythms (CRs), and extremely valuable in obtaining balanced views of, say, carcinogenesis versus positive health effects. Thus, we have reviewed the knowledge about the most important spectra (see section 4).

Most of the positive effects of solar radiation are mediated via UVB production of vitamin D in skin. The fact that human skin has turned white from black every time humans have migrated from their African origin northwards to less sunny places, and that white skin needs about six times lower Sun exposure than black skin to give enough vitamin D, indicates that some Sun exposure is healthy. Evidently, optimal levels of vitamin D and UVB exposure need to be established for people with different skin types. According to one hypothesis the 'original' black skin colour was developed to protect folates in the blood against the high African UVB exposure rates. A brief review of different theories for the development of different human skin colours is included (see section 11).

Some human skin diseases, such as psoriasis, are treated with large doses of UVB. This offers a simple way to obtain clinically valuable data and to probe into the topics of UVB-induced folate degradation and vitamin D generation.

Out of the many diseases for which a high vitamin D level has been reported to act positively, we have briefly reviewed four groups: cardiovascular diseases (CVD), internal cancers,

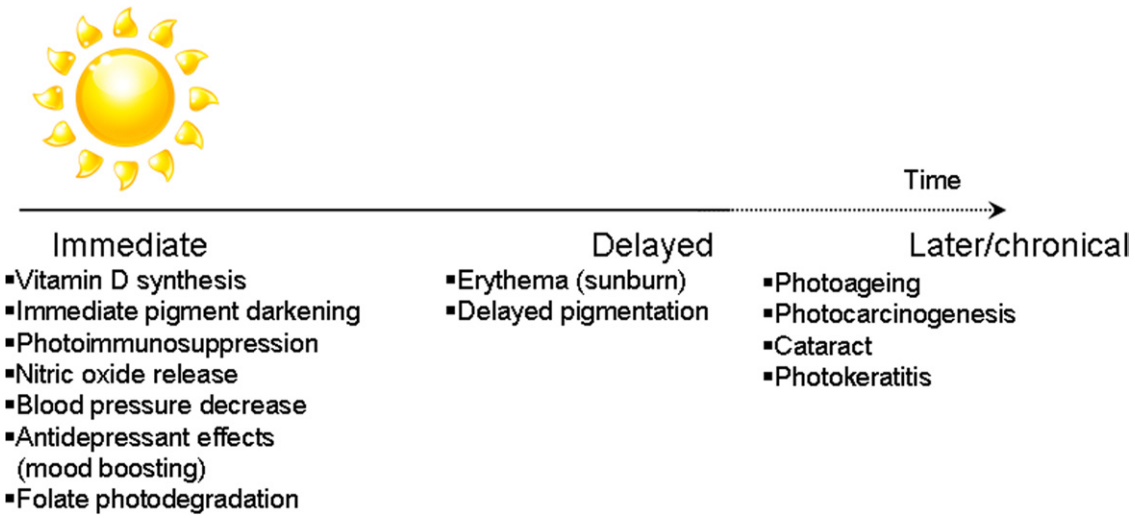


Figure 1. Effects of exposure to solar radiation.

multiple sclerosis (MS) and mental disorders. CVD mortality is twice as high in old, vitamin D-deficient people as in a control group with adequate vitamin D. A number of meta-analyses for internal cancers are reviewed and it is concluded that the incidence rates might, in some cases, be decreased by increasing the 25-hydroxyvitamin D (calcidiol) level. The question of whether both incidence rates and prognosis can be modified by vitamin D supplementation from the Sun and food is discussed. Vitamin D may also reduce the risk of mental and nerve related disorders (see section 7).

In addition to vitamin D generation, a couple of other pathways may exist for the action of solar radiation on humans. One may be the generation of nitric oxide (NO), which lowers blood pressure and interact with nerves. Another pathway may be melatonin suppression via visual and non-visual effects through the eyes. Mental effects of inadequate light exposure are manifested as seasonal affective disorders (SAD) and as seasonal variations of births of children becoming autistic or getting schizophrenia.

Prior to 1990, practically all studies related to Sun exposure and health were dedicated to skin cancer, because of the strongly increasing incidence rates for this type of cancer. This is still important, although it seems now that the incidence rates do not increase any more in several populations, and certainly not with increasing total exposure. This is true for both melanomas and basal cell carcinomas. Intermittent exposures are probably much more dangerous, as suggested for a long time.

UV-induced DNA damage is on the wicked side in the battle, immune effects may be on both sides, while vitamin D is, as far as we know, mainly on the good side.

2. Solar radiation and its variations

2.1. History and evolution of the Sun

Our Sun is a typical middle-aged star, one among billions in our galaxy. It is the source of all the energy received by the Earth, and without comparison the most important star to humanity. Ancient cultures recognized this and worshipped it as a god.

The Sun originated from the collapse of a large interstellar cloud of hydrogen and helium molecules, about 4.7 billion years (Gyr) ago. As it contracted by self-gravitation triggered by a compression caused by a nearby supernova explosion, it got warmer and rotated faster. Thermonuclear reactions were ignited in the solar core, and after a few million years it settled into its present stable state. It is now approximately in the middle of the first, the longest (about 10 Gyr) and most calm stage of stellar evolution, a stage dominated by the burning of hydrogen.

The energy output has increased by about 25% since it was formed. On average its energy emission has increased by 8% per Gyr. In approximately 5 Gyr it will exhaust the hydrogen fuel in its core, then pass through a series of transformations, and finally contract to a white dwarf. Still it will contain most of its original mass. Its density will be about 100 million times that of water.

2.2. Activity

Sunspots have attracted the attention of astronomers ever since the first telescopic and naked-eye observations of Galileo Galilei and his contemporaries in 1610 and 1612 [1, 2]. They showed that sunspots belonged to the Sun and were not small planets revolving around it. These early observations revealed a westward drift of the spots across the solar disc corresponding to a rotation with a period of about 4 weeks. A typical sunspot has a diameter about 10 000 km and lasts for a few hours up to a few months. The sunspots have a dark central region umbra, surrounded by a somewhat lighter region, the penumbra. The temperature of the umbra is around 4300 K and that of the penumbra is about 5000 K. On rare occasions a sunspot group is so large that it can be seen with the unaided eye. The Chinese recorded dark features on the Sun seen with the naked eye in 28 BC.

Solar flares are sudden and intense brightening of the solar atmosphere. The flare phenomenon was first observed

independently in white light by Richard C Carrington and Richard Hodgson in 1859 [3]. Solar flares can be observed across the electromagnetic spectrum, as well as via energetic particle emission into space. In a matter of just a few minutes they heat the plasma to many millions of degrees, and release enormous amounts of energy, of the order of 10^{26} to 10^{32} ergs in a time of 100 to 1000 s. Flares involve an astonishing variety of physical processes, including pre-flare storage of large amounts of energy in magnetic fields, very rapid release of that energy and sudden deposition of heat in the solar corona. Flares are sometimes also related to acceleration of electrons and nuclei to near-relativistic energies and explosive ejection of material. Flares are rarely visible in white light at photospheric level, but in chromospheric extreme ultraviolet (EUV, 121–10 nm) and coronal x-ray wavelengths they display an enormous release of energy and structural changes. Flares always occur in the magnetic active regions on the Sun. The radiation bursts from the flares arrive at the Earth just 8 min after leaving the flare site, well ahead of any emitted particles or coronal material sometime also associated with flares. Moreover, unlike the electrons and ions of the solar wind, plasma and the solar energetic particles, the electromagnetic waves are not affected by the magnetic field of the Earth. In the upper atmosphere on the sunny side of the Earth, UV and x-rays from flares lead to transient temperature increase and ionization.

Activity cycles are quasi-periodic with a period of about 11 years usually related to sunspot numbers. Sunspot cycles have been registered since 1710. They have lasted between 7 and 14 years, with an average of 11.2 years, and the amplitudes of the sunspot *R* number range between 38 and 201. There seems to be a fairly good correlation between solar activity and historical temperature records of the Earth: the medieval warm period around 1250 ('the medieval optimum') occurred during high solar activity. Around 1450 there was a cold period (just when the Nordic people disappeared from Greenland), which occurred during the Spörer minimum of solar activity; a cold period was experienced during the period 1645–1715, referred to as the Maunder minimum of solar activity and sunspots, and the Dalton minimum around 1800–1833 also correlated with a cold period. These minima are manifested via indirect proxy data, such as the concentration of cosmogenic isotopes like ^{14}C and ^{10}Be in natural stratified archives (e.g. tree rings or ice cores) [4]. This method constitutes a solid basis for studies of solar variability in the past, on a time scale of centuries to millennia, i.e. during the Holocene [4]. It is possible that the Sun may have spent as much as a third of its time in grand minima. There are several theories for the mechanism coupling terrestrial temperature to solar activity which are discussed in section 2.6. This includes the solar wind (the stream of charged particles from the Sun) interacting with the magnetic field of the Earth, which strongly influences the penetration of cosmic radiation to the atmosphere. Such radiation can ionize particles in the atmosphere, and thus change the concentration of seeds for condensation of water and formation of clouds. Since the solar wind changes with solar activity, cloud formation will also change with solar activity, and climate perturbations can be initiated [5]. A recent theory claims that a decrease in the solar wind during sunspot minima will weaken the interaction with the magnetosphere of the Earth and increase its rotational speed. This will change the speed and the direction of the big ocean streams and influence the climate [6].

The magnetic activity of the Sun has steadily decreased during its life. While the solar photospheric luminosity was about 30% lower compared with present-day levels 4.6 Gyr ago, when the Sun arrived on the main sequence, its faster rotation generated enhanced magnetic activity; magnetic heating processes in the chromosphere, the transition region and the corona induced UV, far UV and x-ray emission about 10, 100 and 1000 times, respectively, the present-day levels, as inferred from young solar-analogue stars.

2.3. Spectra

The Sun emits radiation of wavelengths from picometre x-rays (10^{-12} m) to decametre radio waves (10 m). Its surface emits a smooth spectrum peaking around 500 nm (10^{-9} m) (figure 2). This gives a yellow-green colour, and our eyes, as well as the photosynthesis of plants, are maximally sensitive to this spectrum.

In the 1970s, it was assumed that the irradiance of the Sun was unchanging and the concept of a 'solar constant' was applied. However, the irradiance fluctuates with the 11-year cycle. Turbulent magnetic fields that course through the interior of the Sun and erupt onto its surface are sources of these fluctuations. Radiometers aboard the Nimbus 7, launched in 1978, and the Solar Maximum Mission, launched two years later, were able to measure accurately the energy output from the Sun. It was found that the solar irradiance changed significantly as the Sun with its sunspots rotated. The irradiance was the lowest, when groups of sunspots faced the Earth. NASA's Solar Radiation and Climate Experiment (SORCE) satellite observed large sunspot patches in 2003 that caused the irradiance to drop by as much 0.34%, the largest short-term decrease ever recorded [7]. However, long-term observations show that the irradiance increases when the activity of the Sun increases even though sunspot numbers may increase (figure 3). Measurements collected during the 1980s and 1990s showed that the irradiance is a balance between darkening from sunspots and brightening from accompanying hot regions called faculae.

When solar activity increases, as it does every 11 years or so, both sunspots and faculae increase in number but the faculae overwhelm the sunspots, so the Sun is actually brighter when the sunspot numbers are the largest.

2.4. Total irradiance

Ten radiometers have monitored the Sun since Nimbus 7 was launched. Fitting the results from different instruments is complicated because many of the radiometers record slightly different absolute measurements, and the areas of overlap between the instruments in the long-term record are not yet sufficiently robust.

The solar fluence rate at the top of the Earth's atmosphere varies on several time scales, ranging from minutes to months and decades. While the short-term (minutes to hour) variability is mainly due to solar oscillations and granulation, the daily to

decadal variability is attributed to the changes in the surface magnetic field combined with the solar rotation that transports solar active regions into and out of view. The solar variability is different at different wavelengths. The relative variability is more than one order of magnitude larger in the UV than in the visible range.

2.5. Variations at different wavelengths

The variability is different for different wavelengths, and in absolute values it is the largest between 400 and 500 nm. The fractional changes, however, are the largest in UV. During the 11-year solar cycle, the total irradiance varies by about 0.08% (1.1 W m^{-2}). Those at 120 nm, 200–300 nm, 300–400 nm, 400–700 nm, 700–1000 nm and at 1000–1600 nm vary by 200%, 1.3%, 0.2%, 0.08%, 0.04% and 0.025%, respectively [8]. However, the long-term trends of the UV fluence rate are poorly known, and these wavelengths have been monitored for only a few years. Degradation of UV optics in space instruments is a big challenge.

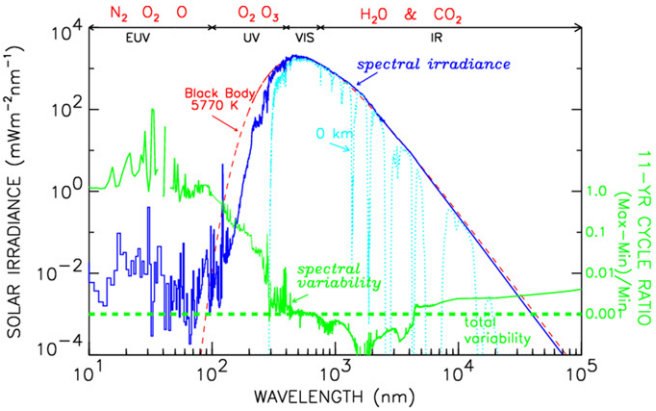


Figure 2. The solar spectrum from extreme UV to far infrared. The illustration shows the spectrum of solar radiation from 10 to 100 000 nm (dark blue), its variability between solar maximum and solar minimum (green) and the relative transparency of Earth's atmosphere at sea level (light blue). The red dashed line is a blackbody fit to the solar spectrum. At wavelengths shorter than about 300 nm, there is a relatively large variation in the Sun's extreme UV and x-ray output (greater than 1%), but the Earth's atmosphere is nearly opaque at those wavelengths (figure courtesy of Judith Lean).

The solar UV spectrum, from 120 to 400 nm, is continuously monitored from space, with SORCE observations, extending the data from 1991 by two instruments on the Upper Atmosphere Research Satellite (UARS) [8, 9]. SORCE also monitors, for the first time from space, solar spectral irradiance in the visible and near-infrared spectrum, providing unprecedented spectral coverage affording a detailed characterization of solar spectral irradiance variability [10]. These results indicate that, as expected, variations occur at all wavelengths, primarily in response to changes in sunspots and faculae.

Since UVC (200–280 nm) of wavelengths below 240 nm is responsible for production and loss of ozone in the stratosphere and troposphere, any variation in the UV emission from the Sun will produce changes in the chemical composition and in the dynamics of the atmosphere. These changes can propagate downwards and cause climate changes and certainly also changes in biologically active area of the solar radiation. In the lower stratosphere, a significant variation in the height of the 30 hPa pressure level correlated with the solar activity variation has been observed [11]. This correlation has been constant during the last four solar cycles.

One of the unanswered questions is how these profound changes in the stratosphere may propagate down to the troposphere. Using both observational data and general circulation model (GCM) simulations it has been shown that when the Sun's activity is high, there is a pattern of response in meteorological fields in the lower atmosphere [12]. Changes in the sub-tropical jets and in the tropospheric Hadley cells have been observed. According to these studies the heating of the atmosphere is not uniform. However, most of these model simulations concentrate on the 11-year cycle variation only. At least one study suggests that lower solar activity

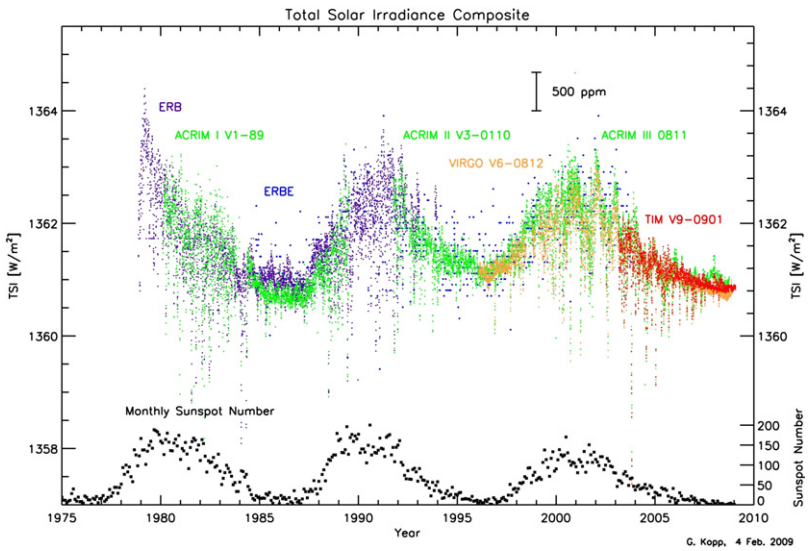


Figure 3. A three-decade record of TSI determined by patching together data from US and European satellites. Fluctuations in irradiance correspond well with the cycling of sunspots. Credit: Greg Kopp, Laboratory for Atmospheric and Space Physics (LASP).

did change the atmospheric circulation in the period 1400–1700, and triggered the Little Ice Age which had a large impact on human activity. Due to the dimmer Sun westerly winds were reduced, cooling the continents during winter time [13].

Proxy data have been used to derive long-term changes in the UV region. At wavelengths just below 300 nm an increase of 3% since the Maunder Minimum (which coincided with the Little Ice Age) was found and may have produced profound long-term effects in the atmosphere of the Earth [14]. More recent measurements from SOURCE suggest that variations in the UV may be larger, by a factor of 4–6, than previously assumed [15]. It would be very interesting to see more of the larger GCM including such effects in modelling the long-term climate due to changes in the UV.

2.6. Sun and climate

Meteorological records show that the global average surface air temperature has increased about 0.8 °C during the last 150 years [8]. Longer term climatic variations, on the other hand, have been inferred from a variety of proxy climate indicators, including growth rings in trees. Because tree growth depends partly on temperature, the width of an individual tree ring can be used to identify paleotemperature trends. Many reconstructions of the past climate have been published in the last 15 years. Some of them seem to show very little past climate variability, while other more recent ones show larger variability. Obviously, climate changes have been spatially uneven, and different forcing mechanisms, both anthropogenic and natural ones, will have different spatial signatures.

The Sun may influence climatic trends in several ways: a change in the total solar irradiance (TSI) may directly produce terrestrial temperature responses on time scales of years to centuries. A change in UV irradiance may modulate the stratospheric ozone level and atmospheric circulation, and then indirectly, terrestrial temperatures and terrestrial UV spectra on time scales of years to centuries. Direct and indirect influence may be caused by solar and cosmic ray particles, modulated by the solar wind and the magnetic field of the Sun. These particles interact with the atmosphere through nuclear collisions producing secondary particles which can penetrate deeper into the atmosphere and act as seeds for cloud formation.

Solar variability as a source of climate forcing is a hot topic. Many attempts have been made to link various aspects of solar variability to climatic changes. Since the Sun is the ultimate driver of the climate system, and since it has a variable emission, it seems natural to look for the source of climate variability in the Sun itself. In recent years there has been a growing concern about the possible anthropogenic forcing of climate change through the increasing atmospheric content of greenhouse gases. This has made the connection between solar variability and global climate change a very controversial research area.

The most obvious candidate for climate forcing is the direct effect of the varying TSI with solar activity. A big step forward came with the launching of the first absolute radiometer into space in 1978. Many were sceptical to such a vast effort with high costs since the Sun was believed to be constant. Luckily, NASA went on, and, for the last three decades, it has been possible to make high-precision measurements of the TSI outside the atmosphere. Difficulties in combining different time series from several satellites complicate the picture. Some data indicate that there has been a slight increase in the minimum level of TSI so that the Sun's activity increased up to 1995. Other reconstructions show no trend over the same time period. However, all reconstructions indicate a decrease in irradiance during the last solar minimum in 2009.

Despite the lack of direct observations, several attempts have been made to estimate the long-term variation since the Maunder Minimum. The general conclusion of these estimates is that the total emission of the Sun has varied somewhere between 0% and 0.6% over the past 300-year period, probably at the lower end of this range. The value often used in climate models is 0.25% increase in total irradiance.

Variations of the solar wind may be important although the energy in the solar wind is negligible compared with the energy in the UV and visible spectral bands. The relative variations are larger. The records of radioisotopes ^{14}C and ^{10}Be give clear signals about changes [6]. But how can these small absolute energy fluctuations affect the climate? The cosmic ray flux is the main cause of ionization of the upper atmosphere and this ionization changes significantly with solar activity. Thus, cosmic rays may play a role in cloud formation. One possible mechanism includes the effects of ionization or electric fields associated with solar activity on the freezing of super cooled water droplets in high clouds. Another possible mechanism involves aerosols and formation of low clouds. A striking correlation between global low cloud cover (measured by satellites) was highly correlated with the cosmic ray flux. A change in cloud cover would, indeed, be a very effective amplifying mechanism for climate forcing. Still this is a controversial idea.

We have a long way to go before we reach a complete understanding of the complexity of the atmosphere and how it interacts with natural and anthropogenic forcing mechanisms, and an even longer way to go before the climate models can include in full detail the indirect effects from solar variability and other atmospheric parameters, such as clouds. We need to monitor the total irradiance, as well as the spectral irradiance, from the Sun over a long time period. It is equally important to improve the monitoring of surface and atmospheric temperatures as well as atmospheric parameters such as clouds, ozone and circulation patterns. Satellites will play an important role in the future, and several planned missions will focus on these topics in the next decades.

The indirect effects, e.g. cloud cover, UV heating of the stratosphere, as well as effects not yet identified, must be investigated, quantified, and included or discarded. The ultimate goal must be a complete understanding of all relevant processes, which can then be combined into an ultimate comprehensive dynamical global climate model.

High-energy particles from the Sun may play terrestrial roles. Solar storms are known for creating space weather

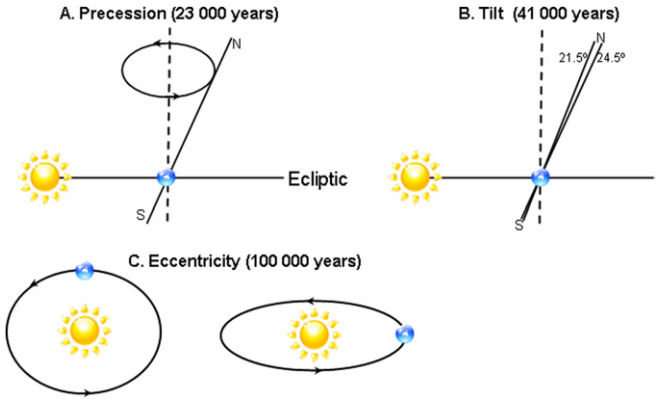


Figure 4. Schematic illustration of the Milankovitch cycles, which drive the ice age cycles. There are three main orbital variations: (*a*) precession or wobble of the Earth's rotational axis, (*b*) obliquity or changes in the tilt of the Earth's rotational axis and (*c*) eccentricity or change in the shape of the Earth's orbit around the Sun.

effects in the environment of the Earth, causing problems for a number of technical systems our society depends on [16]. However, such transient events can also influence the chemistry of our atmosphere, and thus possibly also the climate [16].

Solar storms are coronal mass ejections and solar flares. Coronal mass ejections are huge bubbles of gas ejected from the Sun, and are often associated with flares which are explosions taking place when energy stored in twisted magnetic fields (usually above sunspots) is suddenly released. Some solar storms can accelerate particles to speeds approaching that of light. Such particles can penetrate spacecraft and be a hazard to humans in space. When the particles hit the atmosphere, they dissociate nitrogen and water molecules. Nitrogen atoms can form nitrogen oxides, which can stay for weeks to months in the atmosphere. Once formed, they can react with and degrade ozone. Atmospheric winds can blow them down into the middle stratosphere, where they can stay for months, and continue to keep ozone at a reduced level. The strong proton showers in the autumn of 2003 led to a significant depletion of the ozone levels between 42 and 55 km and this ozone 'hole' stayed for 8 months [17].

The Milankovitch cycles (figure 4) play large climatic role. Over the last few millions of years there have been glacial and interglacial times, times of expansion and contraction of the polar ice caps. The changes in ice volume have been observed to be cyclical, with a rather complex periodicity [18]. The Serbian mathematician Milankovitch proposed that the cycles might have caused ice ages [18]. At present, the Earth is closest to the Sun (i.e. in its perihelion) in the Northern Hemisphere winter (causing relatively warm winters), furthest from the Sun in Northern Hemisphere summer (causing relatively cool summers).

The three orbital parameters are variation in eccentricity or ellipticity of the Earth's orbit with a periodicity of about 100 000 years, precession and obliquity; see figure 4. The shape of the Earth's orbit around the Sun varies, from an almost exact circle (ellipticity 0) to a slightly elongated shape (eccentricity 0.06). The eccentricity influences seasonal differences: when the Earth is closest to the Sun, it gets more solar radiation. If that occurs during the winter, the winter is less severe. If a hemisphere has its summer while closest to the Sun, summers are relatively warm.

The Milankovich theory states that ice caps at the poles increased and decreased in size as a reflection of the solar energy received at fairly high latitudes; the insolation at 65°N is commonly used to observe the waxing and waning of ice sheets. Indeed, the ice volume over the last few millions of years is related to the cycles mentioned above and to Northern Hemisphere insolation and not to the Southern Hemisphere insolation. For instance, we now have relatively warm winters in the Northern Hemisphere (because these winters occur when the Earth is close to the Sun), and our summers are colder because we are so far away from the Sun when our side of the planet is tilted away from it. However, many feedback mechanisms operate to give the observed climate which is more complex than a simple theory can explain.

Spectral variability is also linked to space weather. Variations in the UV irradiance will change the amount of energy deposited in the atmosphere. During a solar maximum the increased solar UV heats the upper atmosphere, causing it to expand. Even larger variations in the UV fluence rates are observed during solar flares. The resulting drag on satellites during these short-lived events may alter an orbit so that the satellite is temporarily 'lost' to communications links. A several kilometre drop in altitude has been observed in connection with one single solar event. At times, these effects may be sufficiently severe to cause premature re-entry of orbiting objects, such as Skylab in 1979 and the Solar Maximum Mission in 1989. Unless low-Earth-orbit satellites are routinely boosted to higher orbits, they slowly fall, and eventually burn up in the atmosphere.

3. Penetration of solar radiation through the atmosphere

Penetration of solar radiation through the atmosphere depends on several factors, e.g. solar elevation, scattering on air molecules and clouds, absorption by trace gases such as ozone, aerosols and reflection properties at the Earth's surface. Considerable progress in this field has been achieved over the last decades. Accurate measurements of atmospheric ozone, which is the most important absorber in the UV part of the solar spectrum, have been performed with ground-based instruments for more than 70 years, and from space with satellites since the late 1970s. Measurements of the spectral distribution of the solar UV radiation reaching the Earth's surface are technically much more demanding than ozone measurements, and reliable time series are only available from the late 1980s.

Measurements of the solar spectrum were performed on top of the Teide mountain, Tenerife, Spain, as early as 1888 [19]. Based on these spectral measurements the lower limit of the solar spectrum was set to 292 nm. Cornu [19] explained the lack of measurable solar radiation below this limit by strong absorption in the atmosphere. Hartley (1880) suggested that the atmosphere contained ozone [20] and Fabry *et al* (1913) later confirmed this by accurate measurements [21]. After the discovery of the Antarctic ozone 'hole' the

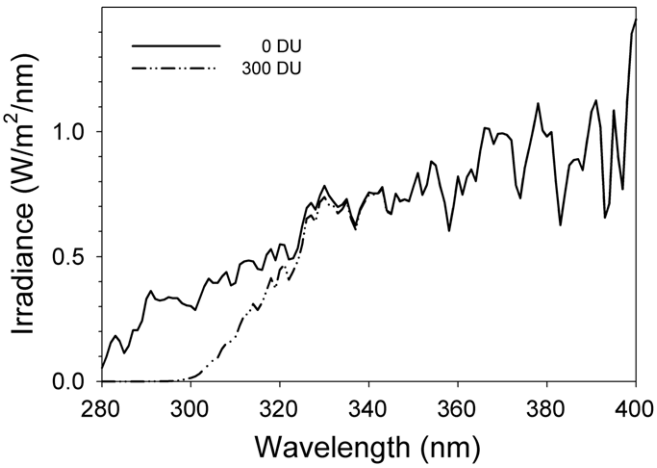


Figure 5. Illustration of the effect of ozone on spectral surface UV irradiances. The calculations were done for an atmosphere with normal ozone conditions represented by 300 DU and the totally unrealistical case with no ozone, 0 DU, with a multiple radiative transfer model for clear-sky conditions, sea level, overhead Sun, 5% surface albedo (typically for bare ground) and no aerosols. Note that with ozone present in the atmosphere practically no radiation reaches the ground at wavelengths below about 290 nm. Ozone has little effect on radiation in the UVA spectral region.

ozone layer has attracted increasing international interest, and measurements of atmospheric ozone and surface solar UV radiation are being carried out worldwide and regularly. Today, solar spectral surface UV radiation is monitored worldwide by accurate, ground-based instruments. Over the last two decades global estimates of solar UV variations and climatology at the surface have been calculated from satellite measurements of atmospheric backscattered solar UV using radiative transfer models. However, satellite surface UV instruments do not provide the same accuracy as ground-based instruments do, mainly because of the inability to measure ground reflection and aerosols near the Earth's surface sufficiently well.

Solar radiation reaching the Earth's atmosphere is mainly in the wavelength range 200–4000 nm. Radiation below 400 nm is called UV radiation and is usually divided into UVC (200–280 nm), UVB (280–315 nm) and UVA (315–400 nm). The World Health Organization [22] recommends to separate UVB and UVA at 315 nm. This has been widely adopted by the geophysical scientific community. However, one should be aware that separation at 320 nm is still used by many authors in other scientific disciplines. Ozone is a strong absorber in the UVC, and even with a strongly depleted ozone layer as found under the Antarctic ozone 'hole', virtually no UVC radiation can be observed at the Earth's surface. The absorption by ozone is weaker in the UVB allowing a fraction of this radiation to reach the Earth's surface. The UVB level is strongly dependent on the amount of atmospheric ozone. UVA is nearly insensitive to ozone variations because absorption by ozone is weak in this wavelength region. The effect of ozone on the spectral distribution at the Earth's surface under clear atmospheric conditions at sea level is illustrated in figure 5.

In this section, we give a brief overview of the present knowledge of how different factors affect the solar radiation penetrating into the Earth's surface, and how surface UV, determined by direct measurements as well as by indirect methods, varies in space and time.

3.1. Radiative transfer in the atmosphere

3.1.1. Scattering and absorption. Penetration of solar radiation through the atmosphere is controlled by scattering and absorption. An absorbed photon is lost to chemical reactions or heat. The bulk of the atmosphere (99% by mass) consists of molecular nitrogen (N_2) and molecular oxygen (O_2). Radiation at wavelengths below 200 nm is effectively absorbed by these molecules in the upper atmosphere. Trace amounts of polyatomic molecules, including ozone, are responsible for absorption at longer wavelengths. A scattered photon changes direction without losing energy. If the size of the scattering particle is smaller than about one-tenth of the wavelength of the radiation, Rayleigh scattering theory describes the scattering to a very good approximation [23]. Rayleigh scattering is strongly wavelength dependent and the probability of a photon being scattered is close to being inversely proportional to the fourth power of the wavelength. This explains the blue colour of the clear sky. For larger particles (e.g. water droplets or aerosols) the scattering is described by Mie theory if the particles can be assumed to be spherical. Mie scattering is characterized by strong forward scattering as opposed to Rayleigh scattering which is symmetric with equal probabilities of scattering into the forward and backward hemispheres. The probability of scattering on Mie particles (i.e. the scattering cross section) and the angular redistribution of the scattered radiation field depend on the size of the particles. This complicates the calculations of radiative transfer in the real atmosphere because the size distribution and particle numbers of cloud droplets and aerosols generally are unknown. A further complication is that ice particles in clouds and aerosols deviate from spherical shapes, and Mie theory is only a rough approximation. Scattering by non-spherical particles is a popular area of research, and considerable progress has been made in recent years [24]. Noteworthy is that the wavelength dependence of scattering by Mie particles is weak. This explains why clouds usually appear to be white or grey.

Solar radiation at the Earth's surface is either direct or diffuse. The direct component is the radiation from the Sun that has reached the Earth's surface without any interaction with the atmosphere. The diffuse component consists of photons that have been scattered once or many times (multiple scattering), and, thus the diffuse radiation is generally coming from all directions. Because the Rayleigh scattered radiation is strongly wavelength dependent, the diffuse radiation is particularly important at UV wavelengths. Radiative transfer calculations [25] show that for a cloud-free atmosphere with the Sun vertically above and a 350 DU total ozone column and bare ground, the fraction of diffuse radiation at sea level amounts to 43% at 310 nm and 21% at 380 nm. For a 35° solar elevation the corresponding percentages are 67% at 310 nm and 36% at 380 nm. If clouds or considerable amounts of aerosols are present, the diffuse component is important for all wavelengths and the diffuse/direct ratio is generally larger than for clear-sky conditions.

3.1.2. Radiometry. Radiation, crossing a flat, horizontal surface from all directions in space, is described by the quantity *irradiance*, denoted by the letter E. It is defined as the radiant energy crossing the surface from all directions per unit area, per unit time and has the unit $\mathrm{W\,m^{-2}}$. For a small wavelength interval, the *spectral irradiance* is given in $\mathrm{W\,m^{-2}\,nm^{-1}}$. The downward irradiance crossing the surface from the upper hemisphere, and the upward irradiance coming from below are often considered separately. The downward irradiance, the spectral irradiance, is the quantity most often measured in solar monitoring instruments since they usually have horizontal, flat front optics.

For an observer at the Earth's surface the radiation field is generally coming from all directions, and in many cases it shows a directional dependence. The *radiance*, I, is the radiation crossing a flat surface within a narrow cone in a specific direction, i.e. the energy per unit area, per unit time and unit solid angle. The unit is thus $\mathrm{W\,m^{-2}\,sr^{-1}}$.

The relationship between the irradiance and radiance is

$$E = \int I \cos\theta \, \mathrm{d}\Omega. \tag{3.1}$$

Here θ is the angle between the direction of incidence and the normal to the surface, and $\mathrm{d}\Omega$ is a small solid angle which represents the small cone containing the radiation that is crossing the surface. The integration is taken over all directions in the upper hemisphere, i.e. 2π steradians. The cosine weighting is needed to account for the variation in the projected area for different angles of incidence. This implies that radiation entering the surface at, for example, 60° has half of the weight of radiation falling normal to the surface.

The radiation incident on a molecule is described by the *actinic flux* which is obtained by integrating the radiance over all directions in space (4π steradians) without the cosine factor in (3.1). Thus, as compared with the downward irradiance, the actinic flux is more sensitive to radiation arriving from a lower reflecting surface (e.g. snow) and radiation arriving from directions closer to the horizontal direction. Measurements of actinic fluxes are technically difficult to perform. Therefore, the actinic flux is usually derived from irradiance measurements [26, 27].

Of particular biological interest is the rate at which an object receives radiative energy capable of initiating a certain biological process. The received radiation is weighted by a specific spectral function $A(\lambda)$ called the *action spectrum.* The dose rate, $\mathrm{d}D/\mathrm{d}t$, assuming exposure on a flat horizontal surface is

$$\frac{\mathrm{d}D}{\mathrm{d}t} = \int_0^\infty A(\lambda) \cdot E(\lambda) \, \mathrm{d}\lambda. \tag{3.2}$$

The *radiation dose*, D, is obtained by integrating the dose rate over a specified time interval.

For a small object that can be approximated by a particle the irradiance, E, in (3.2) is replaced by the actinic flux.

Calculations of UV exposure to human skin are usually represented by irradiances. This implies that the skin is represented by a plane, horizontal surface. This is obviously a bad approximation, and we have performed more realistic calculations by modelling the skin as a vertical cylinder [28, 29].

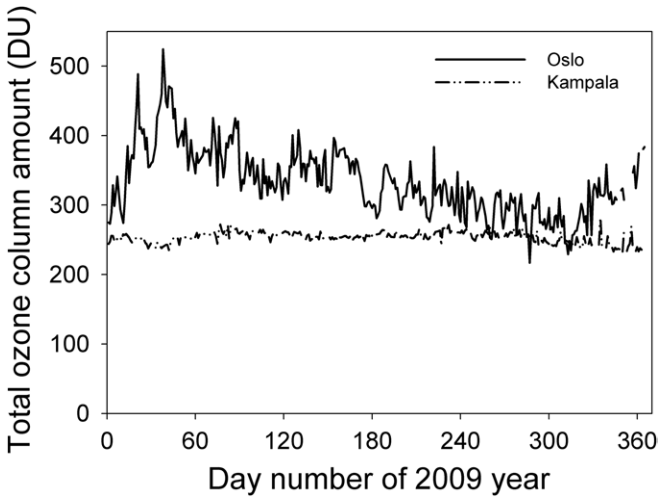


Figure 6. Day-to-day variations of total ozone in 2009 at an equatorial site (Kampala, Uganda, 0.2°N) and at a high-latitude site (Oslo, 59.9°N). The measurements were done with the OMI onboard the Aura satellite.

3.2. Atmospheric ozone

Ozone is the most important absorber affecting the UV radiation reaching the Earth's surface. Therefore, knowledge about how atmospheric ozone varies with space and time is of great interest to understand surface solar UV variability.

Ozone is continuously formed and destroyed in the atmosphere. In 1930, Chapman proposed a photochemical theory, which involves oxygen only [30]. A three-body collision, $\mathrm{O + O_2 + \mathit{M} \rightarrow O_3 + \mathit{M}}$, produces ozone. Here, M is another molecule, usually molecular nitrogen, $\mathrm{N_2}$. Atomic oxygen, which is needed in this reaction, can only be produced when molecular oxygen absorbs solar UV radiation at wavelengths shorter than 242 nm (UVC): $\mathrm{O_2 + \mathit{h\nu} \rightarrow O + O}$. UVC is available mainly in the stratosphere above the equatorial region and the production of ozone is therefore the largest over the tropics. However, the highest ozone columns are observed at high latitudes in winter and spring, while the lowest ozone columns are usually found in the tropics. This is due to a natural circulation pattern in the stratosphere characterized by rising motion in the tropics and descending motion at mid and high latitudes [31]. This transport in the stratosphere is the strongest towards the winter/spring hemisphere and explains the observed seasonal behaviour of total ozone columns at mid and high latitudes. Figure 6 shows the large day-to-day and the pronounced seasonal variations in total ozone at a high latitude site and the small variations at an equatorial site. Large day-to-day variations at high latitudes are caused by a complicated dynamic active stratosphere, particularly in winter and spring.

The modelled global distribution, based on Chapman's photochemical theory alone, leads to an overestimation of atmospheric ozone compared with what is actually measured. Since Chapman's theory was introduced in 1930 [30], a number of additional compounds and reactions have been included. These are hydrogen species, nitrogen oxide, chlorine and bromine. Reactions involving these species along with the Chapman reactions and the atmospheric circulation patterns

explain the natural global distribution of ozone in time and space.

Most of the ozone in the atmosphere is found in the stratosphere and its peak concentration altitude depends on the latitude, about 20 km at high latitudes and 25 km in the tropics. Ozone is also present in the troposphere (below 10–15 km) and the amount is about 10% of the total column. Tropospheric ozone is a result of a series of photochemical and chemical reactions that involve nitrogen oxides, volatile organic compounds and solar UV radiation.

There is less ozone naturally present over Antarctica than over the Arctic in winter and spring [32]. This is due to different circulation patterns in the stratosphere over the two polar regions. Different surface topography explains the different circulation patterns. Large losses of stratospheric ozone over Antarctica were first documented by Farman *et al* [33] in 1985. This is a seasonal depletion of springtime ozone and is known as the ozone 'hole'. The depletion of ozone is limited to altitudes between approximately 12 and 25 km where most of the ozone resides. Even in the most extreme depletion episodes observed in the 1990s, ozone remained undisturbed above and below this altitude region. However, some ozone soundings have shown that virtually all ozone was absent between 15 and 20 km [34]. In the 1990s, the total ozone October averages at the Antarctic stations Halley were 100–150 DU, while the October averages before the ozone hole developed were around 300 DU.

Halogen increases (bromine and chlorine) have been the principal driver of global ozone depletion over the last decades. This has been confirmed by model simulations that agree with the observed long-term ozone changes [35]. Recent analyses of available ozone observations [35] show that the global mean total column ozone values for 2002–2005 were approximately 3.5% below the 1964–1980 average values. The observed changes are different over the Southern and Northern Hemispheres. Over the Northern Hemisphere the changes are the largest in spring, while over the Southern Hemisphere the changes are similar throughout the year. Over the tropics (25°S–25°N) there has been no statistically significant trend over recent decades. The 2002–2005 observed global mean values of total ozone column are similar to the 1998–2001 values and this indicates that global ozone is no longer decreasing.

3.3. Factors affecting penetration of solar radiation through the atmosphere

The spectral distribution of the solar radiation reaching the surface of the Earth depends on a number of factors, the most important ones being the Earth–Sun distance, the scattering and absorption in the atmosphere, the observed solar elevation at the surface, the reflectance properties of the surface and its altitude. The effect of various factors controlling the spectral solar radiation at the Earth's surface is described below.

3.3.1. Extraterrestrial solar radiation. The spectral irradiance of the solar radiation entering the Earth's atmosphere depends on the spectral irradiance emitted by the Sun and the Earth–Sun distance. Due to the elliptical shape of the Earth's orbit around the Sun, the distance varies 3.4% from minimum in early January to maximum in early July. Since the irradiance is inversely proportional to the square of the distance to the Sun, the extraterrestrial radiation varies 6.9% from minimum to maximum. This implies that the irradiance is 6.9% larger in the Southern Hemisphere in January, than at the same latitude in the Northern Hemisphere in July, if the atmospheric and surface conditions are similar.

The radiation emitted by the Sun varies according to the 27-day apparent solar rotation, the 11-year cycle of sunspot activity and occasional solar flares. These variations affect mostly the shorter wavelengths (UVC and shorter) which are completely removed from the radiation field by photoionization and dissociation of N_2 and O_2 and dissociation of O_3 in the upper atmosphere and therefore do not reach the Earth's surface. A recent analysis of spectral data measured by spectrometers onboard satellites reveals that no extraterrestrial radiation variability due to solar cycle variability could be found in the UVB and UVA ranges [36, 37]. Therefore, it is not expected that surface UV radiation should respond directly to solar variability. However, there is a small indirect effect. Statistical analyses of the available ozone data reveal that a small component of global ozone variations are in phase with the 11-year solar cycle [35] which amounts to 2–3% from solar minimum to maximum. These ozone variations are induced by the variability of solar irradiance in the far UV in the upper stratosphere.

3.3.2. Ozone and other trace gases. The effect of ozone absorption on solar UV radiation is well understood. The attenuation of direct solar radiation at the Earth's surface by only a specific absorbing gas is described by Beer's law [38]. The attenuation of direct solar radiation caused by absorption by a particular absorbing gas and assuming a plane parallel atmosphere is proportional to

$$\exp(-N \cdot \sigma_\lambda / \cos Z),$$

where N is the number of molecules (e.g. ozone) in a vertical column from the surface to the 'top' of the atmosphere. σ_λ is the wavelength-dependent absorption cross section which describes the absorption property of the absorbing molecule and is proportional to the probability of a photon being absorbed. Z is the solar zenith angle (SZA), i.e. the angle between the vertical line and the direction to the Sun as observed from the Earth's surface. Because of the exponential behaviour, the attenuation varies strongly with the value of the three parameters. At short UVB wavelengths the absorption by ozone is strong and the diffuse radiation component may dominate over the direct one for high Z (low Sun).

The irradiance of solar radiation at the surface consists of direct radiation and diffuse radiation. The direct component is easily calculated using Beer's law if the number of molecules and particles present in a vertical column as well as their scattering and absorption cross sections are known. However, the diffuse radiation, which is caused by multiple scattering on air molecules, cloud particles and aerosols, is much more

difficult to describe mathematically and calculations must be made with advanced multiple scattering radiative transfer models [38].

The sensitivity of UV variations to ozone variations is often described in terms of the radiation amplification factor (RAF) [39]. It is defined as the relative change in UV radiation (diffuse and direct) caused by a relative change in ozone abundance. The RAF depends strongly on the wavelength because the absorption cross section generally is strongly wavelength dependent. For erythemal radiation the RAF is close to 1 implying that a 1% ozone decrease leads to a 1% increase in erythemal radiation [38].

In the troposphere there are also other gases that absorb solar radiation. These are sulfur dioxide, nitrogen oxides and numerous others. The concentrations of these absorbers are highly variable in time and space but the abundances are usually not large enough to produce measureable effects on surface UV. However, measureable effects on UV have been observed at polluted sites. For example, attenuation of direct and diffuse UVB irradiances in Moscow up to 6% due to NO_2 has been measured by Chubarova [40]. UV reduction due to NO_2 caused by forest fires near Moscow in 2002 was about 11–14%.

3.3.3. Clouds. The most important atmospheric factor affecting solar radiation variability in the troposphere is clouds. Observations from ground and space show that clouds cover on average about 60% of the Earth's surface [38]. However, the effects of clouds on surface solar radiation are very complex due to large variations in space and time of cloud optical depths, cloud shapes and microphysical optical properties such as particle size distributions and particle shapes.

A common way to characterize the cloud effect on surface solar radiation is the *cloud modification factor* (CMF) used in a large number of works published in the scientific literature [41]. The CMF is the ratio of measured solar irradiance to its corresponding clear-sky value:

$$\mathrm{CMF} = E_{\mathrm{meas}}/E_{\mathrm{clear}}.$$

The irradiance can represent various wavelength intervals, e.g. UVB, UVA, erythemally weighted radiation or even integrated over the entire solar radiation band. The clear-sky irradiance is either taken from measurements or it is modelled. The latter is preferred since appropriate corresponding values (at least in SZA, ozone amount, aerosol properties and surface albedo) are often not available [42]. The CMF is expected to be close to 1.0 for clear sky and no aerosols. The CMF can be as low as 0.01 for extremely thick clouds [43], corresponding to 99% attenuation. On the other hand, attenuation may be undetectable for thin cirrus clouds. Typical CMF values for overcast skies range from 0.3 to 0.7, depending both on cloud type and characteristics [41].

The wavelength dependence of CMF is weak and is considered to be wavelength independent if the wavelength band considered is not too wide. Bais *et al* [44] found no spectral dependence of cloud effect in the UV. However, the CMF for UV is larger than the CMF for total global solar radiation (i.e. 290–3000 nm) [41, 45, 46]. Den Outer *et al* [47] studied solar radiation measurements in the Netherlands in the period 1994–2003 and found average CMF of 0.68 for erythemal UV and 0.57 for total global solar radiation. Thus, the total global solar radiation is usually more attenuated by clouds than erythemal UV. This is caused by the much higher contribution from the direct component for total global radiation than for erythemal radiation [48]. One additional reason for the different effects of clouds on erythemal and total global solar radiation is the fact that water does not absorb in the UV, but it has strong absorption bands mainly in the infrared band [48].

Under overcast conditions clouds attenuate the surface irradiance. However, there are situations where clouds can actually enhance the surface irradiance. This can happen in partly cloudy sky if the direct solar beam is not obscured by clouds and therefore is not attenuated while clouds close to the solar disc will lead to enhanced scattering and therefore increased diffuse radiation. Enhancements up to 25% in the UV region have been reported by many investigators [43, 49]. Enhancement episodes can last for hours [48]. Pfister *et al* [50] analysed one year of total global irradiance measurements at Lauder, New Zealand, and found that measured radiation enhancements of more than 10% appeared with a frequency of 5%. Cede *et al* [48] analysed data from the Argentine radiation network and found enhancements of 13% for UV and 33% for total radiation.

It should also be mentioned that cloud layers below the observation site, such as the high-altitude station at Mauna Loa, Hawaii, can increase the solar UV irradiance due to multiple reflections between the cloud layer and the atmosphere above [51].

3.3.4. Aerosols. Aerosols are particles suspended in the atmosphere and their origin can be either natural or a result of human activities. It is difficult to assess their global effect on surface solar radiation because the abundance and optical properties of aerosol particles vary considerable in time and space. Examples of aerosols from natural sources are desert dust aerosols, maritime aerosols, volcanic aerosols and aerosols from forest fires. Examples from anthropogenic sources are aerosols from combustion of fossil fuels and aerosols from biomass burning. They can have a significant effect on the transmission of solar radiation to the surface. However, the magnitude of the effect depends strongly on the vertical aerosol optical depth, and whether the aerosols are absorbing or not. It is common to assume that the aerosol optical depth is proportional to $\lambda^{-\alpha}$, where λ is the wavelength and α is the *Ångström coefficient*. For solar radiation, scattered on air molecules (Rayleigh scattering) α is close to 4. For aerosols α values generally vary with aerosol type and composition, but they have typically values less than 4. Results from a measurement campaign held in June 1996 in Greece showed that α varied between 0.5 and 1.5 [52]. Small values of α may be interpreted as the presence of large aerosol particles, while large values of α are due to small aerosol particles. It was also found that the aerosols during the campaign lowered the UVB irradiance by 3–35%

compared with a similar atmosphere without aerosols. Di Sarra *et al* [53] measured the effect of desert dust on UV irradiances on the Mediterranean island of Lampedusa. They found a 25% reduction in erythemal irradiances due to aerosols that had been transported from the Sahara to the island. The long-term variations of UV irradiances at the Earth's surface may be considerably influenced by temporal changes of pollution from anthropogenic sources [54]. For example, Liu *et al* [55] estimated that anthropogenic sulfate aerosols associated primarily with fossil fuel combustion have decreased surface UVB irradiance by 5–18% in industrial regions of the Northern Hemisphere since the industrial revolution.

Stratospheric aerosols have usually very small effects on UV attenuation. An exception is major volcanic eruptions such as the Mt Pinatubo eruption in 1991 when large amounts of ash and sulfur dioxide were ejected into the stratosphere. The gaseous sulfur dioxide was later converted to sulfate aerosol particles and distributed globally and were observed several years after the eruption. Ground-based measurements after the eruption showed that the decrease in UV irradiance was only a few percent but a strong decrease in the direct/diffuse ratio at all wavelengths was observed, in good agreement with model calculations [45].

3.3.5. Surface albedo. Reflections from different types of surfaces can have significant effects on solar radiation. The reflection property of a surface can be described by the *surface albedo*, which is the ratio between the upward irradiance, reflected from the ground, and the downward irradiance. This implies that the surface albedo can attain values between 0 and 1. The surface albedo depends on the type of surface, topography, wavelength, and to some extent also the angle of incidence. Typical UV albedos for most snow-free surfaces are 0.05–0.08 over water and 0.01–0.04 over land [56, 57]. McKenzie *et al* [57] measured spectral dependence of albedo for grassland. The albedo was determined to be 0.01 in the UV increasing to 0.05 at 450 nm. These results agree with the work of Webb *et al* [58] who measured spectral irradiances from aircraft over flat arable land in the UK and found surface albedos of 0.02 in the UVB increasing to 0.05 at 500 nm (visible).

High surface albedos have been measured for snow-covered surfaces by numerous investigators. Typical values of albedo for snow-covered surfaces are around 0.8 [59]. Snow albedos close to 1.0 in clean environments in Antarctica have been reported by Grenfell *et al* [60] and Wuttke *et al* [61]. However, snow albedos may vary considerably with snow type and snow age [62]. Ageing and snow melting increase the size of the snow grains and result in a decrease in the surface albedo [63]. However, the observed decreases in surface albedo may also be partially caused by absorbing contaminants on the snow surface [64]. The wavelength dependence of snow albedos was investigated by Wuttke *et al* [61] at Neumayer, Antarctica. They found albedos close to 1.0 for wavelengths less than 550 nm and decreasing values to 0.45 at 1000 nm (near-infrared).

Snow-covered areas can have a significant effect on the total downwelling UV irradiances (direct plus diffuse). A reflecting surface has obviously no effect on the direct solar beam. However, the downwelling diffuse radiation will increase with reflectivity of the surface due to Rayleigh scattering (and Mie scattering if clouds or aerosols are present) of any reflected light back to the surface. Even if one assumes a wavelength-independent albedo of the surface, the back scattered radiation will indeed be dependent on wavelength due to the strong wavelength dependence (λ^{-4}) of Rayleigh scattering. Model calculations by Lenoble [65] show that the increase in global irradiance (direct and diffuse radiation) for clear sky is the largest around 320 nm and up to 50% for a surface covered with clean snow compared with no snow. The wavelength dependence is due to the combined effect of wavelength-dependent Rayleigh scattering and ozone absorption. Experimental studies by McKenzie *et al* [66] have shown an increase in global UV irradiance of approximately 40% due to a snow albedo of 0.8. The UV enhancement increases if clouds are present. This is caused by a stronger backscattering by clouds down to the surface compared with a pure Rayleigh scattering atmosphere. McKenzie *et al* [66] found that the enhancement in UV irradiance levels over a snow-covered surface compared with a snow-free surface amounts to 70% when similar cloud cover was present in both cases. Kylling *et al* [67] studied the effect of snow cover in Tromsø, Norway, 70°N. They found that monthly integrated erythemal UV doses increased by 20% compared with similar cloud conditions but without snow cover. The maximum increase in daily dose compared with snow-free conditions was 63% for a cloudy day.

Homogeneous snow cover over large areas is usually only found in polar regions (e.g. Antarctica and the interior of Greenland). At mid- and subarctic latitudes the snow depth, and therefore the local albedo, may vary considerably over short distances. In urban areas streets and buildings are frequently snowless, leading to complex local albedo variability in winter.

The UV irradiance may be considerably affected by snow even if the snow cover is several kilometres away from the observing site [68]. Results from radiative transfer calculations have shown that significant increases in surface UV irradiance (defined as being >5%) may occur even if the snow cover is farther than 20 km from the observing site [69, 70].

3.3.6. Altitude. UV radiation increases with altitude because the number of scattering and absorbing air molecules and aerosols in the atmosphere overhead decreases with altitude. The increase in irradiance per km (the altitude effect) can be determined with simultaneous measurement at different altitudes. However, different atmospheric conditions as well as different surface conditions at the observing sites may certainly affect the determined altitude effect. Cloud layers below an observation site (e.g. at a mountain top) will increase the effective albedo and therefore affect the altitude effect. Further on, the altitude effect is wavelength dependent because scattering and absorption in general depend on wavelength.

McKenzie *et al* [71] and Dahlback *et al* [72] found altitude effects for a clear atmosphere to be 6–7% per km for erythemal irradiances and 3–4% per km for UVA irradiances. The larger

altitude effect for erythemal radiation compared with UVA radiation can be explained by the fact that UVB radiation is considerably more affected by ozone absorption and Rayleigh scattering than UVA radiation. Different values of the altitude effect reported by several investigators are probably due to different atmospheric and surface conditions. Blumthaler *et al* [73] found altitude effects from measurements in the Alps of 15% per km for erythemal irradiances and 9% for UVA radiation. Pfeifer *et al* [74] found altitude effects of 7–16% per km in Germany and between 5% and 23% at different altitudes in Bolivia. Singh *et al* [75] found 11% increase in erythemal irradiances per km in the western Himalayas.

It is worthwhile to mention that Piacentini *et al* [76] measured extremely high solar irradiances in the 300–3000 nm wavelength region at 3900 m altitude in Argentina, up to 1528 W m^{-2}, which is 8% higher than the solar constant adjusted to the actual Sun–Earth distance. Strong reflection at cloud edges and multiple scattering between cloud layers caused this extreme enhancement.

The altitude effect also depends on the altitude itself. Based on radiative transfer calculations Dahlback *et al* [72] showed that the altitude effect for a pure Rayleigh scattering atmosphere at 340 nm (UVA) is 4.8% per km at sea level and at an altitude of 1 km. The corresponding altitude effect based on calculated irradiances at 3700 m and at 5000 m is 2.8%. McKenzie *et al* [51] noted that the altitude effect also depends slightly on SZA. Based on measurements in Lauder, New Zealand, and at the Mauna Loa Observatory, Hawaii, they found a maximum in the altitude effect at an SZA of 70°.

3.4. Measurements

3.4.1. Ozone instruments. The ground-based global network of ozone monitoring instruments consists mainly of Dobson and Brewer spectrophotometers. The Dobson spectrophotometer was first built in the mid-1920s by Gordon M B Dobson [77]. This instrument measures the total ozone amount, i.e. the ozone in a vertical column from the ground to the 'top' of the atmosphere with the technique of differential absorption of UV radiation with the Sun or Moon as the UV source. The total ozone amount is derived from radiance measurements at wavelengths that are differently absorbed by ozone. The world's longest time series of ozone measurements started in Arosa, Switzerland, in 1926 [78]. It is worth mentioning that the reference instrument for the WMO (World Meteorological Organization) global ozone monitoring network is still a Dobson. The Dobson instruments have proven to have long-term stability, suitable for detecting ozone changes as small as 1% per decade. However, the instruments have several disadvantages. Calibration and routine tests are very time consuming and measurements have to be performed by a skilled operator. During the 1970s the Brewer spectrometer [79] was developed. It is based on the same measurement principle as the Dobson. The Brewer spectrophotometer makes automated observations of the total ozone column, and therefore it provides high data quality with much less labour than is required with the Dobson instrument.

Total ozone can also be measured with satellite-based instruments. The most well-known satellite instrument is the Total Ozone Mapping Spectrometer (TOMS) installed onboard several satellites since 1978 [80]. The quality of ozone measured by TOMS instruments is good and the errors are generally less than 2% [80, 81]. Today the Ozone Monitoring Instrument (OMI) onboard the NASA Aura satellite launched in July 2004 continues the TOMS record. Satellite measurements make it possible to map the total ozone on a global basis. The daily satellite overpass over ground-based stations can be valuable for identifying sudden changes in ground-based total ozone measurements. On the other hand, ground-based measurements are still required to assess long-term calibration stability of satellite measurements.

3.4.2. Ground-based UV instruments. Usually, ground-based UV instruments measure spectral or wavelength-integrated irradiances on a flat horizontal surface. UV sensors can be divided into three groups: (1) spectroradiometers designed to measure UV spectra at a spectral resolution of 1 nm or better, (2) multi-channel filter instruments usually having a few channels in the UV spectral region with bandwidths of 2–10 nm and (3) broad-band instruments having one single channel that covers the UV region with spectral sensitivity to measure biologically wavelength-integrated UV doses, e.g. UV indices.

Spectroradiometers are still considered to be the most accurate instruments to measure UV radiation at the Earth's surface. However, they are expensive, and require extensive labour for operation, maintenance and calibration. Therefore, the global coverage is quite limited. Broadband and multi-channel instruments are much easier to operate and require much less attention than spectroradiometers. They are therefore an attractive supplement to spectroradiometers and are currently used in several networks around the world[9]. To ensure good data quality any UV instrument must be optically characterized and frequently calibrated. Since the beginning of the 1990s, periodic intercomparisons of UV instruments from different organizations are set up to assess the agreement of the instruments. Several comparisons between instruments show that agreement of about ±5% is achievable for well-maintained and calibrated instruments [82, 83].

3.4.3. Satellite-derived surface UV. Although ground-based UV radiometers provide the most accurate UV measurements, they are too few to offer a good geographical coverage. UV instruments onboard several solar synchronous polar orbiting satellites cover the globe typically in a day or two. The most famous is the TOMS [80] that were originally designed to monitor the ozone layer accurately. Today the OMI onboard the Aura satellite launched in 2004 continues the long TOMS time series [84]. The satellite instrument measures the radiance of solar radiation at selected UV wavelengths that is backscattered from the Earth's atmosphere to the satellite instrument. The measured backscattered radiation has interacted with molecules (Rayleigh scattering), absorbing gases (e.g. ozone), clouds, aerosols and to a certain extent the Earth's surface. By combining the measurements

[9] See http://www.srb.noaa.gov/UV/ for an overview

with radiative transfer models surface UV irradiances can be estimated. A weakness of the satellite-derived surface UV radiation is that the backscattered radiation does not fully penetrate into the surface and assumptions about the aerosols and ozone in the boundary layer must be made [71]. Furthermore, only 1–2 satellite overpasses are available for each satellite pixel at the Earth's surface per day and therefore the derived irradiance only represents a snapshot and an average over the pixel area, usually at local solar noon. Sabburg *et al* [85] compared daily integrated erythemal UV doses for clear days derived from TOMS measurements with ground-based measurements with Brewer spectroradiometers at four different sites in the USA. They concluded that TOMS UV retrievals have a positive bias between 1.4% and 12.5% at these sites. Fioletov *et al* [86] derived UV index climatologies for Canada and the USA using TOMS data for 1980–1990 and compared with Brewer measurements from several sites. They found that in summer the TOMS UV estimates were 10–30% higher than the Brewer measurements, most likely caused by air pollution and absorbing pollution. With snow on the ground, TOMS retrievals were up to 60% lower than the Brewer data, which were explained by insufficient treatment of snow albedo in the satellite UV algorithm. Arola *et al* [87] found TOMS UV to be 20–30% higher than ground-based irradiance measurements over Thessaloniki, Greece, and Ispra, Italy, due to absorbing aerosols.

3.5. UV climatology and trends

The objectives of performing long-term measurements of surface solar UV radiation are to establish global UV climatology, to quantify short- and long-term changes of UV and to quantify the effects of the UV controlling factors such as atmospheric ozone, clouds, aerosols and surface albedo. Unfortunately, reliable UV records from ground-based instruments are limited in space and time. Continuous spectral UV measurements with frequent and accurately calibrated ground-based instruments started in the late 1980s. Very few of the available measurement records are of sufficient length to perform trend analyses [88].

The variability of surface UV irradiance has been studied using available measurement records from stations around the globe. Some of the datasets are sufficiently long to determine UV climatology that is representative for the region around the measurement site. Short-time variations within seconds are typically due to variable cloud cover. Day-to-day variations are usually also caused mainly by cloud cover variability but changes in the ozone amount and aerosols can have a significant influence. However, in the tropics the ozone variations are very small and the short-term as well as the long-term variations in UV are mainly due to changing cloud cover. Tarasick *et al* [89] developed a UV index climatology based on spectral measurements from 14 UV monitoring stations spanning from 69.0° S to 82.5°N. The most striking feature is the high degree of variability that is caused by clouds and is most pronounced at cloudy sites. Ozone variations cause normally smaller variations than clouds do.

There are also differences between the Northern and Southern Hemispheres. Measurements from New Zealand [71] show that peak erythemal irradiances are about 40% higher than at sites of similar latitudes in the Northern Hemisphere. This is a result of lower ozone and aerosol amounts and smaller Earth–Sun distance during the Southern Hemisphere summer.

Recently, Bais *et al* [54] analysed time series of noon-time erythemal irradiances from 11 stations distributed around the world. Linear regressions of the period from the beginning of the 1990s to the mid-2000s show negative changes for the Southern Hemisphere sites and the Arctic. The negative changes are even more pronounced if the regressions start in 1998 when the first signs of global ozone slowdown in the ozone depletion were observed [35]. In the northern mid-latitudes the changes are positive. This can be a result of decreased aerosol optical depths or the widespread brightening of the atmosphere that has been observed since the late 1980s [90]. Measurements of clear-sky irradiances at 305 nm and 324 nm in Thessaloniki, Greece, in the period 1991–2006, show a statistically significant increase of 8.1% per decade and 11.3% per decade, respectively. The irradiance at 324 nm is almost unaffected by ozone changes and the observed increase at this wavelength can be explained by the observed decrease in aerosol optical depth and SO_2 column [91]. In the same period the observed ozone change was plus 0.8% per decade indicating that aerosol and SO_2 changes could also explain the observed positive change at 305 nm.

Herman [92] analysed data from several satellites in the period 1979–2008 and derived zonal means of surface UV irradiances using different action spectra. A significant increase was found for all latitudes except in the equatorial zone. The largest increase was found in the Southern Hemisphere. For example, at 50°S the increase was 8.5% for erythemal radiation and 12% for vitamin D production. At 50°N the increase was 4% and 6% for erythemal radiation and vitamin D production, respectively. It should be noted that these findings are not valid for regions affected by heavy aerosol loading because satellites are unable to detect aerosols close to the Earth's surface.

The longest time series was obtained for Switzerland [93] in the period 1926–2003. They used existing ozone record, sunshine duration and snow depths as input to a model. High values for erythemal irradiances were found in the mid-1940s, early 1960s and in the 1990s. The UV changes prior to 1980 were explained mainly by changes in cloudiness, while the increase in the 1990s was due to ozone decreases.

Research on the effects of surface solar UV radiation on human health generally requires knowledge about spectral UV climatology and long-term variations over large geographical areas where direct measurements are not necessarily available. Continuous reliable spectral ground-based UV measurements are performed at a limited number of sites worldwide; however, most of them are situated in the Northern Hemisphere. A few of the existing records are of sufficient length to determine UV climatology. The UV climatology may vary considerably over short distances and therefore the UV climatology derived for a particular monitoring site may only represent limited geographical area surround the site. This can, for example, be the case at sites where the cloud climatology varies over

short distances due to the variation in the topography around the site and/or local pollution. There is a particular need to increase the coverage of ground-based UV monitoring stations in the tropics [54] where high UV levels are expected. Satellite instruments, particularly the TOMS instruments, have provided good global coverage since the end of the 1970s. However, comparisons with ground-based instruments have shown that satellite derived surface UV overestimates the true surface UV by up to 30%, mainly due to absorbing aerosols in the lower troposphere that are difficult to detect from satellites. On the other hand, snow- and ice-covered surfaces lead to underestimation of the surface UV because of insufficient treatment of high surface albedos in the satellite UV algorithms.

Analyses of available time series of satellite- and ground-based instruments indicate that global ozone is no longer declining. Models predict that the ozone layer will return to its normal state in about 50 years [94]. Tourpali *et al* [95] have calculated changes in the surface UV based on simulations with chemistry-climate models (CCMs) and radiative transfer models. According to these simulations the surface erythemal irradiances will decrease as a result of the stratospheric ozone recovery. Between 2000 and 2100 the increase is calculated to be 5–15% over mid-latitudes and decrease twice as much over high Southern latitudes. Their calculations were performed under clear-sky conditions and changes in aerosol loading and surface albedo were not included. However, possible future changes in cloud cover, aerosol loading and surface albedo are important for future changes in surface UV levels. Several model simulations suggest that cloud cover will decrease by up to 4% in most of the low and middle latitudes by the end of 21st century [96]. This alone would increase the surface erythemal UV by approximately 4%. The future levels of surface UV will also depend on the future levels of aerosols and surface albedo.

4. Light penetration in skin

This section deals with light propagation in the skin. This field is included as it is of fundamental importance for the main topic of the paper. The first relevant factor in understanding any photobiological mechanism in the skin is obviously to know how light penetrates through different skin layers in order to reach the various chromophores responsible for this dermal photochemistry. This in turn requires the identification of the specific molecules, or chromophores, which absorb the light. These chromophores are partly the same as those responsible for initiating the light-stimulated biological responses. We will focus here especially on light in the near UV wavelength region, as this region is clearly the most interesting for photobiological reactions. Skin, however, not only absorbs light through these chromophores, but also causes strong light scattering due to variations in refractive index on the subcellular level. Light scattering gives rise to the obvious effect that skin tissue is not clear, but highly turbid. This turbidity makes the light transport more complex in nature, motivating this section. The light transport is thus determined mainly by the scattering and absorption properties of the skin, and usually the radiative transport equation is used for its modelling. Historical papers are important in describing for the first time the fundamentals of skin optics and form a basis for further development and understanding of light propagation of human skin tissues [97, 98]. Skin optics has so far been argued to be important for the understanding of skin photobiological processes, but interestingly it is also essential in a few totally unrelated fields, see e.g. recent skin optics research in cosmetics [99] and computer graphics [100, 101]. We will discuss below recent advances in skin optics—the understanding of light transport in skin, and its relation to skin photobiology, with a focus on light in the UV range.

The section reviewing skin optics is divided into four main sections. In the first section a brief background to the field skin optics will be presented. This will be followed by a discussion on different skin types and various important chromophores active in the UV range. We will also discuss novel techniques to measure optical properties of skin, as well as how to model light penetration in tissue.

4.1. Background to skin optics

The skin has an important function of protecting the body from its environment. The skin is built in a complex structure consisting of two main layers separated by a basement membrane—the outer layer is the cellular epidermis and the inner the largely non-cellular dermis. The main function of the epidermis is to produce and support the outermost protecting skin layer, the stratum corneum. The epidermis can be divided into five different layers, depending on the cell types building up the layer. The cell type dominating in the epidermis is keratinocytes, proliferating by cell division in the basal layer at the basement membrane. These cells are at this stage columnar in shape. Non-proliferating keratinocytes subsequently mature whilst being pushed outwards towards the skin surface. In this process they change in shape and in the mid-layer of the epidermis they become flat—squamous. The outermost layer—the stratum corneum—is built by highly packed dead flat cells in a fatty environment. These non-living cells are basically just keratin flakes at this stage and are termed corneocytes. They are shed continuously approximately every two weeks in a rate perfectly matching the proliferation rate in the basal layer, thereby maintaining the epidermis intact. The stratum corneum is approximately 20 cell layers thick, or about 10 μm. This layer represents the first efficient barrier of the human body to the environment. Optically it is characterized by a strong light scattering. Other cell types in the epidermis are melanocytes and Langerhans cells. Melanin, synthesized by melanocytes, is transferred, as large particles called melanosomes, to adjacent keratinocytes. In fair skin these particles are degraded into smaller particles (melanin dust) as they follow the keratinocytes towards the stratum corneum, while this degradation is much less efficient in darker skin types, where some melanosomes keep their original size throughout the epidermis. The melanin is discarded with the corneocytes with desquamation. Langerhans cells have an antigen-presenting function and are an integral part of the systemic immune system.

The thickness of the epidermis varies with body location, but is typically between 50 and 120 μm thick at most parts [102]. In the skin in outer body parts, taking most of the solar radiation exposure, the epidermis is typically 50 μm.

The dermis is located under the epidermis. It contains mainly connective tissue, blood vessels, hair follicles and sweat glands. It has a thickness of several millimetres, sufficiently thick to prevent any UV light from reaching below this layer, into the subdermis.

Light transport in tissue is governed by its scattering and absorption properties. Scattering is a consequence of the interaction between electromagnetic radiation (light) and matter, and is caused by spatial variations in the refractive index within the medium, in which the light is propagating. Scattering can be explained by electrons in the material more or less swiftly following the oscillating electromagnetic field that the light represents (this ability is exactly the property described by the refractive index). When the light propagates from a region with one refractive index into a region with another, the change in how well the electrons can follow the electromagnetic field oscillations would cause a mismatch in the electromagnetic field across the boundary, unless a scattered light field is formed. The characteristics (strength and angular distribution) of the generated scattering are highly dependent on the relation between the size of the region with a different refractive index and the wavelength of the light. Small structures (much smaller than the wavelength of light) yield a much stronger scattering effect for shorter wavelengths than for longer, manifested in the well-known $1/\lambda^4$ dependence of the scattering cross section for sub-wavelength-sized particles. This type of scattering is referred to as Rayleigh scattering. Examples of structures in skin tissue giving rise to Rayleigh scattering are proteins in connective tissue (collagen fibrils) and melanin dust. This scattering is usually dominant in the short wavelength range, while less important at long wavelengths in the visible region due to its strong wavelength dependence. For spherical particles comparable in size to the wavelength of light yielding the so-called Mie scattering, the wavelength dependence of the light wavelength is more complex. Usually, much lower power dependence can be assumed for tissue structures in this size range. In skin, a dependence of $1/\lambda^{0.22}$ has been measured [103]. This scattering is caused by subcellular structures, such as cell nucleus and mitochondria, as well as the entire collagen fibres. It will dominate the scattering spectrum of skin at longer wavelengths with its less strong wavelength dependence [104]. For even larger scale tissue structures, light scattering is well described by geometrical optics (e.g. refraction, a fundamental concept that models change in propagation direction).

So far we have only discussed the microscopic light scattering of a single particle. Most often light is scattered several times before it reaches the observer. The insight into single particle scattering can, however, directly be extended to multiple scattering. Interestingly, scattering from randomly oriented non-spherical particles can be relatively well described by Mie-type multiple scattering, even though Mie scattering requires spherical particles. Skin optics and photon migration in tissue are today, to a large extent, based on multiple scattering concepts.

The scattering properties of a material are normally described using an average scattering coefficient, μ_s (cm^{-1}), which states the probability of scattering per unit path length, and an average angular distribution function for the scattered light (the scattering phase function). The Mie part of scattering is predominantly in the forward direction with an average deviation in the range of 25°, while the Rayleigh part of scattering is isotropic.

The absorption of tissue is caused by a large number of biomolecules [105]. Prominent tissue chromophores absorbing light ranging from UV to near-infrared light include water, proteins, lipids, cytochromes and melanin. The main chromophores responsible for the absorption in the near UV will be discussed in detail below.

The absorption property of a material is described in a similar manner to the scattering by the absorption coefficient μ_a (cm^{-1}), defined as the probability that light is absorbed per unit length travelled. The probability of absorption within a small length ds is thus $\mu_a \cdot ds$. The average path length before an absorption event is given by the reciprocal of μ_a, that is, $1/\mu_a$. In the UV spectral region, high absorption and scattering result in very short optical penetration depths, of the order of a hundred micrometres.

4.2. Different skin types and skin chromophores

The skin functions are believed to have had a large impact on the evolution of humans. The evolution towards hairless skin provided an improved ability to control the body temperature through sweating. This made it possible to keep the sensitive brain at a stable temperature even under different conditions, e.g. warm weather and hard physical work [106]. With the loss of hair, skin pigmentation became central to protect the body from harmful UV radiation. In particular, protection of light sensitive folate molecules in the superficial blood capillaries is considered to have been important in the evolution of skin pigmentation. More pigmented skin absorbs and scatters light better and thus protect the underlying tissue from harmful UV radiation, while absorbing a larger fraction of the light illuminating the skin. Light penetration in tissue is actually modulated by two different mechanisms—increase in the skin pigmentation (meaning increased melanogenesis) or by non-pigmentary photoprotection. Non-pigmentary photoprotection is less understood, but is supposed to be mainly due to epithelial thickening (hyperplasia and hyperkeratinization of the epidermis) [107]. The light transmission depends exponentially on the epithelial thickness [108]. The relative importance of these processes has been studied, and they seem to differ between skin types [109]. For instance, while subjects of Asian origin developed photoadaptation to UV exposure through increased pigmentation, Caucasian subjects primarily adapted to the UV irradiation through hyperplasia of the epidermis. More pigmented skin types also have an overall thicker epidermis, contributing to photoprotection. Various types of skin, with different degrees of pigmentation, are classified according to the scale first presented by Fitzpatrick [110]. The scale starts with type I being fair skin and ends with the very pigmented skin as skin type VI.

4.2.1. Skin chromophores. Light transmission in the skin depends, as described above, on its absorption and scattering properties, as well as on the thickness of the different skin layers. The scattering properties are much less studied than the absorption. The scattering coefficients for the different skin layers are, however, not believed to vary very much between different skin types, while the absorption coefficient and thickness do. In this section we briefly discuss the chromophores responsible for light absorption in the skin. The most important absorption spectra can be found in the freely available database PhotochemCAD [111].

4.2.1.1. Melanin and melanosomes. Melanin is a chromophore providing brownish pigmentation to the skin and its presence is thus the most important parameter for the classification of skin types, as it strongly influences the visual appearance. The absorption of UV radiation by melanin and the following dissipation of this energy as harmless heat constitute major photoprotection mechanisms in human skin. For these reasons melanin is very central to the field of skin optics. Another function of melanin in the skin is that it acts as a singlet oxygen quencher [112]. There are two types of melanin in mammals, the brownish-black eumelanin and the more reddish-yellow pheomelanin. Eumelanin and pheomelanin are present in human hair, eyes and the epidermis. The spectral shape of the absorption profile is very broad (covering the UV and visible wavelength range) for both types, with an absorption that is much higher in the UV and violet wavelength region than in the visible region. This spectral behaviour causes its coloured appearance. Melanin is complex in nature, as it is not a well-defined molecule, but rather a class of aggregated small molecules building up complex clusters, called melanosomes. Melanin is synthesized from tyrosine in melanocytes located in the basal layer of the epidermis. It is deposited as pigment granules—the melanosomes. These are initially spherical in shape with a diameter of approximately 1 μm. When skin is exposed to solar radiation, it tans by increased melanogenesis, transferring more melanosomes from the melanocytes to the keratinocytes. These slowly propagate upwards through the epidermis. Both keratinocytes and melanosomes slowly disintegrate with time. On reaching the uppermost layer of the epidermis, the stratum corneum, the melanosomes of lightly pigmented skin are found in the form of melanin dust, whereas some melanosomes remain intact in the stratum corneum of more strongly pigmented skin of higher skin types. The distribution of melanin in the epidermis varies between tanned and untanned skin. In untanned skin most of the melanin is located in the basal layer, while it is distributed throughout the entire epidermis in tanned skin. Not only the amount of melanin, but also its distribution in the epidermis has a huge impact on how much UV light is actually reaching the living cells (for DNA damage and vitamin D production), while the degradation of folate in the dermal blood (deeper than the epidermis) will be more or less independent of the distribution of melanin within the epidermis [113].

To further understand the distribution aspect of melanin in the skin, several groups have, as will be discussed below, used confocal laser scanning microscopy to investigate differences in melanin content and distribution in various skin types as well as melanin distribution before and after a single UV exposure [114, 115]. The data presented in these studies provide important input for refined calculations on light propagation in the epidermis, again discussed in detail below.

Because of the large and complex structure of the melanin clusters in skin, it is not easy to understand the photophysical properties of melanin or melanosomes in detail. Several groups have recently taken up the task of studying the absorption process and energy dissipation in melanin. They have started to study the well-defined building blocks or precursors to melanin, e.g. the key eumelanin precursor 5,6-dihydroxyindole-2-carboxylic acid (DHICA) in monomeric, dimeric and increasingly bigger aggregate forms. They do this with the goal to gain a better understanding of the absorption properties of melanosomes in skin. The extremely broad absorption spectrum of melanin can be directly explained by the fact that melanin in melanosomes is present as aggregates of different sizes, each exhibiting a unique spectral shape, and the larger aggregates being more spectrally shifted. Thus the sum of the absorption of different melanin aggregates in a melanosome will add up to a very broad absorption profile extending from UV to the entire visible wavelength range. Kollias *et al* [116] also found that the absorption spectrum of melanin in melanosomes varies depending on UV exposure. It can be speculated whether this is due to photo-induced transformations between different aggregation forms, with different absorption properties. It was found that UVA irradiation of skin *in vivo* induced increased absorption in the visible, but not in the UV region. Absorption measurements in different melanin solutions exhibited decreased absorption in the UV and increased absorption in the visible for eumelanin, and a decrease in both the UV and visible regions for pheomelanin. This alteration in absorption properties was shown to be oxygen dependent. It was also speculated by the authors whether this can explain the poor UV protection in less pigmented skin, mostly containing pheomelanin. UVB-induced melanin is increasingly absorbing towards shorter wavelengths with a maximum at 305 nm.

The strong melanin pigment in melanosomes in the epidermis is obviously extremely important for light propagation in the skin, and plays a major role in protecting sensitive tissue structures from harmful UV radiation. The melanosomes, however, not only contribute to attenuating the light penetration by its absorption properties, but light scattering by the melanosomes is also very important in protecting the tissue from UV light [117]. The melanosomes have a much higher refractive index than the surrounding skin (1.55–1.65 and 1.35–1.40, respectively), providing strong light scattering when light propagates in skin containing melanosomes. This scattering is highly dependent on the size of the melanosomes. A large number of larger melanosomes in the stratum corneum of higher skin types yield a higher scattering coefficient, and also with a more forward directed angular distribution. Thus they contribute to a higher light attenuation as compared with lighter skin, with much smaller melanin particles in this outer layer of the epidermis [113]. Interestingly, melanin scattering increases diffuse

reflectance below 300 nm in highly pigmented skin with large melanosomes in the stratum corneum, as compared with skin with less pigmentation [118].

4.2.1.2. Proteins. Skin contains many different proteins. Much research on skin chromophores has concentrated on DNA, as this is believed to be responsible for Sun-induced skin cancer. The cells in the epidermis also contain other aromatic amino acids such as tyrosine (absorption peak at 275 nm, and negligible absorption above 300 nm) and tryptophan (absorption peak at 280 nm, and negligible absorption above 300 nm). Collagen is abundant in the dermis, while haemoglobin is found in the blood vessels in the dermis. They both have significant light absorption, while collagen fibres will also scatter light strongly.

4.2.1.2.1. DNA. As the epidermis is a cellular structure, DNA becomes a significant chromophore in skin. Pure DNA has a well-known absorption spectrum with an absorption peaking at about 260 nm, quickly decreasing towards longer wavelengths. At for instance 300 nm the absorption cross section decreases by an order of magnitude, and at 350 nm by four orders of magnitude. It has been proved that DNA is a prominent chromophore in skin *in vivo* by detecting DNA photoproducts generated following UV irradiation. These photoproducts are believed to be important for mutagenic effects. To be dangerous, such reactions have to take place in the viable cells in the epidermis, meaning probably from the mid-layer of the epidermis and deeper. It has also been shown that UV-induced DNA damage correlates well with skin erythema, with almost identical action spectral shape [119]. This suggests that DNA may be responsible for both these effects, making it possible to, in an indirect way, predict the mutagenic risk of solar exposure.

4.2.1.2.2. Haemoglobin. Apart from melanin, haemoglobin is the chromophore mostly contributing to the colour of the skin. Haemoglobin is the pigment of the red blood cells and is present in the capillaries of the dermis. It has a main absorption peak at 415 nm (when haemoglobin is binding oxygen, HbO_2) and at 435 nm (for the deoxygenized form, Hb). It has further absorption peaks in the visible region, while the absorption falls off drastically at 600 nm. This is what makes it appear reddish. The absorption also falls off quickly towards the UV region, and is only at the most 20% of its peak value in the wavelength range between 250 and 350 nm. As the blood does not really influence the light penetration through skin in the UV region, due to its absence in the epidermis, it could be considered of minor importance for skin optics in the UV range. As mentioned earlier however, erythema visually apparent due to dilated capillaries in the dermis increasing the haemoglobin concentration in the skin, causing the skin to become reddish, has been shown to correlate well with UV-induced DNA damage [119]. This could thus provide means to indirectly measure UV-induced DNA damage in the epidermis.

4.2.1.2.3. Flavins. By flavins or flavoproteins we mean a class of tissue chromophores including some respiratory enzymes occurring widely in the cells. Important flavin molecules include riboflavin, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). The absorption spectrum of flavin in the UV and short visible wavelength region consists typically of four absorption peaks with relatively high molar extinction coefficients. The high absorption suggests that they all are transitions from the ground electronic state to higher excited singlet states. For riboflavin, the four 20–60 nm broad structureless absorption peaks (the broader the peak, the longer the wavelength) are centred at 220, 265, 375 and 450 nm, with a distinct minimum at 310 nm.

4.2.1.3. Cholesterol and folate. Two other groups of molecules in the skin important for photochemical reactions are cholesterol and folate. A vitally important sterol, cholesterol, is among other things an important precursor molecule participating in photo-induced synthesis of vitamin D. One important pathway to generate vitamin D is through absorption of solar radiation in the skin. 7-dehydrocholesterol (7-DHC) present in keratinocytes of the epidermis has been shown to be photolysed to cutaneous vitamin D_3 when irradiated with UVB radiation. The optimal wavelength for such photolysis both for keratinocytes *in vitro* and *in vivo* has been shown to be 300 nm [120, 121]. This information is of importance when considering light propagation in skin, even though it is unclear whether the absorption of cholesterol considerably alters light penetration.

Another important class of molecules strongly influenced by solar radiation is the folate molecules. The term folate describes a group of chemically similar compounds belonging to the vitamin B family. These compounds are related to many biochemical processes in the body, including the metabolism of amino acids, DNA synthesis, DNA repair and methylation of DNA [122]. Folate is present in the blood plasma mostly in the form of 5-methyltetrahydrofolate (5MTHF), and can be photodegraded in the capillaries in the upper part of the dermis. The absorption of 5MTHF peaks at around 200 and 290 nm, and goes to zero at 350 nm. Interestingly, one can conclude that light in the UVB and UVC range, which could be absorbed by 5MTHF, will not penetrate the skin deeply enough to reach the capillaries. It has also been seen that pure 5MTHF is quite photostable upon absorbing UV photons. Therefore folate photolysis is believed to be due to UVA and visible light, and in the presence of endogenous photosensitizers, such as riboflavin [123] or uroporphyrin [124]. Riboflavin absorbs both UVA and blue light as described above, while uroporphyrin has its main Soret absorption peak at about 395 nm.

4.3. Instrumentations and techniques to measure light transmission and optical properties of skin

In the field of skin optics it is essential to be able to measure light propagation in the skin. Although the absorption properties of the biomolecules present in the skin and their distribution in general are more or less known, it is not easy to obtain a good value for the absorption coefficient as a function of depth in tissue. Much attention has been

devoted to such measurements, and we will discuss here some different approaches to experimentally obtain information on light propagation in tissue. The measurements can be divided into different categories depending on the information gained. The techniques can primarily measure absorption or scattering properties as well as the refractive index of tissue, and can be spatially resolved or integrated over the entire sample. Spatially resolved direct absorption measurements are obviously of interest in order to be able to get depth profiles of skin chromophores.

Absorption measurements can be performed *in vivo* or *ex vivo*. *In vivo* studies are naturally the preferred situation as one avoids dehydration, shrinkage and loss of blood containing haemoglobin, all influencing the measurement results. These issues have to be considered if excised tissue samples are studied. UV spectrophotometers for *ex vivo* studies based on an integrating sphere have been developed [125]. This *ex vivo* technique seems useful for UVB radiation where the light penetration is not very deep and is thus not really affected by haemoglobin absorption. Such measurements provide an integrated absorption through the studied sample; therefore, a sample of appropriate thickness has to be prepared. At longer wavelengths (for instance UVA, or visible light), the technique may yield too low absorption values due primarily to loss of haemoglobin in *ex vivo* samples.

There is a strong wish to transfer the technique to the *in vivo* situation. This means that the diffuse re-emitted signal has to be measured rather than a transmitted signal. We will just focus here on the recent published works in this area, although diffuse reflectance spectroscopy has been performed over many years. Two different challenges present themselves in retrieving the information from such measurements: how to model the light propagation in the tissue; and how the depth sensitivity of the measured signal can be understood and controlled. Several modelling approaches have recently been suggested [126–128]. They are based on discrete ordinates, Monte Carlo and a two-flux method, respectively. In order to robustly solve the inverse problem, where the optical properties of different skin layers are to be obtained from diffuse reflectance spectra, it is an advantage to limit the model to a few layers, as that means fewer parameters to fit to the experimentally obtained data. This can relatively correctly be performed for diffuse reflectance of visible light, as light penetrates deep into the dermis, meaning that the epidermis can relatively accurately be considered as one layer. For UV light penetrating much shallower into the skin, it may be essential to fit more layers, making it more difficult for such data to reconstruct concentrations of chromophores in this wavelength region. Also the models used are based on approximations and may be more or less precisely describing the light propagation in the tissue. Yudovsky *et al* have recently demonstrated a simple model to estimate melanosome volume fraction, epidermal thickness, as well as blood volume and saturation from visible diffuse reflectance data [129]. Also Stamatas *et al* have recently used a similar approach to measure chromophore concentrations in the skin [130].

Based on a totally different approach, Chan *et al* described ellipsometric measurements for spectrally resolved *in vivo* investigations of biological tissue [131]. In this method they claim to be able to measure refractive index and absorption coefficients of different skin layers at any one wavelength. The technique used polarized light reflected by the tissue at a certain reflection angle. By studying the polarization of the reflected light, the real and complex part of the refractive index mismatch between the air and skin layer can be obtained. These properties relate directly to the normal refractive index n and the absorption coefficient μ_a of the tissue just under the surface. The technique also provides information on surface roughness. By performing measurements in combination with tape stripping of the skin, it is also possible to scan through the superficial depth of the skin to obtain depth information of these parameters. The technique is then obviously not non-invasive, neither is it simple to control the exact thickness of the cell layer stripped off in each step. The usefulness of this method still has to be evaluated in more clinical studies.

Another approach to extract the absorption coefficients in tissue is to perform any type of direct measurements of absorption in the tissue. The most straightforward one is to use *in vivo* confocal microscopy to directly measure the distribution of absorbing chromophores. Again one usually uses visible or near-infrared light in order to get a deeper penetration of this modality. The depth that can be measured is then usually 200–300 μm, with a resolution of a few μm. The choice to use such long wavelengths restricts the current work to chromophores in this wavelength region. It would have been interesting to investigate whether it would be possible to perform *in vivo* confocal microscopy in the UV region, to measure the distribution of UV chromophores in the epidermis. The challenge would be to obtain depth sensitivity and resolution that would provide the interesting information. Another challenge for this technique is to obtain true absorption data, as the light is attenuated as it penetrates towards the focal point inside the tissue and back. Here one again needs a light propagation model to correctly compensate for the light attenuation in the tissue. For those chromophores that also exhibit fluorescence emission following the absorption of a photon, one can use fluorescence confocal microscopy or multiphoton microscopy. This is also a valuable tool for studying transdermal drug delivery [132].

Another very interesting technique that can potentially provide a spatial map of the absorption coefficient in the skin is photoacoustic microscopy [133]. Photoacoustic microscopy is based on absorption of pulsed laser light. As the light is absorbed it will locally heat the tissue slightly. This heat will generate a very small, but detectable, acoustic signal that can be measured using an ultrasound transducer. The resolution can be as high as 10 μm, with depth sensitivity down to 1 mm. This technique has recently been shown to work for measuring skin absorption coefficients *in vivo* in the UV wavelength region [134]. The results presented show considerable fluctuations in absorption coefficient at nearby sites of the skin, explained by a heterogeneous distribution of the chromophores.

An issue with all these techniques is that they require some model to predict the light penetration at various depths in the skin. These models also require some information regarding the scattering properties of the tissue. One way

to get a spatial map of the scattering properties of the tissue is to use optical coherence tomography (OCT) [135]. This technique provides data similar to photoacoustic imaging, but in the scattering regime. Again most of these measurements are performed in the near-infrared spectral region to obtain as high depth sensitivity as possible, up to more than a millimetre. Because the scattering properties do not change significantly for different wavelengths, this information could still be very interesting for obtaining information as correct as possible regarding the skin optical properties. OCT and confocal laser scanning microscopy have, for instance, been used to measure the thickness of stratum corneum and epidermis [136] as well as photodamage caused by Sun exposure [137]. Although OCT usually uses near infrared radiation in order to get depth sensitivity, it should be able to assess the relative strength of scattering in different skin layers. This should be valuable as a complementary method to diffuse reflectance spectroscopy to obtain absolute numbers of scattering coefficients in different skin layers [138]. Spectrally resolved OCT has also been used to extract concentrations of tissue chromophores [139].

Another technique to measure optical (including scattering) properties in small volumes is based on elastic scattering spectroscopy or differential path length spectroscopy (DPS) [140]. This technique provides a full spectrum of reflectance, but limits the penetration to very small depths, by defining a very small detection probe. In the case of DPS, the diffuse reflected signal from larger depth is also subtracted to ensure the shallow probe volume.

We believe that it would be very interesting to combine a few different techniques to extract the best map of optical properties from skin tissue. The different techniques described above all have different features. All need a model to predict the light penetration to compensate for the attenuation of light as it reaches the measured tissue volume. They also have different sensitivities and all techniques cannot be used at the wavelengths of interest. Therefore it can be of interest to combine several techniques to provide more information and hopefully be able to create maps of chromophores and light penetration in the superficial layers of skin for the UV range.

As skin erythema reactions need to be objectively quantified in order to assess how much light has been absorbed by DNA, we will also briefly discuss how such measurements can be performed. Often erythema reactions are evaluated through visual inspection. More appropriate is to use computer-assisted image analysis as reported by, e.g., Coelho *et al* [141]. The use of multispectral imaging also provides important information to make such an analysis independent of other chromophores [142]. Melanin distribution in the skin was evaluated in a similar way by Antoniou *et al* [143]. In order to perform multispectral imaging of the skin, while effectively suppressing the specular reflection from the skin surface, and also to provide a better depth sensitivity a technique called tissue viability imaging has been developed. It is based on using crossed polarizers for the illumination and detection arms [144].

4.4. Mathematical models of light penetration in skin

Light propagation in tissue is most often based on transport theory, usually represented by the radiative transfer equation (RTE). This is an approximate model neglecting the wave properties of light. This simplification is validated by the turbid nature of skin, resulting in time and space averaging of any interference patterns due to the wave properties of light. The first generally accepted models were described by Diffey [145]. Today there are different approaches to modelling UV light transport in skin tissue. Several groups have adopted the discrete ordinates method [126, 146], or the diffusion approximation [147], to solve the RTE. Diffusion provides a simple analytical expression, but works best in the near infrared region when scattering dominates over absorption. The discrete ordinates method also works in the UV region, but requires numerical solutions in the computer. In addition to these methods, Monte Carlo simulations have also been used [127]. Monte Carlo simulations require even less approximations and could thus be more accurate, but provide no information on the parameter dependence of any solution, as they simulate the result rather than find a solution to the equation. Monte Carlo simulations also require considerable computer capacity to obtain high accuracy. Recently, some available Monte Carlo computer codes have been implemented for graphical processing unit (GPU) platforms, speeding up the simulations up to 1000 fold [148, 149]. This certainly relaxes the need for high computer capacity for Monte Carlo simulations.

It may also be possible in many cases to find even simpler solutions and just rely on the Beer–Lambert law predicting exponential attenuation of the light due to the absorption coefficient. In that case one needs to find an apparent path length for the light, a parameter strongly dependent on the scattering properties of the tissue. Despite the strong assumptions made for this method, it is attractive due to its simplicity. It has also been shown to work well in specific, well-defined geometries [140, 150]. Often it is combined with Monte Carlo simulations for obtaining values for the apparent path length and for calibration purposes.

In addition to the above-discussed effort to model light propagation in skin, another interesting mathematical model of interest in the context of this paper has recently been published. Thingnes *et al* have presented a model for the tanning process in skin following solar radiation [151]. The authors build up a dynamic model based on the current knowledge of the tanning process. They model how melanosomes are produced in the melanocytes in the basal layer, how these are given over to keratinocytes, and then redistributed in the epidermis. The model agrees well with the available experimental data. It thus could be a very important tool in assisting the modelling of light propagation, as the distribution of melanosomes could be predicted in an interesting way.

We have reviewed in this section the recent works of importance for light propagation in skin tissue as this is very important in the understanding of photochemical processes initiated by solar radiation. One of the challenges in this understanding is that the various photochemical reactions of interest take place at different depths in the skin (figure 7).

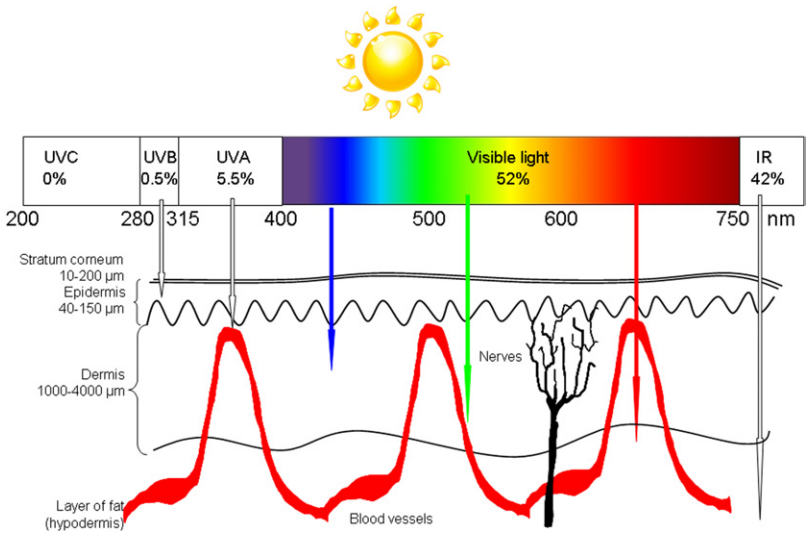


Figure 7. Approximate depth for penetration of optical radiation in fair Caucasian skin.

Another is that the reactions are activated at different wavelengths. Both of these effects contribute to different light attenuation for the solar light initiating the reactions before reaching the molecules responsible for these different photochemical processes. This is further complicated by the huge variation in the light attenuation depending on skin type and degree of tanning, making the light propagation issue even more complex and of great importance for a precise understanding of light-induced skin reactions.

Many techniques have been developed to measure optical properties and the distribution of chromophores in tissue. It seems that no technique has so far been able to map the absorption and scattering properties with sufficiently high accuracy and spatial resolution to meet the needs for accurate modelling of light propagation in skin. In particular, there is no technique that could measure the scattering coefficient for the different skin layers *in vivo*. More precise values of optical properties can be obtained by combining results from different measurement techniques. We especially believe that it is interesting to combine the accuracy of diffuse reflectance spectroscopy with techniques providing depth resolution information. More accurate values of optical properties could probably be obtained by developing such multimodality approaches.

Much of the work in the past focused on measuring the activation spectra for different photochemical reactions in the skin. These measurements obviously provide interesting information for the reactions, but are complex functions of the activation spectra of the molecules responsible for the reactions and light attenuation in the skin before reaching these target molecules. In order to gain a better understanding of the full process, it is important to separate these effects. This would also make it possible to better predict the effects of solar radiation on an individual basis, depending on skin type and degree of tanning.

Another aspect not discussed so far is the need for good Sun protection to avoid the damage of UV radiation. There are different needs for Sun protection for different ethnic groups. This also means that the attenuation spectrum should vary depending on skin type and degree of tanning [152]. Alternatively everybody should have a broadband sunscreen. The primary need today is obviously to protect the skin from light-induced skin ageing [153] and Sun-radiation-induced skin cancer [154]. The action spectra for different kinds of skin tumours are also reported to vary (see section 5), also suggesting a broadband Sun protection.

5. Action spectra relevant for health

Light and UV radiation interact with biological systems by being absorbed in molecules called chromophores. Action spectroscopy is the main tool to identify chromophores for given photobiological processes. The action spectrum of a process taking place in a weakly absorbing and scattering sample is identical to the absorption spectrum of the chromophore, while it may be modified in strongly absorbing or scattering media, especially if absorption or scattering properties vary significantly with the wavelength. The power of action spectroscopy is demonstrated by the fact that the use of the method led to identification of chlorophyll as the chromophore for plant growth [155] and nucleic acids (and not proteins) as the chromophores for the bactericidal effect of UV radiation [156], as well as for induction of mutants [157]. These observations were very early indications (1930 and 1942) of nucleic acids as the genetic material.

Action spectra are usually given in relative units. The value of the action spectrum for a given photobiological effect at a given wavelength and under idealized conditions (low scattering and low absorption) is the inverse value of the number of photons needed to initiate the effect, say killing of 50% of the cells in a sample. Since chromophores have different absorption spectra when bound and free, action spectroscopy can be used not only to identify the chromophores but also to determine whether they act as bound or free entities [158]. Scattering, absorption and involvement of more than one chromophore make the situation complicated, as can be

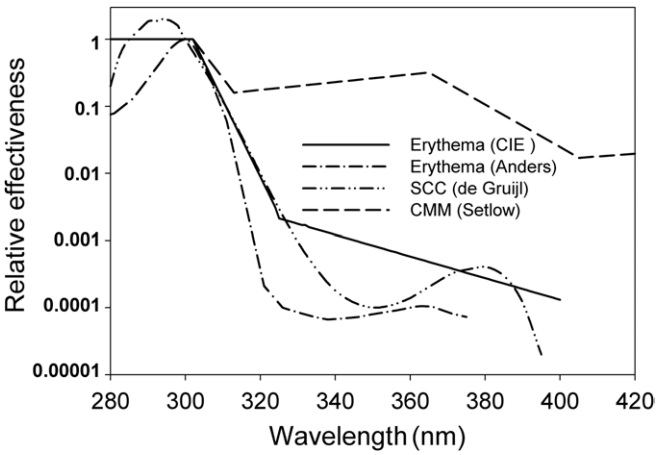


Figure 8. Action spectra for erythema in human skin according to CIE [162] and Anders *et al* [166], for SCC in mouse skin according SCUP [172] and for CMM in fish according Setlow *et al* [176].

exemplified by skin photocarcinogenesis where both DNA (UVB-absorbing) and chromophores absorbing UVA may be important. Several conditions needed for obtaining reliable action spectra were reviewed earlier [159, 160].

To compare the Sun and artificial UV sources, such as sunbeds, with respect to photobiological effects, relevant action spectra are inevitable. We will review the recent determinations of action spectra for the following processes: erythema, squamous cell carcinoma (SCC), cutaneous malignant melanoma (CMM), pigmentation (tanning), delayed pigmentation (DP), immediate pigment darkening (IPD), photoreactivation of DNA damage in human skin, eye damage, vitamin D generation and photointeraction with CRs.

5.1. Erythema

The Commission Internationale de l'Eclairage (CIE) spectrum (figure 8) is a standardized action spectrum for erythema, proposed by McKinlay and Diffey [161, 162]. This idealized spectrum is given a mathematical form, and is based on experimental spectra, obtained using multiple monochromatic light sources [161, 163, 164]. Since the spectrum is very steep between 300 and 320 nm and decreases by almost three orders of magnitude in this small wavelength region, the bandwidth of the exposure radiation is of crucial importance [165]. Thus, the narrow bandwidth of laser radiation is a large advantage over radiation obtained using lamps and monochromators. Thus, a more precise and reliable spectrum can be obtained by means of lasers, as shown by Anders *et al* [166] (figure 8). The mentioned erythema spectra have a larger contribution of UVA radiation than the action spectrum for mutagenesis in human skin [167] and the absorption spectrum of DNA [168]. This shows that, although DNA is the main chromophore for erythema, other chromophores contribute in the UVA region. Oxygen supply plays a large role in UVA-induced erythema and pigmentation, indicating its importance in these reactions [169, 170]. Photosensitization may play an important role in UVA-induced reactions, and one might speculate that these chromophores are porphyrins. These reactions may also be fluence rate dependent [171].

5.2. Squamous cell carcinoma

The only published action spectrum for non-melanoma skin cancer (figure 8) is the so-called Skin Cancer Utrecht–Philadelphia (SCUP) action spectrum for SCC in mice [172]. This spectrum is based on SCC generation in mice exposed to filtered UV radiation from xenon arc lamps, and rather complicated calculations are needed to obtain it [172]. The spectrum resembles the erythema spectra (figure 8).

5.3. Cutaneous malignant melanoma

CMM can be induced only in a few suitable experimental animal models, such as in several types of transgenic mice, in a South American opossum, *Monodelphis domestica*, and in a hybrid fish, *Xiphophorus* [173]. CMM arise also in larger animals such as Angora goats, horses and Sinclair swine [173–175], but they are not suitable as experimental models for obtaining action spectra, since extremely large fluence rates of strictly monochromatic radiation would be needed to cover large skin areas. So far, action spectra for CMM have not been determined in humans. Setlow *et al* [176] measured an action spectrum for the induction of CMM in the small sword fish *Xiphophorus* (figure 8). This spectrum weights UVA and even blue light very strongly (figure 8). If this spectrum is correct and can be applied on humans, important actions would have to be taken. For instance, the UVA and the blue contribution of solar radiation decreases lesser than the UVB contribution with increased SZA Z, because of the strong wavelength dependence of Rayleigh scattering (see chapter 3). Thus, the rate of UVB-induced vitamin D production (see section 8) decreases much faster after noon than the risk of UVA induction of CMM [29]. Consequently, if this action spectrum is correct the common health advice to stay out of the Sun until afternoon is not a good one. Furthermore, sunbeds usually emit much larger fluence rates of UVA than the Sun [177] (since they are made for tanning (see section 5.4)) and may be more melanomagenic than thought. Finally, most Sun lotions (sunscreens) are constructed with better UVB than UVA protection [178, 179], and their use will result in more reduction of erythema risk and vitamin D photosynthesis than in CMM protection. However, recently the original CMM experiments with *Xiphophorus* were repeated and did not show any strong UVA contribution [180]. Similarly, UVB, but not UVA, induced CMM in an HGF/SF transgenic mouse model [181, 182], so the matter is not yet settled. On the other hand, epidemiological studies argue for Setlow's CMM spectrum to be valid for humans: we found that UVB has a steeper north–south gradient than UVA, and that both SCC and BCC have much steeper north–south gradients than CMM [183]. Furthermore, several recent studies indicate that there may be a significant CMM risk associated with the use of sunbeds [183–186], while it has been known for a long time that outdoor work in the Sun does not result in any additional CMM risk [187–189]. Sunbeds have a much higher relative UVA contribution than found in solar radiation under relevant conditions with respect to time and location [177].

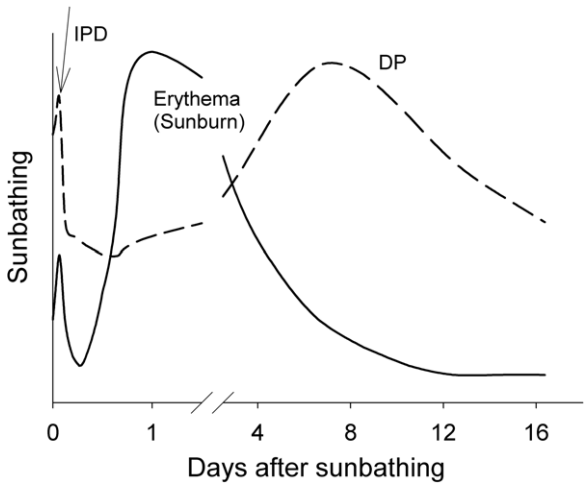


Figure 9. Time course of erythema, IPD and DP [190, 205–208].

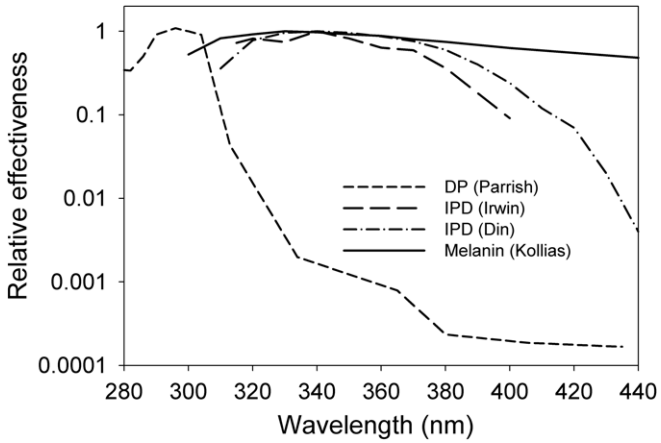


Figure 10. Action spectra for DP according to Parrish *et al* [163] and IPD of human skin according to DIN [211] and Irwin *et al* [210]. Absorbance spectrum of melanin in human skin according to Kollias [212].

5.4. Pigmentation (tanning)

Two types of pigmentation are generated by solar radiation: DP and IPD [190].

5.4.1. Delayed pigmentation. DP appears in skin within 3–5 days after UV exposure (figure 9) [190]. Essentially, melanocytes are stimulated under UV exposure to synthesize both types of melanin: eumelanin (brown/black) and pheomelanin (red/yellow, sulfur containing) [191]. There is a general agreement that pheomelanin is less photoprotective than eumelanin, and that pheomelanin may contribute to CMM formation because it generates hydrogen peroxide and superoxide anions upon UV exposure [192]. The branching between the two melanin types is genetically determined. Red haired people have relatively less eumelanin in their skin, easily burn and are at higher risk of developing skin cancer than dark haired people [192]. According to the Fitzpatrick [110] classification, skin can be categorized into six types: I (white, prone to sunburn and CMM) to VI (very dark, low risk of sunburn, low efficiency of vitamin D photoproduction). Pigmentation in white skin types results in a protection factor of about 2–3 against DNA photodamage and erythema [163, 193].

The action spectrum for DP (figure 10) resembles that of erythema (figure 8), but has a larger UVA contribution. Notably, this is so for people with dark skin colour. Still, generally one can say that because of the similarity of erythema and the DP action spectra [163], it is not possible to construct a radiation source (a sunbed) which gives a significant tan without any erythema and skin cancer risk.

DP can be induced by UVB and UVA [192, 194, 195]. UVB-induced DP is more photoprotective than UVA-induced pigmentation [192, 196]. Pigmentation accounts for only 6–11% of the increased photoprotection after four weeks of UVB exposure; increase in epidermal thickness probably accounting for the rest [197]. The absolute DP generated by UVB is almost independent of pre-exposure pigmentation, and thus the relative DP is the highest for fair-skinned people [198]. In agreement with an earlier work [163] it has recently been confirmed that UVA is more melanogenic than erythemogenic in the dark skin types II–V [199]. Furthermore, DP is built up faster with UVA than with solar radiation [199]. This is why sunbeds are constructed to emit relatively more UVA than the Sun does. Also, UVA-induced DP lasts longer than UVB-induced DP [200]. However, this is of questionable benefit since we [183] and others [176, 201] have found significant epidemiological and experimental evidence for a possible melanomagenic effect of UVA. Also, recent works on the relationship between sunbeds' use versus Sun exposure and CMM risk support this conclusion [184–186] and should be given attention in future regulations of sunbeds. Sunbeds with Sun-like spectra (i.e. less UVA than now) might reduce rather than increase the CMM risk, as does regular, moderate Sun exposure [187, 202]. Both UVA- and UVB-induced pigmentation fade within 4–6 months.

5.4.2. Immediate pigment darkening. IPD was first described in 1927 [203] and later in 1962 [204]. This type of apparent pigment darkening is dependent on pre-existing melanin and takes place during and immediately after exposure to UVA or visible radiation (figure 9) [205–208]. A reorganization of melanosomes in melanocytes and keratinocytes may explain part of IPD, predominantly involving an arrangement of melanosomes in an umbrella-like pattern over nuclei [209]. The evolutionary cause of this process was assumed to be protection of DNA from damage. However, later work indicates that IPD offers little protection against the induction of erythema and DNA damage. The action spectrum of IPD resembles the absorption spectrum of melanin (figure 10) and stretches out further into the UVA and visible range than the CIE erythema spectrum (figure 8) [195, 210]. IPD induction appears to be oxygen dependent [169].

5.5. Photoreactivation

The photoreactivation enzyme, also called photolyase, binds to DNA regions containing pyrimidine dimers [213, 214], one of the main UV-induced products in DNA, thought to be an initiator of skin cancer [215]. This enzyme contains one

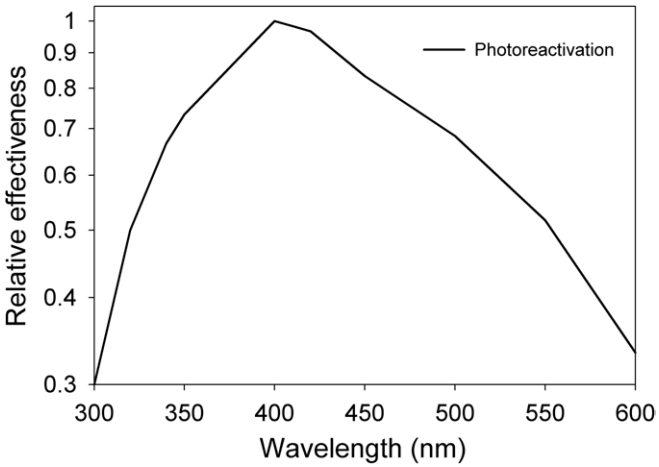


Figure 11. Action spectrum for photoreactivation in human fibroblasts [217].

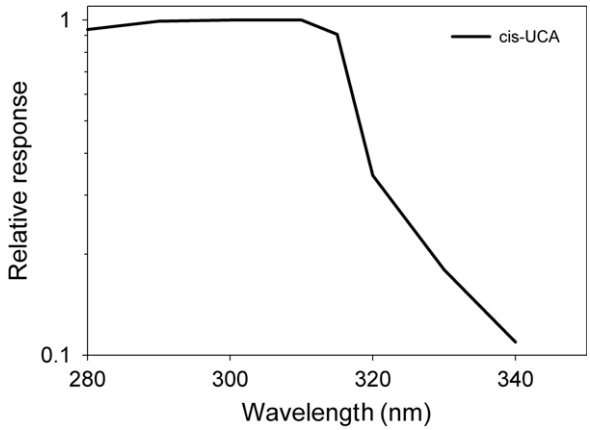


Figure 12. The action spectrum for *cis*-UCA production in human skin [223].

or more chromophores, and absorption of photons within their absorption spectrum leads to the removal of the damage from the DNA within a few hours [216]. It has been claimed that the photoreactivation enzyme is also present in human skin [217] and photorepair of UV-induced damage certainly takes place [218], although some of these experiments appear to be difficult to reproduce, and the existence of the photoreactivation enzyme in humans is debated [219, 220]. It is remarkable if humans—mammals which through evolution lost most of their hair, thus getting more vulnerable to UV radiation—should lack this important DNA repair mechanism, while hairy marsupials should have retained it [221].

The action spectrum initially found for the photoreactivation enzyme in human fibroblasts is shown in figure 11 [217]. If this can be reproduced, it means that artificial UV sources for human use, either in medicine or in cosmetics, should emit some visible, photoreactivating radiation. This would reduce their carcinogenic potential by removing some of the pyrimidine dimers. It should be remarked that folate can be photodegraded by UVA in the presence of endogenous photosensitizers [123, 124]. This means that two processes will compete during the photoreactivation: removal of DNA damage and degradation of the photoreactivation enzyme. Thus, the efficiency of photoreactivation will decrease with time during the repair process.

5.6. Photoimmunosuppression

When human skin is exposed to UV radiation, cell-mediated immune responses are suppressed. Such immunosuppression may allow tumour cells to live and multiply, and may also reduce the resistance of the body against microbial infections in skin and elsewhere. Essentially, two chromophores have been brought to attention: DNA [222] and *trans*-urocanic acid (*trans*-UCA) [223]. Photoisomerization of UCA, from the *trans* to the *cis* form, is thought to be a key reaction, since *cis*-UCA has an immunological effect and since *trans*-UCA is the abundant form in unexposed skin [223]. The action spectrum for photoimmunosuppression in human skin (figure 12) indicates maximal *cis*-UCA production in the UVB spectral region of 280–310 nm [223]. This spectral peak is redshifted compared with the erythemal action spectrum [223]. A demonstration of the significance of photoimmunosuppression for skin carcinogenesis is that UV-induced skin tumours can be transplanted to UV exposed mice but not to unexposed mice [224].

5.7. Photoageing

Sun-exposed skin ages faster than unexposed skin [225]. Photoageing is a general term for degradation of exposed skin with age: wrinkling, loss of elasticity, accumulation of yellowish pigments and thickening, or, sometimes, thinning. Central in this process is degradation and cross-linking of protein fibres, elastin and collagen. It was, therefore, assumed that the action spectrum of photoageing should resemble the absorption spectrum of proteins, i.e. be mainly UVB-weighted. This is, in fact, true according to some of the published spectra (figure 13). However, most of the reported spectra have a much larger UVA contribution (figure 13). Thus, UVA-absorbing chromophores are likely to be involved. UCA, porphyrins and riboflavin are candidates, and photosensitization processes involving oxygen may participate [226].

5.8. Eye damage: photokeratitis and cataract

5.8.1. Photokeratitis ('snow blindness'). It can be regarded as a sunburn reaction of the outer part of the eye: the cornea and conjunctiva. It is transient and has an action spectrum (figure 14) [165] resembling the CIE and the Anders erythema spectra (figure 8).

5.8.2. Cataract. It is a reduction in the transparency and an increase in the turbidity of the lens, and is caused by cross-linking, degradation and aggregation of proteins. Solar radiation accelerates cataract formation. Thus, the incidence rate of cataract increases with ambient solar doses, as revealed in many epidemiological investigations [230]. Since the cornea absorbs the shorter UV wavelengths, the action spectrum of cataract *in vivo* is likely to be redshifted from the spectra of protein degradation. Growth, differentiation and

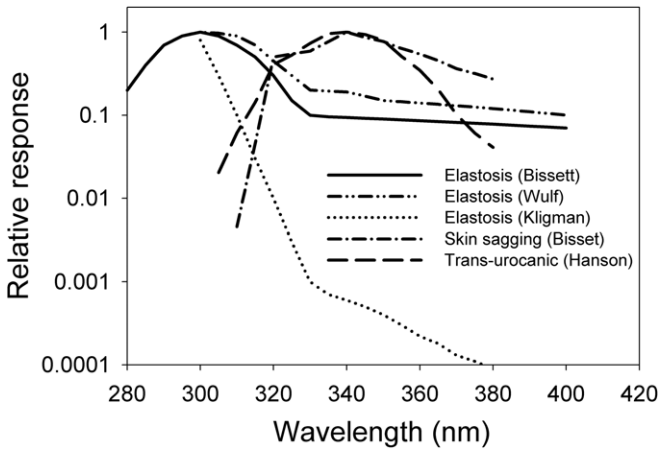


Figure 13. Action spectra for elastosis in hairless mice skin according to Bissett *et al* [227], Wulf *et al* [228] and Kligman and Sayre [229], for skin sagging in hairless mice skin according to Bissett *et al* [227] and for singlet oxygen generation after excitation of *trans*-urocanic *in vitro* (Hanson and Simon) [226].

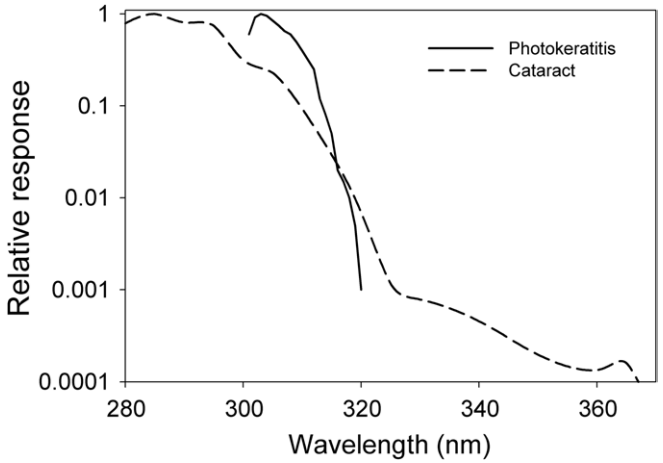


Figure 14. The action spectra for photokeratitis in a human cornea [165] and for cataract formation in a cultured porcine lens [231].

maintenance of the lens are related to a single cell layer just at the back of the lens. The action spectrum for damaging these cells (grown in culture) has been measured (figure 14), and is slightly redshifted compared with that of the *in vitro* degradation of the whole lens [231]. Wavelengths above 320 nm seem to play a role [231, 232]. This indicates that other chromophores than DNA and proteins may be involved, and that attention should also be paid to UVA radiation [165].

5.9. Vitamin D formation

Vitamin D_3 is formed by UVB radiation in skin [233]. This is the most important source of vitamin D in humans, and the process is so beneficial that it was the driving evolutionary force for white skin development when humans migrated from central Africa to higher latitudes where the UVB fluences were lower [234, 235]. Dark skins of types V and VI need up to six times larger UVB doses than white skin to produce enough vitamin D [236].

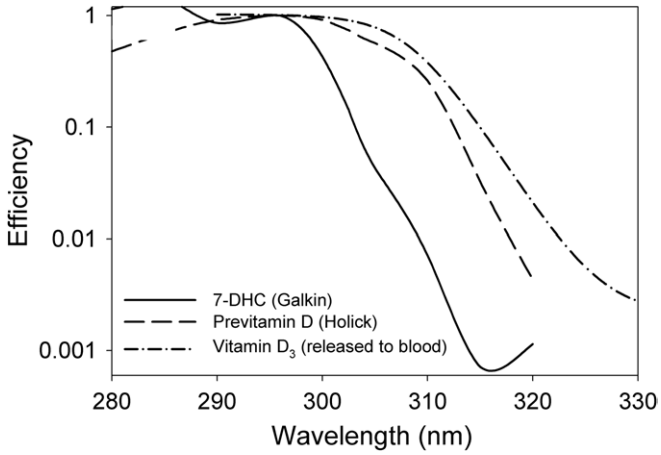


Figure 15. The absorption spectrum of 7-DHC in solution [240], the action spectrum of previtamin D formation from 7-DHC in human epidermis [241], the curve for vitamin D released to blood estimated from the previtamin D curve corrected using the absorption spectrum of the lower epidermis.

Active vitamin D is formed in a series of reactions initiated by absorption of a photon of UVB by 7-DHC, which is present in all skin layers [233]. Then, previtamin D is formed, from which vitamin D is generated in a thermal process, taking about one day at 37 °C. Vitamin D is then bound to vitamin-D-binding protein (DBP) and transported by circulation to the liver, where it is hydroxylated to calcidiol (25(OH)D). Then it is once more bound to DBP and transported to the kidneys and several other tissues for another hydroxylation, now forming calcitriol ($1,25(OH)_2D$), which is the active hormone, crucial for bone formation and maintenance [237]. Calcitriol seems to play an important role in the defence against several diseases, such as influenza, cancer, diabetes, MS and mood disorders [238, 239].

The action spectrum for previtamin D formation from 7-DHC in solution is similar to the absorption spectrum of 7-DHC (figure 15), which almost exclusively lies in the UVB region [240]. In order to calculate the real action spectrum for the formation of active vitamin D *in vivo*, several complicated processes have to be taken into account: (1) the penetration spectrum of UV into skin tissue (penetration increases steeply with wavelength [108], (2) the temperature dependence of vitamin D formation from previtamin D (the temperature increases with depth below the skin surface) and (3) diffusion of vitamin D from the site of formation to the blood vessels (vitamin D formed deeply in the tissue is transferred most efficiently to the blood vessels in the deep dermis). All these factors lead to a significant redshift of the spectrum, so that the *in vivo* spectrum is stretching significantly into UVA. An action spectrum of vitamin D formation in skin has been measured with some confidence, and seems to agree with calculations, as sketched in figure 15 [241]. However, this spectrum should be determined more accurately in the UVA region, since solar radiation contains 100–1000 times more UVA than UVB, depending on time and location.

Vitamin D and almost all of its photochemical precursors are photolabile, and many reactions can go both ways. Thus, solar radiation does not have an optimal spectrum for the

production of vitamin D from 7-DHC: it can transfer only about 20% of the 7-DHC in skin to vitamin D, whereas monochromatic radiation around 295 nm can transfer up to 80% [241].

5.10. Circadian rhythms and mood disorders

All known light effects related to vision in humans are mediated via light absorption in photopigments consisting of the protein opsin with a vitamin A derivative (an 11-*cis*-retinaldehyde) bound to it [242]. The vision process starts with an isomerization of the *cis* form to the all-*trans* form of the chromophores, triggering a nerve transduction cascade. Recently, it has been found that CRs, as well as several other non-visual processes (melatonin suppression, pupil reflex, period lengthening) [243, 244], are entrained by light absorption in a special vitamin A related pigment called melanopsin. This has an absorption maximum around 480 nm, different from that of the visual pigments in cones and rods [244]. Thus, blind animals and humans may still have intact receptors for light interacting with the CR. Nerve cells from these receptors (about 1% of the total number of nerve cells leading from the retina) go in a special bundle to the suprachiasmatic nuclei (SCNs), two small organs residing near the crossing point of the right and the left optical nerve. Practically all cells in the human body have the so-called clock genes, produce clock proteins, follow CRs and are entrained to a 24 h period by the master clocks, the SCNs. Relevant action spectra for light interaction with CRs in animals and humans are shown in figure 16 [245–247].

Circannual rhythms are governed by the day/night ratio [248]. Receptors for light interaction with these rhythms are not known, but are probably the same as those for CRs. The same is true for light-dependent mood disorders, so-called SAD. It seems clear that light therapy works for SAD [249, 250] and that the action spectrum may be similar to that for CRs. Men seem to have lower rates of SAD than women [251], and the rates increase with increasing latitude, as one might expect. Also, the rates may be population dependent and probably genetically dependent [252].

NO is produced enzymatically by nitric oxide synthases which are present in peripheral tissues and in neurons. NO acts as a neuromodulator in the central nervous system and participates in the regulation of brain development, pain perception, neuronal plasticity, memory and behaviour [255]. Recently, it has been demonstrated that UV exposure of human skin leads to an enzyme-independent efficient formation of nitric oxide ($NO^{\cdot}$), which acts systemically as a vasodilator and lowers blood pressure [256]. In 2003 Rodriguez *et al* [257] demonstrated that in rat vascular tissue NO_2^- and nitrosothiols, but not nitrate, are converted back to $NO^{\cdot}$ under UVA exposure (figure 17). Photoliberation of NO may play a central role in the light–mood relationship.

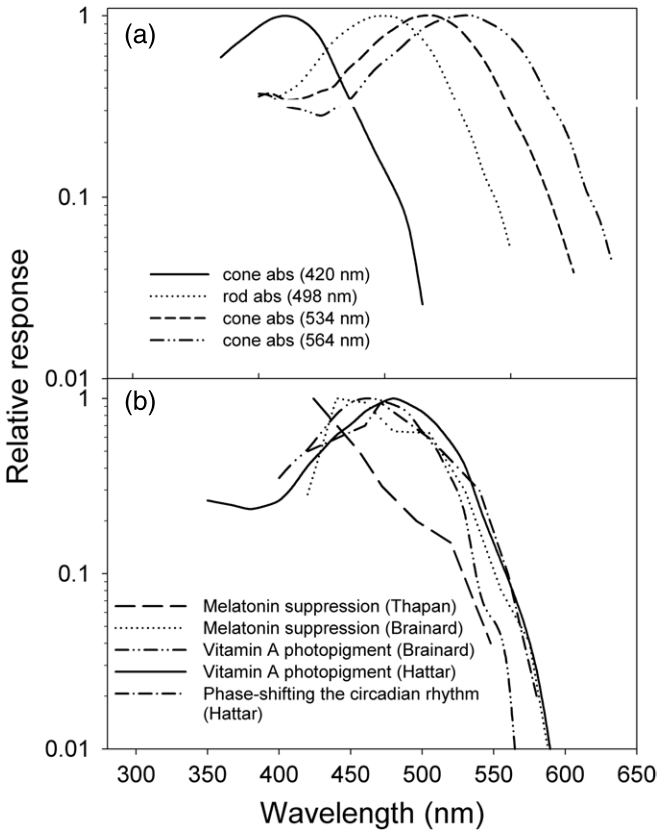


Figure 16. The absorption spectra of cones and rods (*a*) from a human retina [253] and of vitamin A based pigments in mice (*b*) according to Lucas *et al* [245] and Brainard *et al* [247] compared with the action spectra for melatonin suppression in humans (*b*) according to Thapan *et al* [254], Brainard *et al* [247] and Hattar *et al* [246].

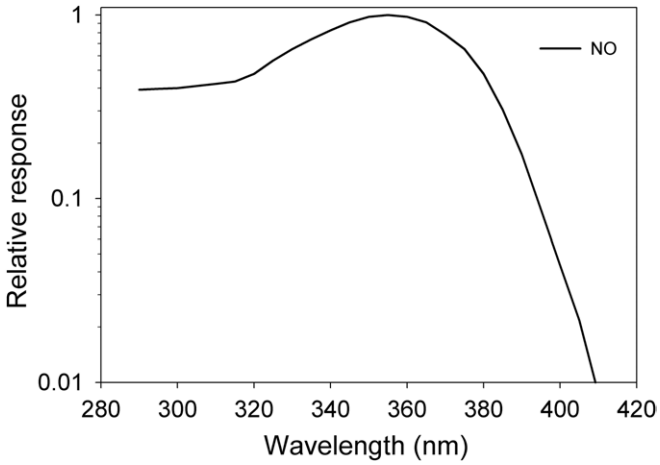


Figure 17. The action spectrum for NO release in rat vascular tissue [257].

6. Solar radiation and skin cancer

Solar radiation is the main risk factor for skin cancer, of which there are three main types: SCC, basal cell carcinoma (BCC) and CMM [258, 259]. The former two are also called non-melanoma skin cancer and have much lower death risks per incidence than CMM; a few percent versus 20–30%. For SCC and BCC the action spectra (figure 8) are likely to be strongly UVB weighted and there is a clear relationship with the total UV exposure, although for CMM not only total exposure, but also sunburn episodes may be important. For CMM the

UV relationship and the action spectrum (figure 8) have been debated for decades [179, 180, 182, 183, 260, 261], but both UVB and UVA are probably CMM-generating in humans.

While BCC and SCC, like most internal cancers, increase in incidence with age, CMM is most frequent among middle-aged people [259, 262]. The localization pattern on the body is also different for the three skin cancer forms, and this pattern is changing with time [259, 262]. The density of SCC and BCC per unit skin area is, and has always been, the largest in the face, as related to the total Sun exposure. The same was true for CMM until the 1980s when the density became larger on the trunk especially for young people [263]. This was attributed to intermittent Sun exposure and sunburns [259, 262]. The fact that the incidence rates of CMM increased over many decades until about 1990 was a serious concern for health authorities worldwide. The use of sunbeds was suspected, and campaigns against such use were launched. A complicating factor is that sunbeds give vitamin D and that the health benefits of vitamin D have become evident in the last decade. Furthermore, in many countries the CMM rates have decreased since 1990, notably for young people [263]. This has taken place in a period with a steep increase in the use of sunbeds [264]. However, recent epidemiological investigations from Australia, USA and Norway indicate that the use of sunbeds increases the CMM risk [185, 186, 265]. Such investigations are difficult to interpret and compare since different countries have different limits for UV fluence rate as well as UVA/UVB ratios in sunbeds. Furthermore, some older investigations show no increased risk, even though the sunbeds were much stronger and more uncontrolled at earlier times [184].

The role of UV in the etiology of CMM is being debated. The main arguments for a relationship include the following [184, 202, 266–268].

(1) In populations with a similar skin type there is a clear latitudinal gradient, which is larger for BCC and SCC than for CMM. The UVB gradient is larger than the UVA gradient.
(2) CMM risk decreases with increasing pigmentation.
(3) CMM risk increases upon migration to more sunny countries.
(4) CMMs often arise in the borders of UV-induced pigmented nevi.
(5) Sunburn episodes are risk factors for CMM.
(6) CMM patients often have low DNA repair capacity and low minimum erythema doses (MEDs).
(7) Lentigo maligna melanoma is clearly related to UV exposure.
(8) Patients with *Xeroderma Pigmentosum* (abnormal DNA repair) have at least 1000 times increased CMM risks.
(9) Some CMMs contain mutations pointing towards UV damage.
(10) CMM can be induced in some animals by UV (examples: Angora goats, Sinclair swine, *Monodelphis domestica* (an opossum), white horses and *Xiphophorus* (a small swordfish).
(11) Patients with CMM have increased risk of BCC.
(12) Some reports indicate increased CMM risk for people frequently using sunbeds.

However, there are also arguments against the significance of UV for CMM risk [263, 266, 269–274].

(1) CMM is more frequent among people with indoor occupations giving low accumulated UV exposure (white-collar workers) than among people with large accumulated UV exposures (farmers, fishermen, etc).
(2) The localization pattern of CMM on the body is different from that of SCC, which is clearly UV related.
(3) CMM appears to be uncommon among albino Africans; opposite to what is found for BCC and SCC.
(4) The incidence rate of CMM in sunny Australia is only twice as high as in the high-latitude country Norway, while the incidence rates of BCC and SCC are 10–20 times higher.
(5) In Europe, CMM is more frequent in the north than in the south. The whole area is mainly populated by Caucasians.
(6) Not all case–control epidemiological studies show an increase in CMM incidence with increasing UV exposure.
(7) There seems to be little CMM protective effect for UVB absorbing sunscreens.
(8) Around CMM lesions little solar elastosis is found. Solar elastosis is related to accumulated UV exposure.
(9) The Sun and artificial sources of UVB are efficient generators of vitamin D which may reduce carcinogenesis and tumour progression.
(10) CMM may be a disease related to affluence, since the incidence rates appear to increase with increasing gross domestic product.

Sun exposure has certainly a dual role in melanomagenesis. Thus, in time periods of increasing rates of CMM on Sun-exposed body localizations (face, trunk, etc), the rates of CMM on non-UV-exposed localizations (the uveal part of the eye, the vulva and the perianal region) seem to decrease and vice versa. Sometimes there is even an opposite latitude gradient for exposed and non-exposed localizations [275, 276]. Also, the prognosis of CMM appears to be the best for CMMs arising on skin with elastosis and signs of high UV exposure [273]. All these observations indicate that UV-induced vitamin D may play a protective role.

The discussion of whether UVA can generate CMM is of particular interest from the point of view of physics. The main argument for a causation include the following. (1) CMM can be induced in the fish *Xiphophorus* by UVA (figure 8) [176]. (2) Albino Africans lacking melanin have very high rates of BCC and SCC but low rates of CMM [277]. This seems to suggest that melanin is a chromophore for CMM. (3) The latitude gradients of CMM and UVA are much smaller than those of SCC, BCC and UVB [183]. (4) Some CMMs contain signs of UVA damage [179, 260]. Arguments against UVA involvements include the following. (1) UVA induces CMM neither in *Monodelphis domestica* nor in transgenic mice. (2) Recently, an attempt to reproduce Setlow *et al*'s original *Xiphophorus* experiments [176] was made, but did not show any CMM-generating effect of UVA [180].

7. Adverse effects of large UV exposures: photoageing and immunosuppressive effects

UV exposure of skin leads to several adverse effects, first of all photocarcinogenesis [278, 279], as well as photoageing [280] and immunosuppression [281]. The deleterious and photocarcinogenic effects of solar UV exposure are predominantly caused by UVB-induced formation of cyclobutane pyrimidine dimers and pyrimidyne-(6-4)-pyrimidone photoproducts, the defective repair of which promotes photocarcinogenesis [278, 279]. The epidermis and dermis are both targets for UVB, but the dermis is also significantly affected by UVA. Thus, photoageing is caused mainly by UVB but UVA seems to play a role as well. However, the exact pathogenesis of cutaneous photoageing is not completely understood and a unifying mechanistic concept is still missing [280]. Although the effects of UVA are less well characterized as compared with those of UVB, there is growing evidence that UVA-induced reactive oxygen species (ROS), which in turn cause DNA damage, may play a major role in photoageing [280, 282]. UVB fluence rates are dependent on the ozone layer which has been and will be a subject of concern in the future [280, 283].

7.1. Large UV exposures and photoageing

The term photoageing was created by Kligman and Kligman in 1986 [284] to describe characteristic changes that develop in the skin after years of exposure to UV. These clinical changes include fine and coarse wrinkling, roughness, dryness, laxity, teleangiectasia, loss of tensile strength and pigmentary changes [280]. Acute responses following exposure to UV (including sunburn and tanning) take hours to days to develop. In contrast, photoageing may take many decades [280]. As mentioned, the pathophysiological mechanisms underlying photoageing are not well understood [280] and well-designed laboratory investigations to identify the cellular and molecular alterations are of high importance [280]. Such investigations are difficult to design and carry out, and relevant *in vivo* models are urgently needed [280].

UV produces ROS in skin cells [280]. These ROS are considered to be of high importance for the pathophysiological process of photoageing [280]. They are able to inhibit the enzyme protein-tyrosine phosphatase-κ, which hypophosphorylates a broad variety of important cell surface receptors, rendering them inactive. This mechanism then causes constitutive activation of cell surface receptors including the epidermal growth factor receptor, interleukin-1 receptor and tumour necrosis factor receptor [280, 285]. These cell surface receptors mediate intracellular signalling through stress-associated mitogen-activated protein kinases (e.g. p38 and JNK) [280, 286] and finally result in the nuclear transcription of a complex known as activator protein-1 (AP-1), which consists of proteins c-Jun and c-Fos [280, 287]. Increased AP-1 transcription results in decreased synthesis of collagens I and III. Moreover, it blocks the effects of transforming growth factor-β (TGF-β), an enhancer of collagen gene transcription and a negative regulator of keratinocyte proliferation [280, 286, 287]. TGF-β has been shown to exert its biologic effects via activation of distinct intracellular signalling proteins, including SMAD2 and SMAD3. The effects of TGF-β are antagonized by the SMAD7 protein, which interferes with TGF-β-SMAD2 and -3 signalling [280, 288, 289]. Furthermore, it was demonstrated that induction of AP-1 transcription increases the levels and activity of distinct matrix metalloproteinases (MMP-1, MMP-3 and MMP-9), which results in increased breakdown of collagen and extracellular matrix proteins, representing important events in wrinkle formation [280, 287].

Notably, UV may damage mitochondria, the powerhouses of the cell. The electron transport chain produces ROS that may exert deleterious effects on mitochondrial DNA (mtDNA) [280]. It has been estimated that the mutation frequency in mtDNA is around 50-fold higher than in genomic, nuclear DNA [280, 290]. This finding is of functional relevance, and a segment of mitochondrial DNA coding for electron transport chain components is consistently deleted in tissues from older individuals. Interestingly, this deletion, known as 'the common deletion', has been reported to be up to ten-fold more common in photodamaged skin than in non-chronically Sun-damaged skin [280, 290]. Notably, there appears not to be any association between the extent of the common deletion in photodamaged skin and age, but rather with the severity of photodamage [280, 291]. Thus, the common deletion may represent a useful molecular biomarker of photodamage [280, 291]. Moreover, decreased mitochondrial function in photodamaged skin may contribute to ROS accumulation and imbalance in cellular energy production [280].

Proteins may also be altered by ROS in photoaged skin. Certain amino acids (i.e. cysteine, methionine, proline) are more sensitive to oxidative damage than others [280, 292].

UV may also be responsible for cross-linking of dermal proteins such as collagens and elastin. [280] Oxidative alterations of proteins may result in loss of function and increased degradation. Cellular accumulation of oxidized proteins decreases proteasomal function, which impedes the cell's ability to degrade other damaged proteins [280, 293].

Telomeres represent a tandem repeat of a short sequence (TTAGGG) that cover the terminal part of chromosomes and prevent their fusion [280]. It has been shown that, because the terminal portion of DNA cannot be replicated, the last 100–200 bases of telomeres are lost following each cell division [280]. Finally, when telomeres reach a critically short length, cells can no longer divide, and enter a state of senescence [280, 294]. It has been speculated that the normal loop configuration of telomeres may also be disrupted as a result of UV-induced cellular damage, exposing the single-stranded overhang on their 3′ end. This may enable interaction between the overhang and the Werner protein, which then activates the p53 tumour suppressor protein and other DNA damage response proteins to induce senescence or apoptosis [280, 295]. These mechanisms may explain some of the commonalities between chronological ageing and photoageing [280, 294].

In the future, the definition of photoageing will likely expand to include pathways not directly involved in the production of cosmetically alarming wrinkles, and to include

pathways that regulate immune function [280]. For example, chronically photodamaged facial skin shows marked reduction in interfollicular Langerhans cells that are at least in part responsible for intact immunosurveillance and thus may act against UVB-induced photocarcinogenesis and skin ageing [296]. Interestingly, compounds such as topical retinoids that reduce the cosmetic effects of photoageing may also result in dramatic replenishment of Langerhans cells [280, 296].

7.2. Immunosuppressive effects of large UV exposures

The immunosuppressive effect of UV was shown in a series of elegant experiments in syngeneic mice, reported from Margaret Kripke's laboratory [281, 297]. In these animal studies, UV-induced skin cancers were transplanted into mice which were either irradiated with UVB or not irradiated [281, 297]. In mice irradiated with UVB the skin tumours continued to grow, whereas those not irradiated were able to reject the transplanted skin tumours [281, 297]. Notably, immunosuppression was also induced when lymphocytes from irradiated mice were injected into non-irradiated mice [281, 297]. It is now well accepted that UV-induced immunosuppression is complex and not exclusively mediated by a single mechanism [281]. Remarkably, the UV action spectrum for induction of CPDs is identical to that of tumour necrosis factor α (TNF-α) [281, 298] which in turn is induced by interleukin-1.

UVB-induced immunosuppression is mediated locally in the skin at least in part via direct effects on Langerhans cells that represent dendritic cells critical for the presentation of antigens to the immune system [281]. As outlined above, UV depletes Langerhans cells in irradiated skin areas even in low doses [296]. In a series of investigations in humans, dose-dependent effects of UV on Langerhans cells have been analysed [281]. Solar-simulated radiation, either given as a single minimal erythema dose (MED), or over ten times the time period but with irradiance at 10% of the dose, or over ten days at one-tenth of an MED, the outcome was the same, in all groups Langerhans cell numbers were depleted [281, 299]. Some studies indicate that the ability to respond in this way may depend on the genetic background. In individuals who fail to deplete Langerhans cells when initially exposed to antigen in the setting of UV exposure, the clinical manifestation is often that of polymorphic light eruption [281]. Notably, this ability to resist UV-induced Langerhans cell depletion appears to be protective against the development of non-melanoma skin cancer [281, 300]. This hypothesis is supported by an epidemiological study where the prevalence of polymorphic light eruption appeared reduced in skin cancer patients as compared with individuals without skin cancer, despite apparently equivalent UV exposure [281, 301].

Kripke's experiments in mice suggest that cutaneous SCCs are highly antigenic and that mechanisms whereby antigen is recognized are of high importance for preventing photocarcinogenesis [281, 302]. In photocarcinogenesis the importance of mutated cells carrying highly relevant p53 mutations has been well described. Clones of cells carrying p53 mutations are found in chronically UV exposed skin [281, 303]. It has been hypothesized that if the immune system is functionally intact, such mutant cells may be policed by antigen-presenting cells and T memory cells and may not develop the malignant phenotype [281, 304]. DNA photoproducts including cyclobutane pyrimidine dimers are connected with the suppression of T memory cells [281, 304], a mechanism that has been implicated in the UV-mediated reduction of immune surveillance. Failure of immune regulation, which may be caused by ongoing Sun exposure, chronic lymphatic leukaemia or by long-term systemic immunosuppression, may therefore result in progression of clones of cells carrying p53 mutations to actinic keratoses and frankly invasive SCCs [281]. Nucleotide excision repair is a very important protective mechanism against photocarcinogenesis [281, 305].

In the skin of UV-irradiated mice, pyrimidine dimer formation not only initiates a tanning response [281]. Following UV, DNA repair results in DNA fragments being excised from the DNA molecule. These small DNA fragments (oligomers) directly cause immunoprotective effects when applied to the skin [306]. Thus cutaneous DNA repair exerts effects on the immune system in a protective way [281].

Another immunosuppressive effect of UV is mediated by the isomerization of urocanic acid in the stratum corneum [281, 307]. Urocanic acid is normally found in its *trans* isoform but on irradiation with UVB is transformed to its *cis* isomer which has been shown to represent a potent systemic immunosuppressant [281]. The action spectrum for the induction of this transformation appears to be in the UVB range [223]. It has been suggested that *cis*-urocanic acid's ability to suppress cutaneous contact hypersensitivity is mediated via TNF-α [308]. Moreover, UV-irradiated urocanic acid inhibits delayed hypersensitivity reactions to herpes simplex in mice [309].

UV can modulate four important families of growth factors: epidermal growth factor receptor, platelet-derived growth factor receptor, fibroblast growth factor receptor and insulin receptor (IR) [281, 310–313]. Moreover, various primary cytokines involved in immunosuppression, including IL-1, IL-6 and IL-10, have been shown to be induced by UV [281]. Induction of IL-1 like activity by UV has been described in functional assays [314]. Interleukin-10 has recently been described as a key mediator of systemic immunosuppression [281, 315]. Induction of tolerance by immunization through UV-irradiated skin is transferable via regulatory T cells (CD4+CD25+) and depends on IL-10 produced by the host [281, 316].

UV also induces platelet-derived growth factor thought to be pivotal both in UVB-induced immunosuppression [281, 317] and also the immunosuppression induced by PUVA (psoralen combined with UVA treatment) [318]. UVB activates receptors for the primary cytokines IL-1 and tumour necrosis factor-α and the death receptor Fas [281, 319, 320]. UV also induces melanin stimulating hormone locally from keratinocytes; such paracrine secretion plays a critical role in local cell regulation from an immunosuppressive and proinflammatory point of view [281, 321]. The receptor for pigment regulation within melanocytes, melanocortin receptor, is also regulated by UV [281, 322].

The mechanisms underlying immune responsiveness following UV have earlier been reviewed [323]. The effects of UV are very complex and are both dose and wavelength dependent [324]. UVB has long been known to be immunosuppressive, but so has UVA and the order of irradiation may determine the outcome [281, 325]. The practical and visible consequences of these immunological perturbations are those of infection, carcinogenesis and, as previously mentioned, photoallergic reactions such as polymorphic light eruption [281]. The action spectrum for induction of herpes simplex has been shown to be in the UVB range [326]. UVB is up to 1000 times more biologically active compared with UVA. However, UVA also has immunosuppressive effects [47], and as the UVA fluence rates are 100 times larger than those of UVB at noon, is prevalent both in winter and in summer and for many hours more than UVB on a daily basis, the immunosuppression caused by UVA is significant [281].

Unfortunately, there is no good measure of immunosuppression [281]. Most studies have measured the effects of UV on abrogating delayed hypersensitivity responses. This is clinically evident in the context of contact dermatitis patch testing where cell-mediated responses are blunted by recent UV exposure and tests may be rendered falsely negative [281].

8. Solar radiation and mental health

Solar radiation has an important influence, not only on physical health, but also on psychological conditions and mental health. It is believed that CRs play important roles in the latter context. However, recent research indicates that also vitamin D photosynthesis, with its seasonal variation, and even UVA-induced release of NO into the circulation may be of significance, NO being an important neurotransmitter. Further, brain responses to complex cognitive tasks, involving working memory, seem to be modulated by light exposure at certain wavelengths [327]. Thus, there seems to be three major types of chromophores for the interaction of light with biological elements of our mental health: photoreceptors in the eye (probably both melanopsin and visual pigments), 7-DHC and chromophores carrying NO in the blood. Action spectra related to these chromophores are reviewed in section 6.

8.1. Circadian rhythms

Many biological processes follow rhythms. The most important rhythm in chronobiology is the CR: a cycle of roughly 24 h [328]. Humans show daily cycles of sleep and wakefulness, also when isolated from temporal and social cues [329]. The rhythms are endogenous, but adjust to the external environment by cues or so-called Zeitgebers. Sunlight is the main Zeitgeber for human CRs, and the daily synchronization of the biological clock prevents us from drifting from the 24 h day [328, 330].

Light affects the central nervous system through photoreceptors in the retina [330] (see also section 6). Sometimes the entrainment works even in blind people with rods and cones out of function [330]. Intrinsically photosensitive retinal ganglion cells (ipRGCs) constitute a third class of photoreceptors and contain melanopsin [331]. ipRGCs transduce light into neural impulses that project via the retinohypothalamic tract to the master biological clock—the SCN in the hypothalamus. The signal is transmitted via the superior cervical ganglion to the pineal gland where melatonin is secreted in the darkness [330].

The retinal photoreceptor cells are hyperpolarized during the day. This inhibits the release of norepinephrine. The photoreceptors release norepinephrine in the darkness of night, thereby activating α_1- and β_1-adrenergic receptors in the pineal gland. The enzyme regulating melatonin synthesis (arylalkylamine *N*-acetyltransferase) is then increased, and melatonin is released into the bloodstream through passive diffusion. Melatonin release starts earlier in the evening after exposure to bright light in the morning, and later after exposure in the evening [332].

Several processes in the human body are regulated by the circadian clock: core temperature, sleep/wakefulness and many processes influenced by hormones. Thus, defects in the CR system may influence health [333]. Notably, the influence on mental health is gaining increasing attention. Disturbances in the CR system and the sleep–wake cycle influence the status of patients suffering from a variety of psychiatric disorders [334, 335].

8.1.1. Mood disorders. *Seasonal affective disorders (SAD)* are characterized by seasonal depressive episodes. In addition to general symptoms of depression, patients with SAD often have atypical depressive symptoms, such as hypersomnia and increased appetite [336]. Usually, depressive episodes occur in winter and fade in spring, year after year. Precise studies document prevalence rates between 0.4% and 2.9% [336], the rates usually increasing with increasing latitude. Patients are predominantly women. Whether SAD can be classified as an independent disorder is being debated. In the present diagnostic system, SAD is a sub-form of depression and bipolar disorders [337]. SAD seems to develop under inadequate winter light, but the physiology behind it is uncertain. Major hypotheses include impairments of the CR system, of neurotransmitter functions and genetic factors. The strongest one is the phase shift hypothesis, which associates SAD with an abnormal phase delay between the internal CR and the external day/night clock [336].

Non-seasonal depression and *bipolar disorders* may also be related to disturbances in CR. Sleep disturbances are extremely common among depressed patients. Non-seasonal depressed patients show circadian patterns of symptoms, predominantly with more severe symptoms in the morning. Early morning awakenings, earlier occurrence of rapid eye movement (REM) sleep relative to sleep onset, and melatonin secretion shift in patients with depression may reflect a phase shift in the circadian oscillator. Oscillations in plasma cortisol and norepinephrine are phase-advanced in depressed patients, and, according to some studies, abnormal melatonin secretion sometimes takes place [335]. Sleep disturbances, often related to CRs, are central to the pathophysiology of bipolar disorders and are the earliest indications of major

mood changes [338]. During periods of mania patients often sleepless, while depressive episodes entail insomnia or hypersomnia. Artificially prolonged darkness may reduce manic symptoms. Some bipolar patients may be hypersensitive to the melatonin suppressing effects of light [335].

8.1.2. Sleep disorders. Sleep is regulated by homeostatic and circadian processes [339]. Certain sleep disorders are characterized by desynchronization between CRs and the light/dark cycle and, hence, are called CR sleep disorders. A rare syndrome, mainly found among elderly, *advanced sleep phase syndrome,* is characterized by sleep onset and awakening hours earlier than desired, while in the more prevalent *delayed sleep phase syndrome*, most common among adolescents, sleep onset and wakening occur several hours later than conventional. *Irregular sleep–wake type* and *free-running type* (common among blind people) are other CR sleep disorders [340]. The mechanisms behind CR sleep disorders are unclear. Frequently given explanations are misalignment between endogenous CRs and the environment, abnormal interaction between CRs and homeostatic processes regulating sleep, genetic factors, anatomical and functional abnormalities of the circadian clock, and underlying neurological condition [340].

8.1.3. Jet lag and shift work. Modern society provides artificial light and daytime conditions at all times. In shift and night work, CRs adjust themselves, but continuous phase changes may be serious. Jet lag is due to slow adjustment of the biological clock to new light/darkness rhythms. Both jet lag and shift work problems may be treated with light and/or melatonin administration for a faster adjustment of the biological clock [333].

8.1.4. Memory and learning. Two additional conditions, attention deficit/hyperactivity disorder (ADHD) and memory impairment, have recently been related to CR disturbances. Hamsters with disabled CRs constantly fail to remember their environment. Although they sleep well, they learn poorly [341]. This implies that CRs are involved in memory and learning independently of sleep. The influence of CRs on learning may be caused by changes of cyclic γ-aminobutyric acid (GABA) output from the SCN to brain sites involved in learning. Chronic inhibition of normal SCN functions in arrhythmic hamsters may interfere with plastic mechanisms encoding learning in the hippocampus. SCN functions may influence learning and memory via the medial temporal lobe through daily cycling of GABA tone. The results may have implications for conditions involving learning or memory deficits, such as Down's syndrome, Alzheimer's disease and age-related decline in memory functions. CRs often weaken with age which may contribute to impaired short-term memory [341].

8.1.5. ADHD and memory. A recent study of adults with ADHD indicates involvement of chronobiological disturbances. Difficulties in falling asleep and waking up at normal times of the day are common among patients with ADHD. Such patients also have an increased prevalence of SAD [341].

8.1.6. Light therapy. Light therapy was introduced in 1984 as a treatment for SAD [330]. Bright, artificial light is used to entrain the biological clock. Timing of light exposure, doses and spectrum vary between different versions of the therapy. A standard treatment is exposure to fluorescent tubes emitting about 10 000 lux for 30 min in the early morning. For comparison, the intensity of room light is usually less than 100 lux, while it may be 50 000–100 000 lux or more on a sunny day. Recent studies have demonstrated that blue light ($\lambda \sim 468$ nm) has a greater phase shifting ability at lower intensities than traditional fluorescent sources and than the rest of the visible spectrum [249, 250]. Light therapy does not have any side effects and seems to be an efficient SAD treatment for many patients. Even for non-seasonal depression and some forms of sleep disorders, light therapy may offer modest effects. Delayed sleep syndrome can be treated with bright light in the morning and light restriction in the evening. New potential applications have been proposed, such as subsyndromal mood and certain eating disorders [330].

8.2. Vitamin D

While some researchers stress the effect of CR for SAD, others propose that the seasonal variation of vitamin D levels may be important. Vitamin D deficiency may affect mental health in several ways. Deficiency in adults may lead to transient depression. More permanent impairment of brain functions may result from prenatal deficiency [342]. The vitamin D status varies through the year (except in tropical regions) and the level can sometimes be twice as large in the summer as in the winter. The effects of vitamin D level have been suggested for autism, births of schizophrenic children and depressions. There are many receptors for vitamin D in the central nervous system. Additionally, due to its fat solubility, vitamin D binds non-specifically to nerve cell membranes and myelin sheaths. This leads to changes in calcium permeation and to alterations of conductance of nerve signals. Low prenatal vitamin D levels have been tentatively linked to *schizophrenia*. Several studies show that children born in winter and spring have a significantly higher risk of developing schizophrenia, and the prevalence of the disease increases with latitude. Further, the prevalence of schizophrenia is significantly higher among dark-skinned migrant populations than among native populations. A large Finnish study indicated that supplementation with vitamin D in the first year of life reduced the risk of schizophrenia in males [343]. Another study pointed to an association between long-term trends in perinatal Sun exposure and schizophrenia births rates for males [344]. Possible explanations may be that UV exposure suppresses immune responses and/or that vitamin D induces genes involved in brain development, including the nerve growth factor [345].

In a group of immigrant patients with psychosis in Norway over 80% had deficient serum levels of vitamin D, and lower levels than Norwegian patients [346]. Furthermore, Norwegians with psychosis had lower vitamin D levels than Norwegians in the reference population [346].

8.2.1. Depression. This may be related to a low status of vitamin D, since depressed people often have less vitamin D than healthy individuals. However, depressed people may have spent less time outdoors than healthy people [347]. A low level of vitamin D leads to increased serum parathyroid hormone (PTH) levels. Overactive parathyroid glands frequently accompany symptoms of depression which disappear after treatment. Furthermore, an association between depression and low levels of vitamin D and increased serum PTH levels was found in elderly people [348].

Some studies suggest that impaired, basic *cognitive functions*, including attention, memory and perception, may be linked to low vitamin D levels. The role of vitamin D deficiency has been proposed for dementia and Alzheimer's disease [347, 349]. Positive associations between vitamin D levels and executive functions have been found, indicating the role of the vitamin in subcortical health. The findings are consistent with the vasculoprotective mechanisms of vitamin D [350]. However, so far, the studies are too few and inconsistent to provide any conclusive answers [349, 350].

8.3. Nitric oxide

NO is a gaseous free radical, passing freely through plasma membranes and playing several physiological roles. NO acts as a neurotransmitter in the autonomic and in the central nervous system. Its action is of systemic nature since it can be transmitted over long distances, in contrast to most other neurotransmitters which are transferred from cell to cell. Furthermore, NO acts on the nervous system in an indirect way, since it can cause vasodilatation and increase cerebral blood flow and improve the oxygenation state of the brain [351–353]. NO is produced endogenously through several mechanisms. There are three isoforms of nitric oxide synthase (NOS), all capable of giving rise to NO by enzyme-dependent mechanisms. This takes place in many tissues, including skin and nerve tissue. NO can be released into the circulation. Further, NO can be produced by reduction of sweat nitrate by bacteria, in particular *Staphylococci* [354]. UV exposure of human skin *in vivo* releases NO into the circulation from photolabile NO derivatives, such as N-nitrite [256]. From the bloodstream, NO can, in spite of the short lifetime (seconds), reach the nervous system. In this way, UV can indirectly influence transmission of nerve signals.

NO has many functions in the brain, and can potentially be involved in mental disorders such as endogenous psychoses. Regulatory polymorphism of NOS may contribute to the genetic risk for schizophrenia, and may modulate prefrontal brain functioning [355].

An interesting role of NO is revealed by the fact that polymorphism in NOS1 was found to be associated with impulsivity and hyperactive and aggressive behaviours in humans [355]. Concentrations of NO, and cytokines involved in NO production, may be high in children with autism [356].

In a yet unidentified way, NO may be involved in neural circuits related to learning and memory [357] and possibly also depressive symptoms [358]. NO is a neuroendocrine modulator of the hypothalamic–pituitary–adrenal (HPA) axis, providing a link between immune functions and neuronal control in affective disorders and stress [359].

Surprisingly, physiological concentrations of NO are neuroprotective, whereas high concentrations are neurotoxic. Cellular damage elicited by excess NO and reactive nitrogen species may be involved in the pathogenesis of neurodegenerative disorders. Such excess may contribute to the development of neurodegenerative disorders, for instance Alzheimer's disease [360].

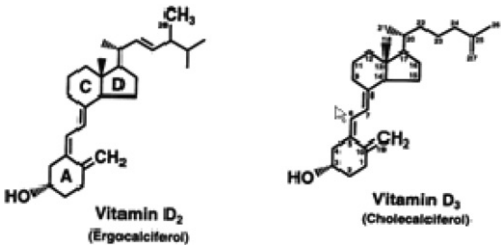
Brain responses to complex cognitive tasks, involving working memory, seem to be modulated by light exposure at certain wavelengths. The melanopsin-dependent photoreception system is more likely than the NO pathway to modulate cognitive functions since the effect ceases when light is switched off [327].

9. Influence of latitude and time on cutaneous production of previtamin D_3, vitamin D_3 and its photoproducts: implications for human health

9.1. Evolutionary perspective of vitamin D

Vitamin D is likely to be the oldest hormone, produced in some of the earliest life forms more than 500 million years ago [361, 362]. During exposure to solar radiation phytoplankton, zooplankton, fungi and most land vertebrates photosynthesize vitamin D. Although we do not know why phytoplankton and zooplankton expend so much energy to produce ergosterol and 7-DHC, it is clear that they have an important role for survival of these organisms, since up to 1% of their total body weight is made up of these provitamin Ds [361]. Ergosterol may have served as a natural sunscreen for phytoplankton, protecting their UV sensitive macromolecules (proteins, RNA and DNA) from damage when being exposed to solar radiation to photosynthesize glucose. Once vitamin D was made in the plasma membrane of these unicellular organisms, it was ejected out of the membrane due to the thermodynamically driven rotation of the A-ring, resulting in a transient opening that may have permitted calcium to enter. As life forms evolved and developed vertebrate skeletons, they took advantage of the plentiful calcium in their ocean environment. However, on land the calcium was locked in the soil, but plants were able to extract it for their needs. Vitamin D became crucial for the evolution of land vertebrates since it was solely responsible for stimulating the intestine to absorb dietary calcium which was essential not only for the development and maintenance of a healthy vertebrate skeleton but played a key role as a second messenger to regulate numerous metabolic functions, as well as neuromuscular activity. The relationship between the Sun, calcium and bone health may have had its beginnings early in evolution when unicellular organisms that made vitamin D were able to regulate membrane calcium transport. Once vitamin D is produced in the skin, it must be activated sequentially in the liver to 25-hydroxyvitamin D (25(OH)D) and then in the kidneys to 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) [363]. 1,25$(OH)_2$D interacts with its vitamin D receptor (VDR) in the small intestine to enhance intestinal calcium absorption. In bones it mobilizes calcium from the

Table 1. Sources of vitamin D_2 and vitamin D_3 in the USA [363].

Source	Vitamin D content IU (international units) = 25 ng
Natural sources	
Cod liver oil	~400–1000 IU/tsp vitamin D_3
Salmon, fresh wild caught	~600–1000 IU/100 g vitamin D_3
Salmon, fresh farmed	~100–250 IU/100 g vitamin D_3, vitamin D_2
Salmon, canned	~300–600 IU/100 g vitamin D_3
Sardines, canned	~300 IU/100 g vitamin D_3
Mackerel, canned	~250 IU/100 g vitamin D_3
Tuna, canned	236 IU/100 g vitamin D_3
Shiitake mushrooms, fresh	~100 IU/100 g vitamin D_2
Shiitake mushrooms, Sun dried	~1600 IU/100 g vitamin D_2
Egg yolk	~20 IU/yolk vitamin D_3 or D_2
Sunlight/UVB radiation	~20 000 IU equivalent to exposure to 1 minimal erythemal dose (MED) in a bathing suit. Thus, exposure of arms and legs to 0.5 MED is equivalent to ingesting ~ 3000 IU vitamin D_3.
Fortified foods	
Fortified milk	100 IU/225 ml usually vitamin D_3
Fortified orange juice	100 IU/225 ml vitamin D_3
Infant formulas	100 IU/225 ml vitamin D_3
Fortified yogurts	100 IU/225 ml usually vitamin D_3
Fortified butter	56 IU/100 g usually vitamin D_3
Fortified margarine	429 IU/100 g usually vitamin D_3
Fortified cheeses	100 IU/100 g usually vitamin D_3
Fortified breakfast cereals	~100 IU/serving usually vitamin D_3
Pharmaceutical sources in the USA	
Vitamin D_2 (Ergocalciferol)	50 000 IU/capsule
Drisdol (vitamin D_2) liquid	8000 IU ml^{-1}
Supplemental sources	
Multivitamin	400, 500, 1000 IU vitamin D_3 or vitamin D_2
Vitamin D_3	400, 800, 1000, 2000, 5000, 10 000 and 50 000 IU

skeleton when there is inadequate dietary calcium to satisfy the calcium needs of the body. Evolution had 500 million years to manipulate vitamin D into playing an important role, not only in calcium metabolism, but also in maintaining cellular health and in regulation of immune functions [363, 364].

9.2. Sources of vitamin D

The vital role of vitamin D is highlighted by the fact that it is provided both by Sun exposure and by food. However, there are very few natural food sources for vitamin D (table 1) [363]. These include oily fish such as salmon, mackerel and herring, liver oils from cod and other white fish and Sun-exposed mushrooms. In the 1920s it was appreciated that the scourge of the bone deforming disease rickets was caused by inadequate Sun exposure [365]. The identification of vitamin D as the antirachitic factor resulted in the fortification of a variety of foods with vitamin D, including milk, cereals and bread. Food fortification with vitamin D made rickets a rare disease. In the 1930s a wide variety of foods and beverages throughout the USA and Europe including soda, beer, custard and even hot dogs were fortified with vitamin D. An outbreak of hypercalcaemia in neonates in England was incorrectly thought to be due to overfortification of milk with vitamin D, and in the 1950s most European nations forbade any fortification of any food or product with vitamin D. The resurrection of rickets, however, led many European countries to fortify margarine and cereals with vitamin D. Finland and Sweden have now once again permitted milk fortification with vitamin D.

Humans, like most vertebrates, have always depended on Sun exposure to satisfy their vitamin D requirement. The body has a huge capacity to produce vitamin D. An adult in a bathing suit exposed to one minimal erythemal dose (MED) of sunlight makes an amount of vitamin D raising the blood level of vitamin D similar to ingesting about 15 000–20 000 international units (IU) of vitamin D. Furthermore, vitamin D produced in the skin lasts 2 to 3 times longer in the circulation compared with vitamin D provided orally [366, 367]. It is likely that our hunter-gatherer ancestors made several thousands of IUs of vitamin D_3 a day, and that the

human body has adapted to this requirement. As people migrated north and south of the equator, their skin pigment devolved in order for them to make enough vitamin D (see section 11 for details). Furthermore, because of low solar elevation in winter even humans with light skin cannot make vitamin D [362, 367]. Therefore, the ability to store vitamin D in body fat during spring, summer and autumn was developed [368, 369].

It has been estimated that for every 100 IU of vitamin D ingested, the blood level of 25(OH)D increases by ∼1.5–2.5 nmol l^{-1} [369, 370]. Most foods in the USA and Europe that are fortified with vitamin D usually contain no more than 100 IU per serving. This is only about 5–10% of what our hunter-gatherer forefathers were producing on a daily basis and what our bodies require. Children need 600–1000 IU/day and teenagers and adults require 2000 IU/day [371, 372]. Without adequate Sun exposure the amount of vitamin D obtained from dietary sources is inadequate to satisfy the requirement and, therefore, is likely to be responsible for the vitamin D deficiency pandemic that is a global problem [363].

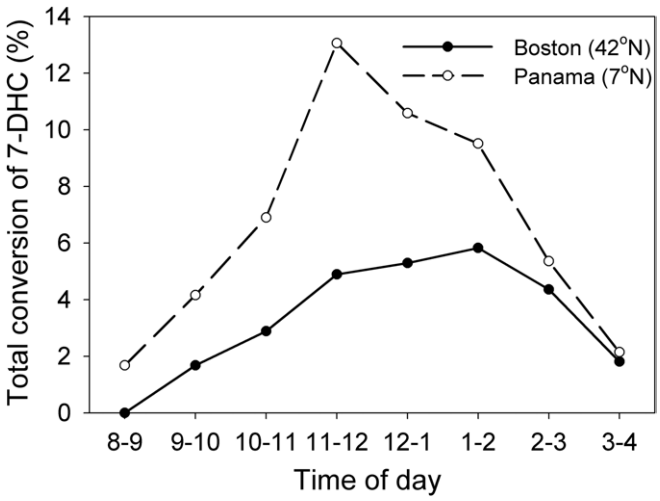


Figure 18. Ampoules containing 7-DHC in ethanol exposed on a sunny day from 9 am until 4 pm in April in Panama City, Panama (Eastern Standard Time), and in Boston, Massachusetts (Eastern Daylight Savings Time).

9.3. Photoproduction of suprasterols and toxisterols in human skin cells

There has been a debate about whether humans need to be exposed to sunlight, since vitamin D can be obtained from diet and supplementary sources [373]. Holick *et al* [374] demonstrated that several photoproducts of previtamin D_3 and vitamin D_3 are produced in human skin when exposed to simulated solar radiation. Two of the photoproducts 5,6-transvitamin D_3 and tachysterol have anti-proliferative activity in cultured human keratinocytes similar to 1,25$(OH)_2$D [375].

UV exposure of previtamin D_3 yields not only lumisterol and tachysterol, but also several additional compounds that are called toxisterols [376]. The story of toxisterols began in the late 1920s with the search for an antirachitic substance. A number of investigators reported that irradiation of ergosterol (provitamin D_2) resulted in a mixture of irradiation products that had an absorption around 250 nm. Originally, it was assumed that this material was vitamin D [376]. However, in 1928, Bills *et al* [377] reported that the material with a wavelength of 250 nm that was isolated from the irradiated mixture had little antirachitic activity. Subsequently, Windaus *et al* [378] as well as Laquer *et al* [379] obtained preparations of irradiation products of ergosterol that absorbed near 250 nm. This material was devoid of any activity. However, it caused toxicity in animals, similar to what was associated with vitamin D intoxication [379]. Based on these early observations, Laquer *et al* [379] introduced the name toxisterin that was later changed to toxisterol to denote the toxic components in their preparations. It was later demonstrated that the toxisterols can only be generated from previtamin D_3 and tachysterol due to the relaxation via rotation about the 6–7 bond.

Havinga [380] recognized that vitamin D_3 exists in a one to one ratio of α and β chair forms. This was important because it provided an explanation for the generation of a new class of photoproducts known as suprasterols. A careful analysis of mixtures resulting from the irradiation of solutions of vitamin D_3 in ethanol revealed the presence of 5,6-*trans*-vitamin D_3 as well as six photoproducts. This is due to the relaxation via rotation about the 5–6 bond. Two of the vitamin D irradiation products were identified as bicyclohexines that were structurally identified by Dauben *et al* [381] and named suprasterol I (S1) and suprasterol II (S2).

A major impediment has been the separation of various toxisterols and suprasterols from their parents and other photoproducts. Indeed, when these compounds were first made, it took 2–3 weeks to obtain crystalline material from the irradiation mixtures [380]. There was a need to develop a new method of separation for the toxisterols and suprasterols that was efficient and could identify the various photoproducts by their UV absorption spectra and other physical chemical properties. High-performance liquid chromatography (HPLC) equipped with a photodiode array detector was instrumental in helping us to separate the various toxisterols and suprasterols and to identify them based on their UV absorption spectra and other physical chemical characteristics.

9.4. Influence of latitude and time on cutaneous production of previtamin D_3, vitamin D_3 and its photoproducts

To determine the effect of time of day and latitude on the photolysis of 7-DHC borosilicate ampoules containing 7-DHC dissolved in ethanol were exposed for 1 h at hourly intervals in April in Boston (42°N) and Panama (7°N) (figure 18). The samples were analysed by HPLC as previously described [362]. The photolysis of 7-DHC begins between 8 and 9 am in Panama even though the Sun rose at 6 am and was reasonably intense by 7 am (figure 18). In Boston which was 34° further north, the photolysis of 7-DHC to previtamin D_3 began between 9 am and 10 am. The efficiency of the Sun to photolyze 7-DHC to previtamin D_3 rapidly increased and reached its maximum of 13.5% by noon time compared with 5.8% in the early afternoon in Boston. Interestingly essentially no 7-DHC photolysis to previtamin D_3 was evident after 3 pm

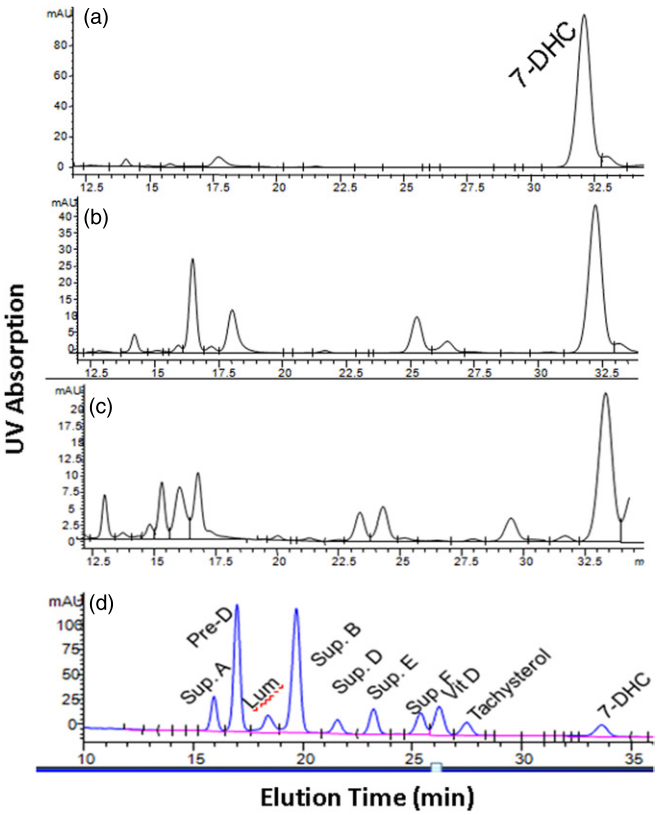


Figure 19. Cultured human keratinocytes incubated with AY9944 (7-DHC reductase inhibitor) (*a*) kept in the dark, exposed to simulated sunlight for (*b*) 3 min or (*c*) 15 min; (*d*) a chromatogram of standards. The cells were collected and a lipid extract was obtained and chromatographed on an HPLC.

whether exposed to sunlight near the equator in Panama or in Boston.

To evaluate whether skin could produce any of the suprasterols and toxisterols after exposure to sunlight we exposed primary cultures of human keratinocytes to simulated sunlight for various periods of time (figure 19). The cells were collected and a lipid extraction was performed as previously described [374, 375]. The lipid extracts were chromatographed on HPLC equipped with a photodiode detector using isocratic elution of 0.2% of n-butanol in n-hexane which eluted the toxisterols and suprasterols.

A comparison of chromatograms from a lipid extract of cultured human keratinocytes at time zero compared with a chromatogram obtained from a lipid extract of cultured human keratinocytes exposed to 3 min of simulated sunlight (equivalent to approximately 12 mJ cm^{-2}; ~0.35 MED for skin type 2) revealed the appearance of several photoproducts that were detected at 265 nm (figures 19(*a*) and (*b*)). Previtamin D_3, tachysterol, lumisterol and 7-DHC were identified, based on their UV absorption spectral characteristics. After 15 min of irradiation the 7-DHC decreased by about 50% and almost all of the previtamin D_3, tachysterol, lumisterol and vitamin D_3 disappeared and at least eight photoproducts were evident (figure 19(*c*)). Based on their chromatographic mobility and UV absorption spectra some of the photoproducts are tentatively identified as suprasterols A, D, E and F. In addition, other unidentified photoproducts appear to be in the family of toxisterols.

These studies have important health implications. It has been suggested that early morning and late afternoon sunlight is the best time to be outdoors because there is less perceived photodamage to the skin [373], and that humans can make vitamin D_3 as long as the Sun is shining [373]. The data in figure 18 clearly demonstrate that the zenith angle of the Sun being more oblique in the early morning and late afternoon is similar to that in the winter time in temperate climates [362], and, thus even at the equator early morning and late afternoon Sun exposure will have little benefit in producing vitamin D_3 in the skin [29]. Indeed at these times of the day UVA radiation is the dominant form of UV radiation that a person would be exposed to which deeply penetrates into the skin that can suppress the immune system, increase damage to the dermal structure of the skin increasing risk for wrinkling and potentially increasing risk for the most deadly form of skin cancer melanoma.

Many dermatological societies, including the American Academy of Dermatology, have suggested that humans should never be exposed to direct sunlight without photoprotection, because of increased risk of skin cancer [373]. The recommendation has been to obtain vitamin D from dietary and supplemental sources and that there was no need to be exposed to sunlight. Although it is true that a person can increase their blood level of 25(OH)D by taking a vitamin D supplement, it is unknown whether this practice can completely mimic the Sun-induced photosynthesis of vitamin D_3 in the skin. As can be seen in figure 19 it appears that exposure to sunlight produces more than 10 photoproducts in skin cells, suggesting that there may be additional benefits of solar exposure, especially if it can be demonstrated that one or more of these photoproducts has unique local and or systemic biologic properties. Studies are underway to characterize these photoproducts structurally and to determine their biologic activities in cultured human skin cells, especially with regard to regulation of skin cell growth. It is possible that the fact why moderate Sun exposure does not increase the risk for non-melanoma and melanoma skin cancers while reducing risk of many other deadly cancers [382–386] is, in part, due not only to the production of vitamin D_3 in the skin but also to one or more of the photoproducts that have been observed in skin cells exposed to simulated sunlight (figure 19). This may also help explain why occupational Sun exposure not only decreases risk of melanoma but also prostate cancer [384, 387].

10. Positive health effects of solar radiation

Solar UVB is the most important human source of vitamin D, and vitamin D deficiency is associated with a number of diseases and conditions. Several recent reviews describe the health benefits of vitamin D [238, 239, 363]. The evidence of vitamin D's effects on disease outcome is based largely on ecological, observational (cohort and case–control), and cross-sectional studies, with limited support from randomized controlled trials (RCTs) and meta-analyses of such studies. The evidence from ecological studies is based on geographic

and seasonal variations in disease outcome. Observational and cross-sectional studies generally use oral intake or serum 25-hydroxyvitamin D (25(OH)D) levels as the vitamin D index, but sometimes include solar UVB. Few good vitamin D RCTs exist to date for two primary reasons: firstly, many of the early RCTs used only 400 IU/day of vitamin D, which is generally too low to have any beneficial effect [388]; secondly, many diseases have been linked to low vitamin D levels only in the past decade, so RCTs, which require several years to plan, execute and analyse, have not been performed yet. The lack of RCTs does not preclude the claim of a causal link between low vitamin D and disease outcome because the criteria for causality in a biological system, as laid down by Hill [389], do not necessarily require experimental verification.

We will draw attention to the positive health effects of an adequate vitamin D status by providing a survey of how a low vitamin D level increases the risk of many types of infectious and chronic diseases, as well as of the vitamin D dose–disease outcome response relations.

10.1. Mechanisms whereby vitamin D reduces risk of disease

Vitamin D reduces the risk of disease primarily through activation of vitamin D receptors (VDRs) by $1,25(OH)_2D$. Activated VDRs modulate gene expression via hetero-dimerization with the retinoid X receptor and recruitment of coactivators or corepressors [390]. $1,25(OH)_2D$ regulates through the VDRs, directly or indirectly, more than 200 different genes responsible for a wide variety of biologic processes [239]. Circulating $1,25(OH)_2D$ is produced largely in the kidneys, but many, if not most, organs have 1α-hydroxylase enabling them to produce $1,25(OH)_2D$ from 25(OH)D for use by that organ [391]. Several studies have discussed the role of VDRs in affecting risk of various diseases: autoimmune diseases [392], including MS [393]; cancer [394, 395]; CVD [396]; and immune function [364]. Several reports review the mechanisms whereby vitamin D reduces the risk of various diseases [238, 397]. We will review important epidemiological studies linking low vitamin D intake, low solar UVB exposure or low serum 25(OH)D levels to increased risk of disease.

Vitamin D plays an important role in calcium absorption and metabolism [237], and calcium plays a synergistic role with vitamin D. Calcium intake raises serum 25(OH)D levels. In a study of premature infants given supplements of vitamin D and calcium at 12 weeks of age, but not before, serum 25(OH)D concentrations were directly correlated with serum levels of calcium ($r = 0.47$, $P < 0.01$) and serum phosphorus ($r = 0.47$, $P < 0.01$), and inversely correlated with alkaline phosphatase values ($r = -0.71$, $P < 0.01$). Mineral availability and 25(OH)D sufficiency both appear to be important and to act synergistically, with neither totally compensating for the other [398]. A combination of calcium and vitamin D supplementation significantly reduced the risk of all-cancer incidence among postmenopausal women [399] and risk of diabetes [400].

10.2. Evidence of beneficial effects of vitamin D on disease risk

10.2.1. Skeletal diseases. Rickets was the first disease linked to low solar UVB and vitamin D, a linkage thoroughly studied and reviewed [401]. In spite of the knowledge, rickets still occurs, especially for breast-fed, dark-skinned infants with vitamin D-deficient mothers [402].

Vitamin D also reduces the risk of falls and fractures [237]. The effects on both the bones and the neuromuscular system are involved. According to a meta-analysis of RCTs vitamin D supplementation in the range 700–1000 IU/day reduces the risk of falls by about 20% [403].

Non-specific musculoskeletal pain is also associated with severe hypovitaminosis D [404]. In a study in Saudi Arabia, young women with osteomalacic myopathy, often with musculoskeletal pain, showed remarkable improvement after supplementation with vitamin D_3 and calcium [405].

10.2.2. Cancer. Vitamin D's role in reducing the risk of cancer is one of the most important health benefits of adequate serum 25(OH)D levels. An ecological study of colon cancer mortality rates in the USA gave the first indication that vitamin D might reduce the risk of cancer. The brothers Cedric Garland and Frank Garland noted that the geographical variation of colon cancer mortality rates in the USA was inversely correlated with annual solar radiation [406], and hypothesized that because vitamin D production is the most important physiological effect of Sun exposure, vitamin D probably reduced the risk of colon cancer. They later showed an inverse correlation between colorectal cancer and dietary vitamin D [407], and between colon cancer and serum 25(OH)D levels [408]. They also extended the UVB link to breast [409] and ovarian [410] cancer.

In 2002, the role of UVB and vitamin D in reducing the risk of up to 15 types of cancer was announced, again using the ecological approach but using July solar UVB doses in the USA [411]. Summertime solar UVB doses in the USA are highly asymmetrical, with highest doses in the southwest, and the lowest in the northeast [412] related to surface altitude and stratospheric ozone layers. This study was extended by including several cancer risk-modifying factors in the analysis [413, 414]. Those wanting a more direct measure of solar UVB, irradiances for ecological studies can be estimated from incidence or mortality rates of non-melanoma skin cancer at latitudes below about 35°–40° [415, 416].

Several reports have been looking at global variations of cancer with respect to a UVB index along with indices for smoking or dietary factors, generally finding that rates are the lowest in the tropics, and the highest at high latitudes, giving rise to characteristic curves [417, 418]. Several recent papers review the history of ecological studies of UVB, vitamin D and cancer risk [417–419].

Many observational studies of cancer with respect to vitamin D indices exist [420]. Meta-analyses of serum 25(OH)D levels have been used to develop dose–response relations for breast [421] and colorectal [421, 422] cancer incidence rates, finding 50% reductions for serum levels of

100 nmol l^{-1} compared with 30 nmol l^{-1} for breast cancer and 70 nmol l^{-1} compared with 20 nmol l^{-1} for colorectal cancer [421].

There is only one good RCT for cancer incidence with respect to vitamin D supplementation, which involved postmenopausal women living in Nebraska. Those taking 1100 IU/day of vitamin D and 1450 mg/day of calcium had a 77% reduction in all-cancer incidence between the ends of the first and fourth years compared with those taking a placebo; those taking only calcium had a 40% reduction [399]. The National Institutes of Health has awarded these investigators an additional grant to extend this important study, this time using 2000 IU/day of vitamin D in addition to calcium.

It has been questioned whether the evidence that vitamin D reduces the risk of cancer might be causal. The Hill criteria are useful to elucidate this question [389]. The important criteria for cancer are the following:

(1) strength of association;
(2) consistency (repeated observation in different populations);
(3) temporality (exposure precedes effect);
(4) biological gradient (dose–response relation, preferably linear);
(5) plausibility (e.g. mechanisms);
(6) coherence (no serious conflict with the generally accepted science of the day);
(7) experimental verification (RCT);
(8) analogy with other causal relationships.

Not all of these need be satisfied for causality to be claimed. Through this type of evaluation it seems likely that several common cancers are vitamin D sensitive, including breast, colorectal and non-Hodgkin's lymphoma [423]. Many other cancers have geographical variations in mortality rates in the USA and are likely to be vitamin D sensitive: bladder, endometrial, oesophageal, gallbladder, gastric, ovarian, renal, vulvar cancer and Hodgkin's lymphoma. Two cancers are more problematic but probably satisfy the criteria as well: pancreatic and prostate cancer. A study in Finland among smokers found a direct correlation between serum 25(OH)D and pancreatic cancer [424], while cohort studies in the USA found an inverse correlation [425]. The difference may be that vitamin D has a different effect on pancreatic cancer for smokers and non-smokers. Furthermore, prediagnostic serum 25(OH)D levels are seldom inversely correlated with prostate cancer incidence rates [426]. The geographical variation in the USA differs from that for other vitamin D-sensitive cancers in that the highest mortality rates are in the northwest, not the northeast. This difference has been explained as linked to viral infections [427] and to genetic risk owing to ethnic background [428]. Support for involvement of viral infections is given by an analysis indicating that prostate cancer incidence is more common in winter, when viral infections are more common [429], and that DNA from xenotropic murine leukaemia virus-related virus (XMRV) was recently documented in 6% and XMRV protein in 23% of prostate tumours investigated [430]. The ethnic link may be due to the apolipoprotein E (ApoE) $\varepsilon 4$ allele, which increases cholesterol production, an important risk factor for prostate cancer, and diet [428].

Surprisingly, the evidence that vitamin D sometimes seem to reduce the risk of even melanoma, a cancer thought to be mainly caused by high UV exposures, is increasing. The primary risk factor for melanoma from non-burning UV irradiance appears to be UVA which does not produce vitamin D. Evidence includes the latitudinal dependence for those of Northern European ancestry living in different countries [431], that using sunscreens that do not block UVA well is a risk factor for melanoma [432], and that some VDRs are correlated with melanoma risk [433]. Furthermore, north–south gradients of melanoma incidence point to UVA (see the skin cancer section).

Despite the mounting evidence that vitamin D reduces the risk of many types of cancer, the International Agency for Research on Cancer found the evidence inconclusive for all but colorectal cancer in a study released in 2008 [434]. The committee was heavily weighted with dermatologists. A critique of the report pointed out that, to reach its conclusion, the committee made many errors such as making the least favourable interpretation of findings in particular studies, as well as omissions such as ignoring at least one well-cited report that used an ecological approach and that countered with the contention that ecological studies do not include confounding factors in the analysis [435].

Ecological studies are very useful for studying risk-modifying factors for cancer since ecological studies integrate the effects of risk-modifying factors such as UVB, vitamin D, diet and smoking, over an entire lifetime, and much of the risk for cancer occurs in the first 20 years of life and throughout life, with often a 20–40 year lag between cancer initiation and detection or death.

10.2.3. Cardiovascular disease. The evidence for the beneficial role of vitamin D in the reduced risk of CVD comes primarily from observational studies. The UVB–vitamin D–CVD hypothesis seems to have been proposed first by Robert Scragg in 1981, on the basis of the geographical and seasonal variation in CVD mortality rates [436]. He later extended the hypothesis on the basis of serum 25(OH)D levels and incidence of myocardial infarction in a community [437].

More recently, the results of CVD incidence and mortality rates in cohort studies have been reported. Wang *et al* [438] found a significant inverse correlation between serum 25(OH)D and cardiovascular event. Additional reports were made for acute myocardial infarction event [439] and CVD mortality. Four recent studies include the following.

- A prospective cohort study of 3258 consecutive male and female patients (mean [SD] age, 62 [10] years) scheduled for coronary angiography at a single tertiary centre in southwest Germany [440].
- A study in the same location but including 3316 study participants [441].
- A secondary analysis of this nationally representative, prospective observational cohort of the non-institutionalized US civilian population taken from those

of the Third National Health and Nutrition Examination Survey (NHANES III), limited to older adults (aged ⩾65 years) [442].

- A study based on the Mini-Finland Health Survey and included 6219 men and women aged ⩾30 years who were free from CVD at baseline (1978–1980). During follow-up through 2006, 640 coronary disease deaths and 293 cerebrovascular disease deaths were identified [443].

When the results of these studies [439, 440, 442, 443] were plotted in terms of hazard ratio with respect to serum 25(OH)D by quantile from each study in a preliminary pooled analysis, a very significant inverse correlation was found. The hazard ratios for serum 25(OH)D levels compared with 107 nmol l^{-1} are 1.2 for 80 nmol l^{-1}, 1.4 for 56 nmol l^{-1}, 1.6 for 43 nmol l^{-1} and 2.0 for 26 nmol l^{-1}.

Possible mechanisms for this include the following. Coronary artery calcification is an important risk factor for CVD [444], and risk of developing coronary artery calcification is inversely correlated with serum 25(OH)D levels [445], but other vitamin D-mediated mechanisms could also be involved [396].

It is remarkable that the beneficial role of vitamin D in reducing the risk of CVD seems to be similar to that for cancer, yet inspection of geographical variations in coronary heart disease or stroke mortality rates in the USA and other countries do not show an inverse correlation with solar UVB doses. Diet certainly plays an important role in the risk of CVD, as does smoking, yet both also play important roles in cancer [414, 446]. Evidence exists that the seasonality of CVD is linked to solar UVB [447]. However, the effect of colder temperatures in winter cannot be completely ruled out as an explanation for the observed seasonality [448, 449], although probably not as important as vitamin D, on the basis of findings regarding seasonality of CVD deaths in warm countries such as Australia [450].

10.2.4. Congestive heart failure. Congestive heart failure seems to be linked to low serum 25(OH)D and notably to low $1,25(OH)_2D$ levels [451]. In a cohort study in Austria with a median follow-up time of 7.7 years, 116 patients died from congestive heart failure. After adjustment for cardiovascular risk factors, the hazard ratio for death due to congestive heart failure was 2.84 (95% confidence interval [CI], 1.20–6.74) when comparing patients with severe vitamin D deficiency [25(OH)D <25 nmol l^{-1})] with people in the optimal range [25(OH)D ⩾75 nmol l^{-1}] [452]. A study in Australia found a 23% increased risk of death from heart failure in winter. Because winter in Australia is mild, this finding strongly implicates lower serum 25(OH)D levels rather than low winter temperatures [450].

10.2.5. Type 2 diabetes mellitus. Low vitamin D intake or production combined with low calcium intake is an important risk for developing type 2 diabetes mellitus. A Harvard University cohort study found a 33% reduction for those taking >800 IU/day of vitamin D and >1200 mg/day of calcium compared with <400 IU/day and <500 mg/day [400]. A cohort study in The Netherlands found an odds ratio of 0.28 (95% CI, 0.10–0.81) for >75 nmol l^{-1} versus <25 nmol l^{-1} (males) but no effect for females [453]. A cohort study in Japan found an odds ratio of 0.62 (95% CI, 0.41–0.94) for males and 0.59 (95% CI, 0.38–0.91) for females for highest versus lowest calcium intake with higher vitamin D intake [454].

10.2.6. Infectious diseases. In the early part of the 20th century, patients with tuberculosis were often sent to sanitoria where solar UVB irradiance (heliotherapy) was an important part of the treatment [455]. It was not until 2006 that the mechanism was discovered. It was reported that Toll-like receptor activation of human macrophages upregulated expression of the VDR and the vitamin D-1-hydroxylase genes, leading to induction of the antimicrobial peptide cathelicidin and killing of intracellular *Mycobacterium tuberculosis* [456]. Human cathelicidin, LL-37, has both antimicrobial and antiendotoxin properties [457].

Cannell *et al* hypothesized that epidemic influenza was largely seasonal because of annual variations in solar UVB doses [458]. That hypothesis was quickly supported by findings in an RCT involving vitamin D supplementation for black postmenopausal women in Long Island. Those taking 800 IU/day had 40% as many colds or influenza cases as those taking the placebo, whereas those taking 2000 IU/day had 10% the rate [459]. It also has support from an RCT involving school children in Japan. Those taking 1200 IU/day had a relative risk for type A influenza of 0.36 (95% confidence interval, 0.17, 0.79) compared with those taking 200 IU/day [460].

An ecological study of the 1918–1919 A/H1N1 pandemic influenza extended the role of vitamin D in reducing the risk of death after development of influenza. In the USA, case fatality rates were much lower in southern communities than in northern communities, on the basis of comprehensive surveys in 12 cities and counties [461]. An ecological study of the case fatality rates with respect to summertime and wintertime solar UVB indices found that 45% of the variance was explained by UVB variations [462]. Most deaths occurred about ten days after infection and were due to bacterial pneumonia. Many suffered from the cytokine storm that accompanied the influenza infection. Thus, the mechanism leading to death seems to be disturbance of the epithelial lining of the lungs by the cytokine storm followed by opportunistic infection by bacteria normally present in the lungs. The compound $1,25(OH)_2D$ is effective in reducing the cytokine storm by shifting cytokine production from T helper 1 (Th1) cells to Th2 cells.

Current swine flu has all the hallmarks of a vitamin D-sensitive disease, including seasonality, with highest rates in winter, and that vitamin D-deficient groups such as pregnant women [463] and Australian Aborigines [464] appear to be the hardest hit.

Another vitamin D-sensitive disease is sepsis [457]. A review showed that the epidemiology of sepsis in the USA is strongly linked to indices of vitamin D production from solar UVB irradiance: highest rates in winter, lowest rates in summer, black people are more susceptible than white people, and many of the comorbid diseases are vitamin D sensitive [465]. Jeng *et al* [466] quickly reported an observational study

in support of this hypothesis with the finding that patients in an intensive care unit with sepsis had very low serum 25(OH)D levels.

An assumption that vitamin D (2000 IU per kg of body weight per day for 3 days) may produce enough of the naturally occurring antibiotic cathelicidin to cure common viral respiratory infections, such as influenza and the common cold, awaits further scientific validation [467].

Vitamin D also reduces the risk of Epstein–Barr virus infection. One line of evidence is that Epstein–Barr virus-related diseases, such as infectious mononucleosis and Hodgkin's lymphoma, have peak incidence rates in the low vitamin D season (March) [468]. Another is that MS, thought to be caused largely by Epstein–Barr virus [469], has a geographical variation in the USA based on servicemen at the time of enlistment into World War II and the Korean War [470] highly correlated with latitude, an index of solar UVB doses in winter [427].

Both dental caries and periodontal disease have been linked to low vitamin D status. An ecologic study in the USA in the 1930s found that the number of dental caries among adolescent white males living in the west, where there is >3000 h of sunlight/year, was half that of those living in the northeast, where there is <2200 h of sunlight/year [471]. Bacteria are involved in the development of dental caries, and are sensitive to cathelicidin produced by vitamin D. Chronic adult periodontitis is a bacterially induced chronic inflammatory disease that destroys the connective tissue and bone that support teeth and for which the mechanisms involved are still being worked out [472]. Low serum 25(OH)D levels were associated with periodontal disease [473] and gingival inflammation [474].

Many reports suggest that periodontal disease is correlated with CVD [475]. However, it is a possibility that both diseases are linked to low serum 25(OH)D levels, so that combating periodontal disease may not reduce the risk of CVD.

10.2.7. Autoimmune diseases. There is a strong latitudinal dependence incidence of MS in Australia [476], Europe [477] and the USA [470]. The data in the USA for servicemen at the time of entry into World War II and the Korean War [470] have been related to latitude, an index of wintertime solar UVB but not summertime UVB [412, 427]. A study involving veterans showed a strong inverse correlation between stored serum 25(OH)D and subsequent development of MS [478]. Incidence rates seem to be linked to Epstein–Barr virus infection [479]. Also, higher serum 25(OH)D levels reduce the symptoms associated with MS through regulation of T cells and the cytokines they produce [480].

Type 1 diabetes mellitus is another autoimmune disease linked to low serum 25(OH)D, especially in infancy. A study in Finland found that children who regularly took the recommended dose of vitamin D (2000 IU daily) had an RR of 0.22 (95% CI, 0.05–0.89) compared with those who regularly received less than the recommended amount [481].

Asthma may also be linked to infections early in life, and adequate vitamin D intake may reduce the risk. The increased risk of specific respiratory infections in susceptible hosts may contribute to some cases of incident asthma [482].

10.2.8. Dementia. All brain cells have VDRs, implying that vitamin D is involved in brain functions. It activates receptors on neurons in regions implicated in the regulation of behaviour, stimulates neurotrophin release, and protects the brain by buffering antioxidant and anti-inflammatory defences against vascular injury and improving metabolic and cardiovascular function [349]. Cognitive impairment is often the first sign of approaching dementia. In a cross-sectional study in the UK, the odds ratios for cognitive impairment in the first (8–30 nmol l^{-1}), second (31–44 nmol l^{-1}) and third (45–65 nmol l^{-1}) quartiles of serum 25-hydroxyvitamin D, compared with the fourth (66–170 nmol l^{-1}), were 2.3 (95% CI, 1.4–3.8), 1.4 (95% CI, 0.8–2.4) and 1.1 (95% CI, 0.6–1.9), respectively, after multifactorial adjustment ($P_{\text{linear trend}} = 0.001$) [483]. In a cross-sectional study that included 3369 men aged 40–79 years from eight centres enrolled in the European Male Ageing Study, 25(OH)D levels were associated only with score on the Digit Symbol Substitution Test (β per 10 nmol l^{-1} = 0.15; 95%, CI 0.05–0.25) [484].

10.2.9. Pregnancy outcomes. Pregnant and nursing women require 4000–6000 IU/day [485]. It was found that risk of preeclampsia was significantly increased for those with lower serum 25(OH)D levels [486]. Also, risk of bacterial vaginosis [487], which can increase the risk of preterm delivery [488], was increased. Low serum 25(OH)D levels lead to higher rates of primary caesarean section delivery [489]. In the USA, 9% of births are associated with primary caesarean section, of which 40% could be reduced by serum 25(OH)D levels >87.5 nmol l^{-1} [489].

Low vitamin D levels can influence the pregnancy outcome. Vitamin D deficiency may be a plausible neurobiological explanation for births of children getting schizophrenia: (1) the excess winter/spring birth rate, (2) the increased incidence of the disease in second-generation Afro-Caribbean migrants and (3) the increased urban birth rate [490] can be explained. In rats the brains of offspring from developmental vitamin D-deficient dams are characterized by (1) a mild distortion in brain shape, (2) increased lateral ventricle volumes, (3) reduced differentiation and (4) diminished expression of neurotrophic factors [490].

Low serum 25(OH)D during pregnancy also increases the risk of infectious diseases. Developing influenza during pregnancy, which may be due to low vitamin D levels, increases risk of the foetus developing with physical [491] or brain birth defects, such as schizophrenia [492]. Good evidence also indicates that the risk of autism is linked to low maternal vitamin D [493].

Hollis reported that in an RCT with vitamin D supplementation of 400, 2400 and 6400 IU/day for pregnant and nursing women, there were no adverse effects such as hypercalcaemia and hypercalciuria, and that the two lower doses could not raise the nursing infants' serum 25(OH)D level above 50 nmol l^{-1} [494].

10.2.10. Mortality rates. Because low serum 25(OH)D levels are associated with many chronic and infectious diseases, cancer and CVD, one would expect that mortality

Table 2. Estimates of reductions[a] in mortality rates by raising mean population serum 25(OH)D levels to 105 nmol l^{-1}.

Factor	Western Europe [498]	Canada [499]	The Netherlands [500]	Nordic countries [501]
Mean 25(OH)D level (nmol l^{-1})	55	67	50	70
Cancer reduction*	10.0	16.8	38.8	28.9
CVD reduction*	25.7	16.4	42.8	44.0
Diabetes reduction*	1.9	1.2	1.9	1.4
MS reduction*	0.5	0.2	0.5	0.3
Falls reduction*		0.3	0.5	0.5
Lower respiratory infection reduction*	5.0	1.7	7.4	2.3
Sepsis reduction*		0.4		
Dementia reduction*				1.7
Vitamin D reduction (death rate and 95% CI)	47.2 (18.1–76.2)	37.0 (22.3–52.2)	91.9 (54.0–119.3)	79.1 (46.0–112.6)
All-cause mortality rate	388.2	230.1	503.6	429.2
Vitamin D reduction (% of all-cause) mortality rate)	12% (5%–20%)	16% (10%–23%)	18% (11%–24%)	18% (11%–26%)

[a] Reductions are in terms of deaths/100 000 $year^{-1}$.

* Deaths/100 000 $year^{-1}$.

rates would be inversely correlated with serum 25(OH)D levels. That is indeed the case. Several recent cohort studies have found death rates as a function of serum 25(OH)D levels [442, 495–497]. A preliminary pooled analysis of the last three studies found that, compared with a mean value of 108 nmol l^{-1}, the hazard ratio increased to 1.2 at 70 nmol l^{-1}, 1.4 at 47 nmol l^{-1}, and 1.8 at 25 nmol l^{-1}.

10.2.11. Estimates of benefit from raising serum 25(OH)D levels. Because higher serum 25(OH)D levels are associated with reduced risk of many types of disease, and because mean population serum 25(OH)D levels generally lie between 45 and 75 nmol l^{-1}, it seems reasonable that if mean population levels were raised, say, to 105 nmol l^{-1}, disease rates would drop accordingly. This hypothesis has been applied on the populations of Western Europe, Canada, The Netherlands and the five Nordic countries. The approach taken was to use vitamin D dose–disease outcome relations for major vitamin D-sensitive diseases along with mean population serum 25(OH)D levels to estimate the reduction in mortality rates for each disease, and then to sum them to determine the premature mortality rate due to low serum 25(OH)D levels. Table 2 gives some of the results. From actuarial tables for those aged 65–67 years in the USA, 18–19% corresponds to a two-year increase in life expectancy.

This overview of the epidemiological and other evidence in support of beneficial effects of vitamin D in reducing specific and total disease rates represents a snapshot of an active field of research. The links to some diseases are so new that the evidence should be considered preliminary and tentative. However, with the well-documented benefits for so many diseases, these tenuous links will deserve attention.

11. Solar radiation and development of human skin colours

There are signs that human ancestors lived in Africa 6–7 million years ago. Most likely, they had white skin colour which gradually turned dark. Humans have migrated out of Africa numerous times, mainly northwards, and each time their skin colour changed as an adaptation to lower fluence rates of solar UV radiation [235]. Today, populations with recent ancestors from lower latitudes have darker skin than populations which have stayed for a long time at high latitudes. Diet, climate and/or sexual selection are secondary determinants of human skin pigmentation. Numerous hypotheses exist for skin darkening and whitening, some of which will be briefly discussed.

11.1. Hypothesis for skin darkening

11.1.1. Protection of sweat glands and blood vessels. Melanin, which is responsible for skin colour, has many biological functions, including photoprotection, thermoregulation, antioxidant and radical scavenging properties. The photoprotective properties of melanin are directly related to the absorption and scattering of incoming radiation. Melanin is produced by melanocytes in the basal layer of the epidermis, from where it moves upwards, as the basal cells divide and migrate to the stratum corneum, and thus protects all layers of the skin, as well as the blood vessels under it, against UV damage [502]. Compared with white skin (Fitzpatrick skin type I), moderately pigmented skin (Fitzpatrick skin type III) remains without erythema up to 3–5 times larger exposures, and black skin (Fitzpatrick skin type VI) up to 30 times larger exposures [190]. Surprisingly, dark and white skin have the same number of melanocytes, although they differ in size, and structure of melanosomes (organelles containing melanin). Dark skin produces more melanin than white skin. The strong African Sun can damage sweat glands and blood vessels in naked, white skin. Thus, thermoregulation will be impaired, and development of a dark, protective skin colour will occur [503]. This hypothesis, based on heat protection is not supported by physical arguments since a black body absorbs more energy, and, consequently, becomes warmer than a white body.

11.1.2. Skin cancer prevention. The most widely accepted hypothesis is that melanin absorbs harmful UV radiation which is a major risk factor for all types of skin cancer [504], which are the most common cancers among Caucasians but rare in populations with darker skin (Africans, Asians, Latin-Americans and American-Indians) [505]. This is an unlikely hypothesis since skin cancer usually develops late in human life, after the reproductive age, which was low for early humans.

11.1.3. Protection against vitamin D overproduction. Already in the 1960s it was known that solar radiation was an extremely efficient vitamin D producer, and that high doses of vitamin D supplementation might have toxic effects [506]. In 1967 Loomis proposed that a dark skin had developed to prevent against vitamin D intoxication [506]. This hypothesis is incorrect because once previtamin D_3 is formed from 7-DHC in the skin, UV radiation degrades it as well as vitamin D_3 (which is formed in a thermal process from previtamin D) into inert photoproducts. For this reason vitamin D intoxication from Sun exposure is not possible and has never been observed [233].

11.1.4. Camouflage. Melanin provides camouflage, which plays a vital role for the survival of some animals. Human skin, exposed to UV becomes immediately darker through reversible, photochemical processes and spatial rearrangements of melanin structures. This is called IPD. IPD appears during the first minutes of Sun exposure, reaches a maximum within 1–2 h and then fades and is dependent on pre-existing melanin and its precursors in the epidermis [208]. No photoprotective effects of the IPD, such as less skin cancers or sunburns, have been observed [206]. The evolutionary significance and the biological role of IPD can, at present, only be speculated on.

11.1.5. Defence against microorganisms. Melanocytes, melanosomes and melanin in human skin can inhibit the proliferation of bacterial, fungal and parasitic infections in the epidermis and dermis [507]. Radicals and other compounds produced during melanogenesis have strong antimicrobial activity [507]. Melanocytes have the phagocytic and enzymatic machinery necessary for antigen presentation [508], and express immunologic surface markers [509], involved in cellular immune response. Melanocytes should probably be regarded as true members of the immune system [507–509]. Bacteria and fungi are more abundant and troublesome in tropical than in cold regions. This supports the defence hypothesis, since people living in tropical regions usually have more melanin and darker skin than people living in colder regions at high latitudes.

11.1.6. Protection of folates in the blood. Folate is a B vitamin of vital importance for several biochemical processes, such as DNA synthesis and DNA repair, and is essential for cell division and growth. Mammals cannot synthesis folate, and, therefore, depend on dietary sources, such as fruits and vegetables. Folate deficiency causes massive incorporation of uracil into human DNA, leading to chromosome breaks, and has been linked to neural tube defects, pregnancy complications, male infertility, several types of cancer, megaloblastic anaemia, Alzheimer's disease, Down's syndrome, mood disorders, several athero/thrombogenic phenomena, etc [510, 511]. Branda and Eaton [512] demonstrated a significant destruction of folate by UVA in plasma samples *ex vivo* from healthy volunteers and in serum from psoriatic patients treated with methoxsalen. They, and later Jablonski and Chaplin [234], proposed a new hypothesis for human skin darkening. Dark skin may have been developed to protect folates against the strong equatorial solar radiation. Solar, or artificial UV radiation, can probably deplete folates in humans, although this is not certain [513]. It seems likely that single, high doses of UV radiation (above 50 J cm^{-2}) can deplete blood folates. Human ancestors had white, naked skin daily directly exposed to sunlight with high doses of UV.

Additionally, not only UVB can degrade folate in blood, but also UVA and visible light (where folates do not absorb) whenever endogenous photosensitizers such as riboflavin or uroporphyrin are present [123, 124, 514]. The most biologically active form of folate, 5-methyltetrahydrofolate, acts as an antioxidant in a similar manner as the vitamins C and E and other natural antioxidants [515]. When 5-methyltetrahydrofolate is exposed to ROS, it oxidizes [123, 124].

11.2. Hypothesis for skin whitening

11.2.1. Sexual selection. In most populations women have a slightly whiter skin than men, but the evolutionary purpose of this is unknown [234, 516]. One possible explanation of this sexual dimorphism in skin pigmentation is that vitamin D deficiency has larger negative evolutionary consequences for women than for men, due to their greater need for calcium and vitamin D during pregnancy and lactation [234, 517]. Another explanation may be a perceived affinity towards lighter skin by men [234, 518], which can be regarded as a sign of youth and fertility [516]. Skin gets slightly darker upon ageing, notably during puberty [519]. A third hypothesis is that women's whiter skin can be regarded as a form of infantile mimicry [520]. Because white skin characterizes the early infant stage of primates, it may have become a visual cue that triggers appropriate adult behaviour towards infants, i.e. decreased aggressiveness and increased desire to provide care and protection. These hypotheses are not mutually exclusive. Women are lighter skinned, not only because they have less melanin, but also because they have less blood in the outer layers of the skin [521]. Selection may have acted via paleness, rather than solely via vitamin D production. Variations in human skin colour have been correlated with natural selection (latitude, UV radiation) and sexual selection (male mortality rates, female participation in food gathering), and have been described in the literature [521]. In fact, Darwin discussed the sexual selection hypothesis [522]. This hypothesis posits that human skin colour results from an equilibrium between natural selection forced by solar UV (sunburn, skin cancer, vitamin D deficiency, etc) and sexual selection by men for lighter skinned women.

11.2.2. Adaptation to colder climates. Migration northwards led humans to colder climates. It has been reported from the Korean War and from Alaska that dark-skinned people are more prone to frostbite than light-skinned people [523]. This was supposed to be caused by a higher emission of heat from dark than from light skin. According to one of the laws of physics a high absorption coefficient (dark skin) is linked to a high emissivity. Skin colour would be important if human skin emitted light or infrared radiation up to a wavelength of about 2 μm. For these wavelengths dark skin has a higher absorption coefficient than light skin [524]. However, for a skin temperature of 32 °C, Wien's law of displacement says that the wavelength of maximal emission (λ_{max}) should be λ_{max} (μm) $\approx$ 2900(μm K)/T (K) $\approx$ 9.5 μm. Around this wavelength dark and light skins have similar absorption coefficients [525]. Thus, after being heated to skin temperatures, a kettle painted white loses its heat as fast as a kettle painted black [526]. Even more than that, up to 2 μm dark skin will absorb more radiation from the environment, and, therefore, maintain the heat better than light skin. As far as we know, light and dark skins are similar with respect to vascularization. Thus, the evidence for this hypothesis is weak.

11.2.3. The vitamin D synthesis. Large populations are vitamin D deficient, especially African Americans (even in southern Arizona) [527], aboriginal people in Canada [528], immigrants from Pakistan, Turkey and Somalia in Norway [529], etc. Vitamin D deficiency leads not only to rickets and osteomalacia but also to increased risks of CVD, MS, rheumatoid arthritis, type 1 diabetes mellitus, many types of cancer and influenza (see section 10). Dark skin needs about six times more UVB than light skin to generate a given amount of vitamin D. The vitamin D hypothesis is a likely one, although, some questions remain unanswered [530].

African Americans have lower serum 25-hydroxyvitamin D concentrations and yet few show signs of calcium deficiency, but have a lower prevalence of osteoporosis, a lower incidence of fractures and a higher bone mineral density than white Americans, with a better vitamin D status [531]. Vitamin D deficiency is a risk factor for CVD, diabetes and some cancers, which are more prevalent among black people than white people [532, 533].

Traditional diet may also play a significant role in human skin colour preservation at high latitudes. Yupiks and Inuits (Eskimo), who live far north, have a darker skin than Europeans. Some of them live inland, but may have a history of coastal habitation. Their original diet was, until recently, traditionally rich in fish which is high in vitamin D. It is believed that their traditional diet compensated for the low fluence rates of vitamin D producing UVB radiation, and, therefore, there was no need for skin whitening in Eskimos. However, modern Inuits living on a westernized low vitamin D diet instead of traditional diet (rich in vitamin D) suffer from vitamin D deficiency [534].

11.2.4. The introduction of agriculture and its relation to vitamin D. Agriculture arose around 10 000 years ago. Agricultural food was an insufficient source of vitamin D, and people were not eating so much fatty fish, containing significant amounts of vitamin D as before [535]. Development of agriculture has occurred in several places, and did not necessarily lead to skin whitening if the ambient UVB level was sufficiently high for adequate vitamin D synthesis. However, at high latitudes the fluence rate of solar UVB radiation was too low to produce sufficient amounts of vitamin D in dark skin. This would speed up the need for skin whitening. It is possible that agriculture played a role in the evolution of light skin in modern humans, but the main objection to this hypothesis is its recency: a few thousands of years may not be enough for such genetic changes although the matter is disputed.

11.2.5. Genetic drift. Another hypothesis for skin whitening is that genes that influence variation in skin and hair pigmentation are only under strong selection close to the equator, while selection is relaxed in human populations living at higher latitudes [502, 536, 537]. Accordingly, just by chance, there were changes in the allele frequencies of genes underlying skin pigmentation that occurred to produce lighter skin in some populations. This hypothesis would predict the existence of some groups with light skin away from the equator but also some groups who maintain dark skin.

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