SOLAR AND ULTRAVIOLET RADIATION

Solar and ultraviolet radiation were considered by a previous IARC Working Group in 1992 (IARC, 1992). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

Terrestrial life is dependent on radiant energy from the sun. Solar radiation is largely optical radiation [radiant energy within a broad region of the electromagnetic spectrum that includes ultraviolet (UV), visible (light) and infrared radiation], although both shorter wavelength (ionizing) and longer wavelength (microwaves and radiofrequency) radiation is present. The wavelength of UV radiation (UVR) lies in the range of 100–400 nm, and is further subdivided into UVA (315–400 nm), UVB (280–315 nm), and UVC (100–280 nm). The UV component of terrestrial radiation from the midday sun comprises about 95% UVA and 5% UVB; UVC and most of UVB are removed from extraterrestrial radiation by stratospheric ozone.

Approximately 5% of solar terrestrial radiation is UVR, and solar radiation is the major source of human exposure to UVR. Before the beginning of last century, the sun was essentially the only source of UVR, but with the advent of artificial sources the opportunity for additional exposure has increased.

1.1 Nomenclature and units

For the purpose of this *Monograph*, the photobiological designations of the Commission Internationale de l'Eclairage (CIE, International Commission on Illumination) are the most relevant, and are used throughout to define the approximate spectral regions in which certain biological absorption properties and biological interaction mechanisms may dominate (Commission Internationale de l'Eclairage, 1987).

Sources of UVR are characterized in radiometric units. The terms dose (J/m^2) and dose rate (W/m^2) pertain to the energy and power, respectively, striking a unit surface area of an irradiated object (Jagger, 1985). The radiant energy delivered to a given area in a given time is also referred to as 'fluence', 'exposure dose' and 'dose' (see IARC, 1992 for further details).

A unit of effective dose [dose weighted in accordance with its capacity to bring about a particular biological effect] commonly used in cutaneous photobiology is the 'minimal erythemal dose' (MED). One MED has been defined as the lowest radiant exposure to UVR that is sufficient to produce erythema with sharp margins 24 hours after exposure (Morison, 1983). Another end-point often used in cutaneous

photobiology is a just-perceptible reddening of exposed skin; the dose of UVR necessary to produce this 'minimal perceptible erythema' is sometimes also referred to as a MED. In unacclimatized, white-skinned populations, there is an approximately 4-fold range in the MED of exposure to UVB radiation (Diffey & Farr, 1989). When the term MED is used as a unit of 'exposure dose', a representative value for sun-sensitive individuals of 200 J/m^2 is usually chosen. Since 1997, the reference action spectrum for erythema on human skin (McKinlay & Diffey, 1987) has become an International Standards Organization (ISO)/CIE norm, which, by convolution with the emission spectrum of any UVR source, enables the calculation of the erythemal yield of the source. A Standard Erythema Dose (SED) has been proposed as a unit of erythemally effective UVR dose equivalent to 100 J/m^2 (Commission Internationale de l'Eclairage, 1998).

Notwithstanding the difficulties of interpreting accurately the magnitude of such imprecise units as the MED and the SED, they have the advantage over radiometric units of being related to the biological consequences of the exposure.

The UV index is a tool intended for the communication of the UVR intensity to the general public. It has been developed jointly by the World Health Organization, the United Nations Environment Program, the International Commission on Non-Ionizing Radiation Protection and was standardized by ISO/CIE. It expresses the erythemal power of the sun as follows:

UV Index = 40 times the erythemally effective power of the sun in W/m^2

The clear sky UV Index at solar noon is generally in the range of 0–12 at the Earth's surface, with values over 11 being considered extreme.

1.2 Methods for measuring UVR

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

The solar UV irradiation of large portions of the Earth is currently measured using multifrequency imaging detectors on meteorological satellites.

1.3 Sources and exposure

1.3.1 Solar UVR

Optical radiation from the sun is modified substantially as it passes through the Earth's atmosphere, although about two-thirds of the energy from the sun that enters the atmosphere penetrates to ground level. The annual variation in extraterrestrial radiation is less than 10%; the variation in the modifying effect of the atmosphere is far greater (Moseley, 1988).

On its path through the atmosphere, solar UVR is absorbed and scattered by various constituents of the atmosphere. It is scattered by air molecules, particularly oxygen and nitrogen, by aerosol and dust particles, and is scattered and absorbed by atmospheric pollution. Total solar irradiance and the relative contributions of different wavelengths vary with altitude. Clouds attenuate solar radiation, although their effect on infrared radiation is greater than on UVR. Reflection of sunlight from certain ground surfaces may contribute significantly to the total amount of scattered UVR (Moseley, 1988).

The levels of solar UVB radiation reaching the surface of the Earth are largely controlled

by the stratospheric ozone layer, which has been progressively depleted as a result of accumulation of ozone-destroying chemicals in the Earth's atmosphere – mostly chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs), whose main use has been in refrigeration and air-conditioning. The accumulation of ozone-depleting chemicals in the atmosphere ceased largely as a result of the Montreal Protocol on "Substances that deplete the ozone layer," which was opened for signature in 1987, and has been ratified by 196 states.

Global climate change due to the accumulation of carbon dioxide (CO_2) in the atmosphere can also adversely affect stratospheric ozone. This will influence whether, when, and to what extent ozone levels will return to pre-1980 values. The current best estimate is that global (60°S–60°N) ozone levels will return to pre-1980 levels around the middle of the 21st century, at or before the time when stratospheric concentrations of ozone-depleting gases return to pre-1980 levels. Climate change will also influence surface UV radiation through changes induced mainly to clouds and the ability of the Earth's surface to reflect light. Aerosols and air pollutants are also expected to change in the future. These factors may result in either increases or decreases of surface UV irradiance, through absorption or scattering. As ozone depletion becomes smaller, these factors are likely to dominate future UV radiation levels (World Meteorological Organization, 2007).

The amount of solar UVR measured at the Earth's surface depends upon several factors as follows:

- *Time of day*: In summer, about 20–30% of the total daily amount of UVR is received between 11:00 and 13:00, and 75% between 9:00 and 15:00 (sun time not local time; Diffey, 1991).
- *Season*: Seasonal variation in terrestrial UV irradiance, especially UVB, at the Earth's surface is significant in temperate regions but much less nearer the equator (Diffey, 1991).
- *Geographic latitude:* Annual UVR exposure dose decreases with increasing distance from the equator (Diffey, 1991).
- *Altitude:* In general, each 300 metre increase in altitude increases the sunburning effectiveness of sunlight by about 4% (Diffey, 1990).
- *Clouds:* Clouds influence UV ground irradiance, through reflection, refraction, absorption and scattering, and may increase or, more usually, decrease UV ground irradiance. Complete light cloud cover prevents about 50% of UVR energy from reaching the surface of the Earth (Diffey, 1991). Very heavy cloud cover absorbs and can virtually eliminate UVR even in summer. Even with heavy cloud cover, however, the scattered UVR component of sunlight (as opposed to that coming directly from the sun) is seldom less than 10% of that under clear sky. While most clouds block some UV radiation, the degree of protection depends on the type and amount of clouds; some clouds can actually increase the UV intensity on the ground by reflecting, refracting and scattering the sun's rays. For example, under some circumstances (haze, cirrus skies, solar zenith angles ranging from 40–63°), the solar irradiance at Toowoomba, Australia (27.6°S, 151.9°E), was found to be 8% greater than that of an equivalent clear sky (Sabburg & Wong, 2000; Sabburg *et al.*, 2001).
- *Surface reflection:* The contribution of reflected UVR to a person's total UVR exposure varies in importance with several factors. A grass lawn scatters 2–5% of incident UVB radiation. Sand reflects about 10–15%, so that sitting under an umbrella on the beach can lead to sunburn both from scattered UVB from the

sky and reflected UVB from the sand. Fresh snow may reflect up to 85–90% of incident UVB radiation while water, in particular white foam in the sea, may reflect up to 30%. Ground reflectance is important, because parts of the body that are normally shaded are exposed to reflected radiation (Diffey, 1990).

- *Air pollution:* Tropospheric ozone and other pollutants can decrease UVR.

(a) Measurements of terrestrial solar radiation

Because UVR wavelengths between about 295–320 nm (UVB radiation) in the terrestrial solar spectrum are thought to be those mainly responsible for adverse health effects, several studies have focused on this spectral region. Accurate measurements of UVR in this spectral band are difficult to obtain, however, because the spectral curve of terrestrial solar irradiance increases by a factor of more than five between 290–320 nm. Nevertheless, extensive measurements of ambient UVR in this spectral band have been made worldwide. Measurements of terrestrial solar UVA are less subject to error than measurements of UVB, because the spectrum does not vary widely with zenith angle and the spectral irradiance curve is relatively flat (IARC, 1992).

The total solar radiation that arrives at the Earth's surface is termed 'global radiation'. Global radiation is made up of two components, referred to as 'direct' and 'diffuse'. Approximately 70% of the UVR at 300 nm is in the diffuse component rather than in the direct rays of the sun. The ratio of diffuse to direct radiation increases steadily from less than 1.0 at 340 nm to at least 2.0 at 300 nm. UVR reflected from the ground (the albedo) may also be important (IARC, 1992).

Solar UV levels reaching the Earth's surface can now be measured by satellites using hyperspectral imaging to observe solar backscatter radiation in the visible and ultraviolet ranges. NASA's Total Ozone Mapping Spectrometer (TOMS) device was installed on several spacecraft, including the Earth Probe spacecraft for collecting data during 1996–2005. TOMS is no longer available but the continuity of satellite-derived global UV data is maintained via the new Ozone Monitoring Instrument (OMI), on board the Aura satellite (http://aura.gsfc.nasa.gov/index.html). The presence of aerosols, clouds and snow or ice cover can lead to significant biases, and new algorithms have been developed to improve the satellite-derived measurement of surface UV irradiance using Advanced Very High Resolution Radiometer (AVHRR) and Meteosat images. Currently the European Solar Data Base (SoDa) is capable to perform on-the-fly fast interpolation with a non-regular grid and to provide data for any geographic site with a limitation to a 5-km grid cell. The SoDa contains information going back to the year 1985, available at http://www.soda-is.com/eng/services/services_radiation_free_eng.php.

Satellite data have been used to draw maps of UV exposure, and are available for use for epidemiological and other purposes. For example, data sets of UV irradiance derived from TOMS data for the period 1979 to 2000 are available by date, latitude and longitude for UVB and UVA. Data from satellites and ground-level measurements show that UV irradiation does not vary steadily with latitude but that local conditions may greatly influence actual UV irradiation levels (a good example of this situation may be found in the extremely elevated UV levels recorded in the summer 2003 during the heat wave that killed thousands of people in France and Northern Italy).

(b) Personal exposures

Individual sun exposure can be estimated through questionnaires, which are at best semi-quantitative, and do not give any detailed

information on the wavelength of UV exposure. Individual UV dosimeters have been used in epidemiological studies, but cannot be used for the large-scale monitoring of UV exposure of populations.

Exposure data for different anatomical sites is of value in developing biological dose–response relationships. The exposure of different anatomical sites to solar UVR depends not only on ambient UVR and the orientation of sites with respect to the sun, but also on cultural and social behaviour, type of clothing, and use of sunscreen. The most exposed skin surfaces, such as the nose, tops of the ears and forehead, have levels of UVB exposure that range up to one order of magnitude relative to that of the lesser exposed areas, such as underneath the chin. Ground reflectance plays a major role in exposure to UVB of all exposed body parts, including the eye and shaded skin surfaces, particularly with highly reflective surfaces such as snow. The solar exposure of the different anatomical sites of outdoor workers has recently been calculated (Milon *et al.*, 2007) [Computerised models that integrate direct, diffuse and reflected radiation are currently being developed].

Sunscreens can be applied to control the dose of UVR to exposed skin. While undoubtedly useful when sun exposure is unavoidable (IARC, 2001), their use may lead to a longer duration of sun exposure when sun exposure is intentional (Autier *et al.*, 2007).

The cumulative annual exposure dose of solar UVR varies widely among individuals in a given population, depending to a large extent on the occupation and extent of outdoor activities. For example, it has been estimated that indoor workers in mid-latitudes (40–60°N) receive an annual exposure dose of solar UVR to the face of about 40–160 times the MED, depending on their level of outdoor activities, whereas the annual solar exposure dose for outdoor workers is typically around 250 times the MED. Because few actual measurements of personal exposures have been reported, these estimates should be considered to be very approximate. They are also subject to differences in cultural and social behaviour, clothing, occupation, and outdoor activities.

1.3.2 Artificial sources of UVR

Cumulative annual outdoor exposure may be increased by exposure to artificial sources of UVR. Indoor tanning is a widespread practice in most developed countries, particularly in northern Europe and the United States of America, and is gaining popularity even in sunny countries like Australia. The prevalence of indoor tanning varies greatly among different countries, and has increased during the last decades (IARC, 2006a). The majority of users are young women, and a recent survey indicated that in the USA, up to 11% of adolescents aged 11–years had ever used an indoor tanning device (Cokkinides *et al.*, 2009). The median annual exposure dose from artificial tanning is probably 20–30 times the MED. Prior to the 1980s, tanning lamps emitted high proportions of UVB and even UVC. Currently used appliances emit primarily UVA; and in countries where tanning appliances are regulated (e.g. Sweden and France), there is a 1.5% upper limit UVB. However, commercially available "natural" UV-tanning lamps may emit up to 4% UVB. UV emission of a modern tanning appliance corresponds to an UV index of 12, i.e. equivalent to midday tropical sun (IARC, 2006a).

Other sources of exposures to UVR include medical and dental applications. UVR has been used for several decades to treat skin diseases, notably psoriasis. A variety of sources of UVR are used, emitting either broad-band UVA or narrow-band UVB. A typical dose in a single course of UVB phototherapy can be in the range of 200–300 times the MED (IARC, 2006a).

UVR is also used in many different industries, yet there is a paucity of data concerning human exposure from these applications,

probably because in normal practice, sources are well contained and exposure doses are expected to be low. In some settings, workers may be exposed to radiation by reflection or scattering from adjacent surfaces. Staff in hospitals who work with unenclosed phototherapy equipment are at potential risk of overexposure unless protective measures are taken. Indoor tanning facilities may comprise 20 or more UVA tanning appliances, thus potentially exposing operators to high levels (> 20W/m^2) of UVA (IARC, 2006a).

Acute overexposures to the eyes are common among electric arc welders. Individuals exposed to lighting from fluorescent lamps may typically receive annual exposure doses of UVR in the range of 0–30 times the MED, depending on illuminance levels and whether or not the lamps are housed behind plastic diffusers. It is also worth noting that tungsten–halogen lamps used for general lighting may emit broad-band UVR (including UVC) when not housed behind a glass filter.

2. Cancer in Humans

2.1 Natural sunlight

2.1.1 Basal cell carcinoma and cutaneous squamous cell carcinoma

In the previous *IARC Monograph* (IARC, 1992), the evaluation of the causal association of basal cell carcinoma and squamous cell carcinoma with solar radiation was based on descriptive data in Caucasian populations, which showed positive associations with birth and/or residence at low latitudes and rare occurrence at non-sun-exposed anatomical sites. The evaluation was also based on case–control and cohort studies whose main measures were participants' retrospectively recalled sun exposure. The majority of analyticalal studies published since have also used recalled amount of sun exposure, though some more recent studies have made objective measures of ambient UV and used clinical signs of cumulative UV damage to the skin such as solar lentigines and actinic keratoses (Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.1.pdf, Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.2.pdf, and Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.3.pdf).

With regard to basal cell carcinoma, all studies except one (Corona *et al.*, 2001) showed significant positive associations with sunburns at some stage of life or overall. Of the studies that collected information on the presence of actinic keratoses (Green *et al.*, 1996; Corona *et al.*, 2001; Walther *et al.*, 2004; Pelucchi *et al.*, 2007), all showed this also to be a strong risk factor (Tables 2.1 and 2.3 on-line). It was proposed that the association of basal cell carcinoma with sun exposure may vary by histological subtype and anatomical site (Bastiaens *et al.*, 1998). Although a case–control study showed this variation for recalled sun exposure (Pelucchi *et al.*, 2007), a cohort study did not (Neale *et al.*, 2007).

For squamous cell carcinoma, while case–control studies tended to demonstrate little association with sunburns (Table 2.2 on-line), cohort studies uniformly showed significant positive associations (Table 2.3 on-line). The presence of actinic keratoses, a proportion of which are squamous cell carcinoma precursors, was the strongest risk factor identified (Table 2.3 on-line; Green *et al.*, 1996).

2.1.2 Cutaneous malignant melanoma

Cutaneous malignant melanoma occurs in the pigment cells of the skin. Until 10–15 years ago, with the exception of two histological subgroups, melanoma was usually regarded as a single entity in analytical studies assessing the association with sunlight. The two subgroups,

lentigo maligna melanoma and acral lentiginous melanoma, were usually excluded from studies, the former paradoxically because of its known causal link with cumulative sun exposure, the latter for the opposite reason because it typically occurs on the soles of the feet.

In the previous *IARC Monograph* (IARC, 1992), the evaluation of the causal association between solar radiation and melanoma was based on descriptive data and on data from case–control studies. The main measures of exposure were participants' recalled sun exposure. 'Intermittent' sun exposure, which loosely equated with certain sun-intensive activities, such as sunbathing, outdoor recreations, and holidays in sunny climates, generally showed moderate-to-strong positive associations with melanoma. However, 'chronic' or 'more continuous' exposure, which generally equated with 'occupational' exposure, and total sun exposure (sum of 'intermittent'+'chronic'), generally showed weak, null or negative associations.

These results were collectively interpreted under the 'intermittent sun exposure' hypothesis (Fears *et al.*, 1977) as showing that melanoma occurs as a result of a pattern of intermittent intense sun exposure rather than of more continuous sun exposure. Studies that had also assessed objective cutaneous signs of skin damage that were generally assumed to be due to accumulated sun exposure, e.g. presence or history of actinic keratoses, or signs of other sun-related skin damage, showed, almost uniformly, strong positive associations with melanoma. This inconsistency of evidence with the apparently negative associations of reported 'chronic' sun exposure with melanoma was noted but not satisfactorily explained.

Several systematic reviews and meta-analyses of analytical studies of the association of melanoma with sun exposure have been published since (Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.4.pdf). The summary melanoma relative risk (RR) estimates of one of the largest meta-analyses, based on 57 studies published up to September 2002 (Gandini *et al.*,, 2005a, b) were: sunburn (ever/never), 2.0 (95%CI: 1.7–2.4); intermittent sun exposure (high/low), 1.6 (95%CI: 1.3–2.0); chronic sun exposure (high/low), 1.0 (95%CI: 0.9–1.0); total sun exposure (high/low), 1.3 (95%CI: 1.0–1.8); actinic tumours (present, past/none), 4.3 (95%CI: 2.8–6.6).

Case–control studies and the cohort study (Veierød *et al.*, 2003) that have been published since September 2002 have shown results that are generally consistent with the meta-analysis, and have not been included in this review (Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.5.pdf and Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.6.pdf).

(a) Anatomical site of melanoma

Melanoma–sun-exposure associations according to the anatomical site of the melanoma have recently gained greater consideration. Several studies reported differences in age-specific incidence rates by site of melanoma (Holman *et al.*, 1980; Houghton *et al.*, 1980; Elwood & Gallagher, 1998; Bulliard & Cox, 2000). The numerous analytical studies of risk factors by site of melanoma (Weinstock *et al.*, 1989; Urso *et al.*, 1991; Green, 1992; Krüger *et al.*, 1992; Rieger *et al.*, 1995; Whiteman *et al.*, 1998; Carli *et al.*, 1999; Håkansson *et al.*, 2001; Winnepenninckx & van den Oord, 2004; Cho *et al.*, 2005; Purdue *et al.*, 2005; Nikolaou *et al.*, 2008) collectively show that melanomas of the head and neck are strongly associated with actinic keratoses, and melanomas on the trunk are strongly associated with naevi. Similar findings have been reported from recent detailed case–case studies (Whiteman *et al.*, 2003, 2006; Siskind *et al.*, 2005; Lee *et al.*, 2006).

(b) Skin pigmentation

Two observations from epidemiological studies may help explain the paradox of the lack of association of melanoma with chronic sun exposure. First, outdoor workers are not at a substantially increased risk of melanoma (IARC, 1992; Armstrong & Kricker, 2001); second, outdoor workers tend to have a higher-than-average ability to develop a tan (Green *et al.*, 1996; Chang *et al.*, 2009). Outdoor workers tend to be constitutionally protected from solar skin damage and at a lower risk of skin cancer than workers in other occupations because of self-selection based on skin pigmentation. Indeed, such self-selection has been observed in a non-Hispanic white study population from Philadelphia and San Francisco, USA, whereby the average number of hours outdoors in general increases with an increasing ability to tan (Fears *et al.*, 2002). The role of baseline sun sensitivity in influencing sun exposure in the etiology of melanoma has long been recognized (Holman *et al.*, 1986; Nelemans *et al.*, 1995).

(c) Latitude

The assessment and reporting of sun exposure may vary among studies at different latitudes, due to latitude differences in sun exposure opportunity and behaviour (Elwood & Diffey, 1993; Gandini *et al.*, 2005a, b). One approach to avoid the problems of quantifying individual sun exposure at different latitudes has been to use ambient UV flux (Fears *et al.*, 2002; Kricker *et al.*, 2007) for individuals through life, calculated from their residential histories, to accurately quantify at least potential solar UV exposure.

Two case–control studies, both done at comparatively high latitudes (Connecticut, USA; Chen *et al.*, 1996) and (Italy; Naldi *et al.*, 2005), and one pooled analysis stratified by latitude (Chang *et al.*, 2009), have presented site-specific melanoma risk estimates in relation to latitude (see Table 2.5 on-line). Recalls of sunburns throughout life were generally predictive of melanomas at all sites in both case–control studies and in the pooled analysis (RR, 1.0–2.0). Those who had objective signs of cumulative sun damage were at increased risk of melanoma at specific sites: the presence of solar lentigines increased the risk of melanoma on the lower limbs (Naldi *et al.*, 2005; RR, 1.5; 95%CI: 1.0–2.1, with reference to absence of solar lentigines), while actinic keratoses increased the risk of melanoma on the head and neck (Chang *et al.*, 2009; RR, 3.1; 95%CI: 1.4–6.7; based on three studies from high to low latitudes in which solar keratoses were measured). [The Working Group noted that the omission from many studies of the lentigo maligna melanoma subgroup, which is known to be associated with cumulative sun exposure, potentially results in an underestimation of the association with melanomas on the head and limbs.]

2.1.3 Cancer of the lip

Cancer of the lip has been associated with outdoor occupations in several descriptive studies (IARC, 1992). Three early case–control studies reported increases in risk for cancer of the lip with outdoor work, but use of tobacco could not be ruled out as an explanation for this association in any study (Keller, 1970; Spitzer *et al.*, 1975; Dardanoni *et al.*, 1984).

Two case–control studies have been published since that include information on tobacco smoking. The first (Pogoda & Preston-Martin, 1996), which included women only, found increased risks of cancer of the lip with average annual residential UV flux, recalled average annual hours spent in outdoor activities, and having played high-school or college sports; risk estimates were adjusted for complexion, history of skin cancer and average number of cigarettes smoked per day. Risk was not increased in women whose last occupation was outdoors (odds ratio (OR)), 1.2; 95%CI: 0.5–2.8). The dose–response

relationship with recalled average annual hours spent in outdoor activities was inconsistent: with < 30 hours as the reference category, the odds ratios were 2.6 (95%CI: 1.0–6.5) for 30–99 hours; 1.8 (95%CI: 0.7–4.6) for 100–299 hours; and, 4.7 (95%CI: 1.9–12.1) for > 300 hours. The second, which included men only (Perea-Milla López *et al.*, 2003), found no evidence of an increased risk for cancer of the lip with estimates of cumulative sun exposure during leisure time or holiday. Risk was increased with cumulative sun exposure in outdoor work during the summer months, but without any dose–response (OR, 11.7–12.7; with wide confidence intervals). The odds ratios were adjusted for cumulative alcohol and tobacco intake and "leaving the cigarette on the lip," among other things. In a meta-analysis of cancer in farmers (Acquavella *et al.*, 1998), the pooled relative risk for cancer of the lip from 14 studies was 1.95 (95%CI: 1.82–2.09) (*P* for heterogeneity among studies, 0.22). [The Working Group noted that given the relative risks for oesophageal cancer and lung cancer were 0.77 and 0.65, respectively, confounding by smoking was unlikely, but confounding with other farm-related exposures could not be excluded.]

See Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.7.pdf and Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.8.pdf.

2.1.4 Cancer of the eye

(a) Squamous cell carcinoma of the conjunctiva

(i) Descriptive studies

Incidence of squamous cell carcinoma of the eye was inversely correlated with latitude across a wide range of countries (Newton *et al.*, 1996), and directly associated with measured ambient UVB irradiance across the original nine Surveillance Epidemiology and End Results (SEER) cancer registry areas of the USA (Sun *et al.*, 1997).

(ii) Case–control studies

Three small case–control studies included only or mainly cases with conjunctival intraepithelial neoplasia (Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.9.pdf). Napora *et al.* (1990) compared 19 patients with biopsy-proven conjunctival intraepithelial neoplasia (including one with invasive squamous cell carcinoma) with 19 age- and sex-matched controls. The odds ratio for "office work" was 0.21 [95%CI: 0.04–0.99; Fisher Exact 95%CIs calculated from numbers in authors' table]. Lee *et al.* (1994) included 60 [probably prevalent] cases of ocular surface epithelial dysplasia (13 were conjunctival squamous cell carcinoma) diagnosed over 19 years (40% participation), and 60 age- and sex-matched hospital-based controls. Among others, positive associations were observed between ocular surface epithelial dysplasia and history of solar keratoses [OR, for history at < 50 and ≥ 50 years of age combined, 9.4 (95%CI: 2.8–31)] and duration of residence at ≤ 30° south latitude for 31–49 years (OR, 2.2; 95%CI: 0.6–8.3), and for 50 years or more (OR, 3.9; 95%CI: 1.0–14.8) relative to ≤ 30 years. Cumulative years of life in which > 50% of daytime was spent outdoors were similarly but more weakly associated with ocular surface epithelial dysplasia. Tulvatana *et al.* (2003) studied 30 cases of conjunctival squamous cell neoplasia (intraepithelial or invasive) and 30 age- and sex-matched control patients having extracapsular cataract extraction from whom diseased conjunctiva was taken [site of biopsy not specified]. Solar elastosis [representing pathologically proven solar damage] was observed in the conjunctiva of 53% of cases and 3% of controls, resulting in an odds ratio of 16.0 (95%CI: 2.49–671). [The Working Group noted that while pathologists were said to be "masked," it was not stated that tissue sections from cases were free of neoplastic tissue.]

In the only case–control study of exclusively conjunctival squamous cell carcinoma, Newton *et al.* (2002) studied 60 Ugandan patients with a clinical diagnosis of conjunctival squamous cell carcinoma and 1214 controls diagnosed with other cancers not known to be associated with solar UV exposure or infection with HIV, HPV or Kaposi Sarcoma herpesvirus. The risk for conjunctival squamous cell carcinoma increased with "time spent cultivating": with reference to 0–9 hours a week, the odds ratios were 1.9 for 10–19 hours and 2.4 for ≥ 20 hours (P = 0.05), adjusted for age, sex, region of residence, HIV-1 status, and low personal income. Both HIV-1 status and personal income were strong predictors of risk.

(b) Ocular melanoma

(i) Descriptive studies

No increase in the incidence of ocular melanoma was recorded by the US SEER programme during 1974–98, which is in contrast with the increasing incidence of cutaneous melanoma over the same period (Inskip *et al.*, 2003).

Three studies have reported on the distribution of choroidal melanomas within the eye in relation to the presumed distribution of choroidal sun exposures across the choroid. The first of these (Horn *et al.*, 1994), which analysed 414 choroidal, 20 ciliary body and 18 iris melanomas, concluded that choroidal and iris melanomas were located most frequently in "the areas that are presumably exposed to the most sunlight." Specifically, melanomas in the posterior choroid were observed to preferentially involve the central area. The second (Schwartz *et al.*, 1997), which analysed 92 choroidal melanomas, concluded that there was no preferential location for tumours on the choroid, having rigorously estimated "the average dose distribution on the retina received in outdoor daylight." A third study (Li *et al.*, 2000), which analysed 420 choroidal and ciliary body melanomas, mapped incident melanomas on the retina and observed that rates of occurrence were concentrated in the macula area, and decreased progressively with increasing distance from the macula to the ciliary body. It was concluded that this pattern was consistent with the dose distribution of light on the retinal sphere as estimated by Schwartz *et al.* (1997).

(ii) Case–control and cohort studies

Nine case–control studies and one cohort study reported on associations of sun exposure with ocular melanoma (Gallagher *et al.*, 1985; Tucker *et al.*, 1985; Holly *et al.*, 1990; Seddon *et al.*, 1990; van Hees *et al.*, 1994; Pane & Hirst, 2000; Håkansson *et al.*, 2001; Vajdic *et al.*, 2002; Lutz *et al.*, 2005 (incorporating also data from Guénel *et al.*, 2001); and Schmidt-Pokrzywniak *et al.*, 2009). In addition, one previously reported case–control study reported new analyses of occupation and ocular melanoma (Holly *et al.*, 1996; Tables 2.8 and 2.9 on-line).

Four studies (Gallagher *et al.*, 1985; Holly *et al.*, 1990; Seddon *et al.*, 1990; Tucker *et al.*, 1985) found an increased risk for ocular melanoma in people with light skin, light eye colour or light hair colour. Outdoor activities were associated with ocular melanoma in one study (Tucker *et al.*, 1985).

Four studies (Tucker *et al.*, 1985; Seddon *et al.*, 1990; Håkansson *et al.*, 2001; Vajdic *et al.*, 2001, 2002) reported statistically significant associations between a measure of sun exposure and ocular melanoma. Tucker *et al.* (1985) observed an increased risk of ocular melanoma in people born in the south of the USA (south of 40°N) relative to those born in the north (OR, 2.7; 95%CI: 1.3–5.9), which appeared to be independent of duration of residence in the south. Seddon *et al.* (1990) reported on two separate series of cases and controls. In the first series, increased risks of uveal melanoma with residence in the south of the USA were observed (OR, 2.4; 95%CI: 1.4–4.3

for up to 5 years; and OR, 2.8; 95%CI: 1.1–6.9 for more than 5 years). In the second series, the risk increased with increasing years of "intense sun exposure" (OR, 1.5; 95%CI: 1.0–2.2 for 1–40 years; and, OR, 2.1; 95%CI: 1.4–3.2 for > 40 years); this association was only weakly present in the first series; the odds ratio for uveal melanoma with birthplace in the south of the USA was 0.2 (95%CI: 0.0–0.7), which was statistically independent of the positive association between duration of residence in the south and uveal melanoma risk. Vajdic *et al.* (2001, 2002) found that the risk of choroid and ciliary body melanoma was increased in the highest categories of total sun exposure (OR, 1.6; 95%CI: 1.0–2.6), weekdays sun exposure (OR, 1.8; 95%CI: 1.1–2.8), and occupational sun exposure (OR, 1.7; 95%CI: 1.1–2.8); the underlying trends across quarters of exposure were reasonably consistent and statistically significant. These associations were largely due to stronger associations confined to men. Finally, the one cohort study (Håkansson *et al.*, 2001), based in the Swedish construction industry's health service, observed an increasing risk of ocular melanoma with increasing occupational sun exposure based on recorded job tasks (RR, 1.4; 95%CI: 0.7–3.0, for medium sun exposure; and, RR, 3.4; 95%CI: 1.1–10.5, for high sun exposure).

Five of the case–control studies limited their study to uveal melanoma (melanoma in the choroid, ciliary body, and iris), and one of these excluded iris melanoma because of small numbers. Two studies reported results for iris melanoma (Tucker *et al.*, 1985; Vajdic *et al.*, 2002). One study observed odds ratios of 3–5 for iris melanoma with the use of an eye shade when outdoors occasionally, rarely or never, relative to almost always (Tucker *et al.*, 1985), and the other observed an increased risk of iris melanoma in farmers (OR, 3.5; 95%CI: 1.2–8.9; Vajdic *et al.*, 2002). One study also reported results for conjunctival melanoma, but found no positive associations with measures of sun exposure (Vajdic *et al.*, 2002).

(c) *Meta-analyses*

Shah *et al.* (2005) and Weis *et al.* (2006) reported the results of meta-analyses of risk of ocular melanoma in relation to sun sensitivity characteristics and sun exposure, including both case–control and cohort studies (Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.10.pdf). A fixed-effects model was used except when statistically significant heterogeneity was found between the effects of individual studies and a random-effects model was used instead. A summary relative risk was reported only when four or more studies were included in the analysis. In the analysis by Shah *et al.* (2005), neither latitude of birth nor outside leisure was appreciably associated with ocular melanoma. There was weak evidence that occupational exposure to the sun increased ocular melanoma risk (RR for highest exposed category, 1.37; 95%CI: 0.96–1.96). [The Working group noted that this analysis did not include results of Lutz *et al.* (2005) or Schmidt-Pokrzywniak *et al.* (2009), but included those of Guénel *et al.* (2001), which are a component of Lutz *et al.* (2005). When the results of Lutz *et al.* (2005) are substituted for those of Guénel *et al.* (2001) and those of Schmidt-Pokrzywniak *et al.* (2009) added to the fixed effects meta-analysis, the meta-RR is 1.25 (95%CI: 1.02–1.54).]

The meta-analysis of Weis *et al.* (2006) provides strong evidence that having blue or grey eyes, fair skin and/or burning easily rather than tanning when exposed to the sun are associated with an increased risk of ocular melanoma. Hair colour was not associated with this cancer.

2.1.5 *Other sites*

Prompted at least in part by the hypotheses arising from ecological studies, case–control and cohort studies have been conducted in

which measures of personal exposure to solar radiation (loosely referred to here as sun or sunlight exposure) have been related to cancers in internal tissues (Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.11.pdf and Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.12.pdf). Studies that infer high sun exposure from a past history of skin cancer (basal cell carcinoma, squamous cell carcinoma or melanoma) were excluded (see for example, Tuohimaa *et al.*, 2007). It has been argued in respect of these studies that "the incidence of second cancers in individuals is elevated by several known and unknown mechanisms, including common etiological factors and predispositions, and influenced by possible biases in the ascertainment of second cancers […] The net direction of these influences will mostly be in the direction of elevated occurrence of second cancers, against which a possible effect of sunlight and vitamin D […] could be difficult to detect." (IARC, 2008). Thus, such studies are unlikely to be a reliable source of evidence for determining whether sun exposure causes or prevents any other cancers.

(a) Cancer of the colorectum

Two case–control studies have related estimates of individual sun exposure to risk of cancer of the colorectum. Based solely on death certificates, Freedman *et al.* (2002) observed a somewhat reduced risk (OR, 0.73; 95%CI: 0.71–0.74) with high ambient sunlight in the state of residence at the time of death, adjusted for age, sex, race, occupational sun exposure (inferred from usual occupation), physical activity, and socioeconomic status. In a large population-based study in which participants were interviewed, no appreciable association was found between cancer of the colon and sun exposure recalled for each season for the 2 years before case diagnosis. With the exception of the second quintile of exposure in women (OR, 1.3), the odds ratios for each quintile of exposure in each sex varied from 0.9–1.1, and were not significantly increased (Kampman *et al.*, 2000).

(b) Cancer of the breast

Three case–control and two cohort studies have examined the association between measures of sun exposure and breast cancer. In three studies reporting results for sun exposure assessed from location of residence, one found slightly higher risks in women residing in California (using 'south' as a reference; Laden *et al.*, 1997); the other two studies found reduced relative risks (0.73 and 0.74) with residence in areas of high mean daily solar radiation (John *et al.*, 1999; Freedman *et al.*, 2002), significantly so in one of these studies (Freedman *et al.*, 2002). Sun-related behaviour was recorded in three studies (John *et al.*, 1999; Freedman *et al.*, 2002; Knight *et al.*, 2007) and was inversely associated with risk for breast cancer for some measures. For example, the relative risks for breast cancer with frequent recreational and occupational sun exposure relative to rare or no exposure were 0.66 (95%CI: 0.44–0.99) and 0.64 (95%CI: 0.41, 0.98), respectively, in 5009 women from the NHANES Epidemiologic Follow-up Study (John *et al.*, 1999). For the highest category of estimated lifetime number of outdoor activity episodes at 10–19 years of age, the odds ratio was 0.65 (95%CI: 0.50–0.85) in a large Canadian case–control study (Knight *et al.*, 2007). In each study, these effect measures were adjusted for a measure of socioeconomic status and some other variables associated with breast cancer.

(c) Cancer of the ovary

In a case–control study, based on death certificates, the relative risk of cancer of the ovary was reduced in those residing in areas with high mean daily solar radiation (OR, 0.84; 95%CI: 0.81–0.88), but not in those with high occupational sun exposure (Freedman *et al.*, 2002).

(d) Cancer of the prostate

Four case–control studies (two hospital-based) and one cohort study (John *et al.*, 2004, 2007) examined the association between measures of sun exposure and risk for cancer of the prostate. In one case–control study conducted in two consecutive periods and with patients with benign prostatic hypertrophy as controls, the odds ratio for prostate cancer with highest lifetime sun exposure was [0.32 (95%CI: 0.20–0.51); combined odds ratio calculated from two reported odds ratios]. Odds ratios were similarly low with indirect measures of sun exposure, such as regular foreign holidays or childhood sunburn (Luscombe *et al.*, 2001; Bodiwala *et al.*, 2003). Two other studies showed weaker evidence of an inverse association of residence in a high solar radiation environment with cancer of the prostate (Freedman *et al.*, 2002; John *et al.*, 2004, 2007). Outdoor occupation, self-reported recreational sun exposure, physician-assessed sun exposure or actinic skin damage had no effect on prostate cancer risk in these studies. In a case–control study that included only cases of primary advanced cancer of the prostate (John *et al.*, 2005), a reduced risk for cancer of the prostate was reported with high values of sun exposure index (based on comparison of the measured reflectance of usually exposed and usually unexposed skin; OR, 0.51; 95%CI: 0.33–0.80), but with little evidence of similar associations with residential ambient solar radiation or total or occupational lifetime outdoor hours.

(e) Non-Hodgkin lymphoma and other lymphomas

While some early, mainly ecological studies, suggested that sun exposure might increase risk for non-Hodgkin lymphoma, studies of individual sun exposure suggest that recreational sun exposure may decrease its risk.

Two earlier studies in individuals assessed sunlight exposure based on place of residence, occupational title and, in one study, industry (Freedman *et al.*, 1997; Adami *et al.*, 1999). The results for residential exposure were conflicting: one study, in the USA, found a reduced relative risk with residence at lower latitudes (Freedman *et al.*, 1997); and the other, in Sweden, an increased risk (Adami *et al.*, 1999). They concurred, however, in finding reduced relative risks in people with high occupational sun exposure with values of 0.88 (95%CI: 0.81–0.96) in the USA and 0.92 (95%CI: 0.88–0.97; combined result for men and women) in Sweden. Subsequent studies focusing specifically on occupational sun exposure have not observed a reduced risk of non-Hodgkin lymphoma with higher exposure (van Wijngaarden & Savitz, 2001; Tavani *et al.*, 2006; Karipidis *et al.*, 2007). A study of non-Hodgkin lymphoma in children reported a reduced risk in those who had spent 15 or more days annually at seaside resorts, with an odds ratio of 0.60 (95%CI: 0.43–0.83; Petridou *et al.*, 2007).

All other studies (Hughes *et al.*, 2004; Smedby *et al.*, 2005; Hartge *et al.*, 2006; Soni *et al.*, 2007; Weihkopf *et al.*, 2007; Zhang *et al.*, 2007; Boffetta *et al.*, 2008; Kricker *et al.*, 2008) were included in a pooled analysis of original data from 8243 cases of non-Hodgkin lymphoma and 9697 controls in ten member studies of the InterLymph Consortium (Kricker *et al.*, 2008; Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.13.pdf). [The Working Group noted that results on sun exposure and non-Hodgkin lymphoma in three of these studies have not yet been published separately.] In eight studies in which a composite measure of total sun exposure (recreational plus non-recreational exposure) could be defined, the pooled odds ratio fell weakly with increasing sun exposure to 0.87 (95%CI: 0.71–1.05) in the fourth quarter of exposure. There was a steeper downtrend for recreational exposure to an odds ratio of 0.76 (95%CI: 0.63–0.91; *P* for trend, 0.005), and no appreciable downtrend for non-recreational exposure. Physical activity and obesity, which

might be confounding, were not controlled for in the analysis of any of the pooled studies.

Four case–control studies have reported on the association between sun exposure and Hodgkin lymphoma (Table 2.11 on-line); there was no consistent pattern of decreasing or increasing risk with different sun exposure measures (Smedby *et al.*, 2005; Petridou *et al.*, 2007; Weihkopf *et al.*, 2007; Grandin *et al.*, 2008). The same was true for multiple myeloma in two case–control studies (Boffetta *et al.*, 2008; Grandin *et al.*, 2008). One study found weak evidence of an increased risk of mycosis fungoides [a cutaneous lymphoma] in people with high occupational sun exposure [OR: 1.3 (95%CI: 1.0–1.9; combined result for men and women] (Morales-Suárez-Varela *et al.*, 2006).

2.2 Artificial UV radiation

2.2.1 Use of artificial tanning devices (sunlamps, sunbeds, solaria)

(a) Cutaneous melanoma, squamous cell carcinoma, and basal cell carcinoma

Two meta-analyses of skin cancer in relation to sunbed use have been undertaken over the past few years (Table 2.14). The first (IARC, 2006a, 2007a) was based on 19 informative published studies (18 case–control, of which nine population-based, and one cohort, all in light-skinned populations) that investigated the association between indoor tanning and skin cancers, and included some 7355 melanoma cases (Table 2.14). The characterization of the exposure was very varied across reports. The meta-relative risk for ever versus never use of indoor tanning facilities from the 19 studies was 1.15 (95%CI: 1.00–1.31); results were essentially unchanged when the analysis was restricted to the nine population-based case–control studies and the cohort study. A dose–response model was not considered because of the heterogeneity among the categories of duration and frequency of exposure used in the different studies. All studies that examined age at first exposure found an increased risk for melanoma when exposure started before approximately 30 years of age, with a summary relative risk estimate of 1.75 (95%CI: 1.35–2.26) (Table 2.14). The second meta-analysis (Hirst *et al.*, 2009) included an additional nested case–control study of melanoma (Han *et al.*, 2006), bringing the total number of melanoma cases to 7855, and the summary relative risk for melanoma in relation to ever versus never use of sunbeds was reported as 1.22 (95%CI: 1.07–1.39).

Regarding basal cell carcinoma and squamous cell carcinoma, a meta-analysis of the three studies on ever use of indoor tanning facilities versus never use showed an increased risk for squamous cell carcinoma of 2.25 (95%CI: 1.08–4.70) after adjustment for sun exposure or sun sensitivity (IARC, 2006a, 2007a). One study had information on age at first exposure of indoor tanning facilities and suggested that the risk increased by 20% (OR, 1.2; 95%CI: 0.9–1.6) with each decade younger at first use. The four studies on basal cell carcinoma did not support an association with the use of indoor tanning facilities (IARC, 2006a, 2007a).

(b) Ocular melanoma

Four case–control studies have reported explicitly on the association of artificial tanning devices and ocular melanoma (Tucker *et al.*, 1985; Seddon *et al.*, 1990; Vajdic *et al.*, 2004; Schmidt-Pokrzywniak *et al.*, 2009; Table 2.15). Odds ratios for the highest exposure categories in each were: 2.1 (95%CI: 0.3–17.9) (Tucker *et al.*, 1985); 3.4 (95%CI: 1.1–10.3) and 2.3 (95%CI: 1.2–4.3) for the population-based comparison and case–sibling comparison, respectively (Seddon *et al.*, 1990); 1.9 (95%CI: 0.8–4.3) (Vajdic *et al.*, 2004); and 1.3 to 2.1 depending on the control category (Schmidt-Pokrzywniak *et al.*, 2009). The only study to analyse dose–response found evidence of increasing risk with increasing duration of use (P = 0.04) and, less strongly, estimated

Table 2.14 Meta-analyses of use of artificial tanning devices and skin cancers

Reference, study location & period	Study description	Number of cases and controls	Exposure assessment	Exposure categories	Relative risk (95%CI)	Adjustment for potential confounders	Comments
IARC (2007a) Europe, north America and Australia 1971 to 2001	18 case–control studies (10 pop-based) and 1 cohort published in 1981–2005, with exposure assessment to indoor tanning	Cutaneous melanoma: 7355 cases and 11275 controls from case–control studies; cohort: 106379 members BCC-SCC (No. of cases not stated) from 5 case–control studies	All studies except two presented estimates for ever versus never	*Indoor tanning* Never use Ever use *Age first use* Never < 35 yr Never use Ever use Never use Ever use	**Melanoma** 1.0 1.15 (1.00–1.31) 1.0 1.75 (1.35–2.26) **BCC** 1.0 1.0 (0.6–1.9) **SCC** 1.0 2.25 (1.1–4.7)	All analyses adjusted for the maximum of potential confounders	One study presented results for men and women separately; Dose–response was not considered because of the heterogeneity among the categories of duration and frequency of exposure between studies.
Hirst *et al.* (2009) Europe, north America and Australia 1971 to 2002	18 case–control studies and 2 nested-cohort studies published in 1981–2006, with exposure assessment to indoor tanning	Cutaneous melanoma: 7885 cases and 24209 controls from all studies BCC/SCC: 1812 cases and 2493 controls from 6 case–control studies		*Indoor tanning* Never use Ever use Never use Ever use	**Melanoma** 1.0 1.22 (1.07–1.39) **BCC/SCC** 1.0 1.34 (1.05–1.70)		One study presented results for men and women separately; No summary risk estimate for BCC or SCC separately

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

Table 2.15 Case–control studies of exposure to artificial tanning devices and ocular melanoma

Reference, study location and period	Cases	Controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential cofounders	Comments
Tucker *et al.* (1985), USA, 1974–79	439 White patients with intraocular melanoma confirmed histologically or from highly reliable ancillary studies; participation rate, 89%	419 White patients with detached retina not due to tumours; matched by age, sex, race, date of diagnosis; participation rate, 85%	Telephone interview with detailed information about medical history, family history, employment, exposure to environmental agents, sunlight; details from ophthalmologic examination and medical history abstracted from medical records; interview with next-of-kin for 17% of cases and 14% of controls, half of them with spouses	*Sunlamp use* Never Rarely Occasionally Frequently	 1.0 1.3 (0.8–2.3) 1.3 (0.5–3.6) 2.1 (0.3–17.9)	Age, eye colour and history of cataract	
Seddon *et al.* (1990), Massachusetts, USA, 1984–87	White patients with clinically or histologically confirmed melanoma of the choroid, ciliary body or both, identified at local hospital or by mailing to ophthalmologists, diagnosed within previous yr; age range, 17–88 yr, mean, 57 yr; participation rate, 89% (see comments)	Series 1: selected by random digit dialing, matched 2:1 by sex, age, city of residence, 85% response rate Series 2: living sibling of cases, up to 4 siblings per case, median, 2; participation rate, 97%	Telephone interview including constitutional factors, ocular and medical histories, and exposure to environmental factors including natural and artificial sources of UV	**Case–control series 1*** *Sunlamp use* Never Rarely Occasionally or frequently **Case–control series 2*** *Sunlamp use* Never Rarely Occasionally or frequently	 1.0 0.7 (0.4–1.4) 3.4 (1.1–10.3) 1.0 0.9 (0.6–1.4) 2.3 (1.2–4.3)	Age, eye and skin colour, moles, ancestry, eye protection, outside work, fluorescent lighting, southern residence, yr of intense exposure	*Series 1: population-based, 197 cases and 385 controls; Series 2: not population-based, 337 cases and 800 sibling controls. 140 cases were included in both series.

Table 2.15 (continued)

Reference, study location and period	Cases	Controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential cofounders	Comments
Vajdic *et al.* (2004), Australia, 1996–98	246 White Australian residents, aged 18–79 yr, with histopathologically or clinically diagnosed melanoma originating in the choroid, ciliary body; participation rate, 87% among those eligible	893 controls matched 3:1 by age, sex, residence, selected from electoral rolls; participation rate, 47%	Self-administered questionnaire, and telephone interview regarding sun exposure, sun-protective wear and quantitative exposure to welding equipment and sunlamps	*Sunlamp use**		Age, sex, place of birth, eye colour, ability to tan, squinting as a child and total personal sun exposure at 10, 20, 30 and 40 yr of age	*Sunlamps use includes use of sunbeds and tanning booths
				Never	1.0		
				Ever	1.7 (1.0–2.8)		
				Duration of use			
				≤ 1 mo	1.2 (0.5–2.8)		
				2 mo to 1 yr	1.8 (0.8–3.9)		
				> 1 yr	2.3 (0.9–5.6)		
				Lifetime hours of use			
				0.1–1.4	1.3 (0.5–3.2)		
				1.5–7.8	1.8 (0.8–4.2)		
				> 7.8	1.9 (0.8–4.3)		
				Period of first use			
				< 1980	1.4 (0.7–2.7)		
				1980–90	2.0 (0.8–4.7)		
				> 1990	4.3 (0.7–27.9)		
				Age at first use			
				> 20 yr	1.5 (0.8–2.6)		
				≤ 20 yr	2.4 (1.0–6.1)		
Schmidt-Pokrzywniak *et al.* (2009), Germany, 2002–05	459 cases of incident primary uveal melanoma diagnosed at 1 clinic, aged 20–74 yr	Control 1: 827 population-based, selected from mandatory list of residence, matched 2:1 on age (5-yr age groups), sex and region Control 2: 187 sibling controls, matched 1:1 by (+/– 10 yr) and sex when possible	Self-administered postal questionnaire and computer-assisted telephone interview	*Regular sunlamp use*			†Results presented for population controls. Odds ratios with sibling controls were somewhat higher, but with wider confidence intervals and not significant; *Sunlamps use includes use of sunbeds and tanning booths
				No	1.0		
				Yes	1.3 (0.9–1.8)		
				Age at first use			
				Never used	1.0		
				> 20 yr	1.3 (0.9–1.9)		
				< 20 yr	1.7 (0.8–3.6)		

yr, year or years

cumulative time of exposure (P = 0.06) (Vajdic *et al.*, 2004). The two most recent studies (Vajdic *et al.*, 2004; Schmidt-Pokrzywniak *et al.*, 2009) calculated odds ratios for exposure that started at or before 20 years of age and after this age; in both, the odds ratio was greater for exposure starting at the younger age. The results of Seddon *et al.* (1990) and Vajdic *et al.* (2004) were adjusted for sun sensitivity and personal sun exposure. [The Working Group noted that Schmidt-Pokrzywniak *et al.* (2009) found little evidence of associations between measures of personal sun exposure and ocular melanoma.]

(c) Internal cancers

Five case–control studies (Table 2.16) have reported on the association of the use of artificial tanning devices and cancer of the breast (one study), non-Hodgkin lymphoma (four studies), Hodgkin lymphoma (three studies), multiple myeloma (two studies), and lymphoproliferative syndrome (one study) (Smedby *et al.*, 2005; Hartge *et al.*, 2006; Knight *et al.*, 2007; Boffetta *et al.*, 2008; Grandin *et al.*, 2008). In all the studies of non-Hodgkin lymphoma, the risk was lower in people who had used artificial tanning devices than in those who had not; in two there was also a dose–response relationship across exposure categories with a P value for trend of ≤ 0.01 (Smedby *et al.*, 2005; Boffetta *et al.*, 2008). Odds ratios were also below unity for cancer of the breast (Knight *et al.*, 2007) and for Hodgkin lymphoma (Smedby *et al.*, 2005; Boffetta *et al.*, 2008), with a significant dose–response relationship (P value for trend = 0.004) in one study of Hodgkin lymphoma (Smedby *et al.*, 2005). Confounding with exposure to natural sunlight cannot be ruled out as an explanation for these inverse relationships because none of the studies adjusted the results for sun exposure.

2.2.2 Welding

Six separate case–control studies (seven reports) and one meta-analysis have reported on associations between welding and risk of ocular melanoma (Table 2.17). All studies reported an odds ratio for ocular melanoma above unity in most categories of exposure to welding. Seddon *et al.* (1990) reported on two sets of cases and controls and found an increased risk in only one of them. Lutz *et al.* (2005) found an increased risk with a "history of at least 6 months' employment in welding or sheet metal work," but not for "working with welding"; the increase observed was restricted to the French component of the study, which Guénel *et al.* (2001) had previously reported. The strongest associations of welding with ocular melanoma (although based on small numbers) were reported in those studies that restricted the exposure definition to "work as a welder," i.e. not including being in proximity to welding (Tucker *et al.*, 1985; Siemiatycki, 1991; Guénel *et al.*, 2001; Lutz *et al.*, 2005). Several studies showed evidence of dose–response relationships (Holly *et al.*, 1996; Guénel *et al.*, 2001; Vajdic *et al.*, 2004) with duration of employment or of use.

The meta-analysis (Shah *et al.*, 2005) estimated a meta-relative risk of 2.05 (95%CI: 1.20–3.51) for welding, using a random-effects model. [The Working Group noted that this study included results from Ajani *et al.* (1992), which overlap with those from case–control Series 1 of Seddon *et al.* (1990), and did not include those from the case–control Series 2 of Seddon *et al.* (1990). It also did not include results from Siemiatycki (1991).]

2.3 UVA, UVB, and UVC

Epidemiology has little capacity to distinguish between the carcinogenic effects of UVA, UVB, and UVC. UVC is not present in natural sunlight at the surface of the earth and is therefore not

relevant; in almost all circumstances humans are exposed simultaneously to UVB and UVA, and UVB and UVA exposures vary more or less in parallel (see Section 1). Several epidemiological approaches have been used in an attempt to distinguish the effects of UVA and UVB on skin cancer risk. Their major focus has been to assess whether solar UVA exposure contributes to the increased risk of cutaneous melanoma, for which there is some conflicting evidence in experimental studies (see Section 4). These include studies on exposure to UVA for artificial tanning, effect of sunscreens on melanoma risk, and UVB phototherapy without associated exposure to PUVA (psoralen-UVA photochemotherapy).

PUVA is the combination of psoralen with UVA radiation, and is used in the treatment of psoriasis. PUVA has been reviewed previously by two IARC Working Groups and there is *sufficient evidence* that PUVA therapy is *carcinogenic to humans (Group 1*), causing cutaneous squamous cell carcinoma (IARC, 1986, 2012), and these studies will not be reviewed here.

2.3.1 Descriptive studies

Garland *et al.* (1993) noted that "rising trends in the incidence of and mortality from melanoma have continued since the 1970s and 1980s, when sunscreens with high sun protection factors became widely used." They related this observation to the fact that commonly used chemical sunscreens had blocked UVB but not UVA; and the possibility that by preventing erythema, sunscreens would permit extended sun exposure and thus substantially increase exposure to UVA. However, nearly half of the melanoma mortality increase between 1950–54 and 1990–94 in the USA in white men and more than half of that in white women had occurred by 1970–74, with only a minor upward perturbation in the trend after 1970–74. Thus, there probably was not a close association between increasing use of sunscreens blocking UVB and the increasing risk of melanoma.

Moan *et al.* (1999) plotted the relationships of UVB and UVA irradiances and incidence rates of cutaneous basal cell carcinoma, squamous cell carcinoma and melanoma using data from Australia, Canada, the Czech Republic, Denmark, Finland, Iceland, Norway, New Zealand, Sweden, Scotland, USA, and the United Kingdom. As expected, all were inversely related to latitude but the slope of the fitted linear relationship was numerically smaller for UVA than for UVB, and for melanoma than for basal cell carcinoma and squamous cell carcinoma. Estimates of biological amplification factors (relative increase in risk per unit increase in exposure) based on these slopes for UVB were, in men and women respectively, 2.8 and 2.8 for basal cell carcinoma, 3.1 and 2.9 for squamous cell carcinoma, and 1.3 and 1.0 for melanoma. Those for UVA and melanoma were 3.8 and 2.9, respectively, suggesting that UVA may play a significant role in the induction of melanomas.

2.3.2 Exposure to artificial UVA for tanning purposes

Early artificial tanning devices emitted both UVB and UVA. UVB emissions were subsequently reduced relative to UVA, presumably to reduce skin cancer risk, but have been increased again recently to mimick the sun and to produce longer lasting tans (see Section 1). In principle these periods of different relative exposures to UVA and UVB during artificial tanning could be used to evaluate the relative effects of UVA and UVB on skin cancer risk. Veierød *et al.* (2003, 2004) attempted this analysis in a cohort study of Norwegian and Swedish women who had reported their use of a sunbed or sunlamp (solarium) in different age periods on entry to the cohort. They defined three subgroups of women: those who had used solaria in the period 1963–83 (mainly before they became mainly

Table 2.16 Associations of use of artificial tanning devices with cancers of internal tissues[a]

Reference, study location and period	Cancer type	Exposure assessment	Exposure categories	Relative risk
Knight *et al.* (2007), Canada, 2003–04	Breast cancer	Telephone interview	**Ever sunlamp use**	
			Age 10–19	
			No	1.0
			Yes	0.81 (0.57–1.14)
			Age 20–29	
			No	1.0
			Yes	0.88 (0.66–1.18)
			Age 45–54	
			No	1.0
			Yes	0.84 (0.64–1.11)
Hartge *et al.* (2006), USA, 1998–2000	Non-Hodgkin lymphoma	Self-administered questionnaire and computer assisted personal interview	*Use of sunlamp or tanning booth*	
			Never	1.0
			Ever	0.88 (0.66–1.19)
			Only after age 20	0.97 (0.69–1.37)
			Before age 20	0.72 (0.45–1.14)
			< 5 times	0.78 (0.46–1.32)
			5–9 times	0.90(0.52–1.58)
			10+ times	0.90 (0.61–1.30)
Smedby *et al.* (2005), Denmark and Sweden, 1999–2002	Non-Hodgkin lymphoma	Computer assisted telephone interview	*Solaria/sun lamp use*	
			Never	1.0
			< 10 times	1.0 (0.9–1.2)
			10–49 times	0.9 (0.8–1.0)
			50 times or more	0.8 (0.7–1.0)
	Hodgkin lymphoma		Never	1.0
			< 10 times	0.8 (0.6–1.0)
			10–49 times	0.7 (0.5–0.9)
			50 times or more	0.7 (0.5–0.9)

Table 2.16 (continued)

Reference, study location and period	Cancer type	Exposure assessment	Exposure categories	Relative risk
Boffetta *et al.* (2008), France, Germany, Ireland, Italy, and Spain, 1998–2004	Non-Hodgkin lymphoma	Interviewer administered questionnaire	*Sunlamp use*	
			Never	1.0
			1–24 times	0.79 (0.59–1.04)
			25 times or more	0.69 (0.51–0.93)
	Hodgkin lymphoma		Never	1.0
			1–24 times	0.86 (0.53–1.39)
			25 times or more	0.93 (0.57–1.50)
	Multiple myeloma		Never	1.0
			1–24 times	0.76 (0.41–1.41)
			25 times or more	1.10 (0.59–2.05)
Grandin *et al.* (2008), France, 2000–04	Non-Hodgkin lymphoma	Self and interviewer administered questionnaires	*Aesthetic use of artificial UV radiation*	
			No	1.0
			Yes	1.1 (0.7–1.7)
			Regularly	0.5 (0.2–1.3)
			Occasionally	1.4 (0.8–2.3)
	Hodgkin lymphoma		No	1.0
			Yes	1.6 (0.7–3.6)
			Regularly	0.6 (0.1–3.3)
			Occasionally	2.2 (0.9–5.5)
	Lymphoproliferative syndrome		No	1.0
			Yes	1.5 (0.7–3.5)
			Regularly	0.9 (0.2–4.6)
			Occasionally	1.9 (0.7–4.7)
	Multiple myeloma		No	1.0
			Yes	1.2 (0.4–3.6)
			Regularly	0.8 (0.1–7.3)
			Occasionally	1.4 (0.4–4.9)

[a] In none of these studies was potential confounding with exposure to natural sunlight controlled in the analysis

yr, year or years

Table 2.17 Case–control studies on welding and ocular melanoma

Reference, study location and period	Cases	Controls	Exposure assessment	Exposure categories	Relative risk	Adjustment for potential confounders	Comments
Tucker *et al.* (1985), USA, 1974–79	439 White patients with intraocular melanoma confirmed histologically or from highly reliable ancillary studies; participation rate, 89%	419 White patients with detached retina not due to tumours; matched by age, sex, race, date of diagnosis; participation rate, 85%	Telephone interview with detailed information about medical history, family history, employment, exposure to environmental agents, sunlight; details from ophthalmologic examination and medical history abstracted from medical records; interview with next-of-kin for 17% of cases and 14% of controls, half of them with spouses	*Ever worked as a welder* No Yes	 1.0 10.9 (2.1–56.5)	Age, eye colour and history of cataract	
Seddon *et al.* (1990), Massachusetts, USA, 1984–87	White patients with clinically or histologically confirmed melanoma of the choroid, ciliary body or both, identified at local hospital or by mailing to ophthalmologists, diagnosed within previous yr; age range, 17–88 yr, mean, 57 yr; participation rate, 89% (see comments)	Series 1: selected by random digit dialing, matched 2:1 by sex, age, city of residence, 85% response rate Series 2: living sibling of cases, up to 4 siblings per case, median, 2; participation rate, 97%	Telephone interview including constitutional factors, ocular and medical histories, and exposure to environmental factors including natural and artificial sources of UV	**Case–control series 1** *Exposure to welding arc* No Yes **Case–control series 2** *Exposure to welding arc* No Yes	 1.0 1.3 (0.5–3.1) 1.0 0.9 (0.6–1.5)	Age, eye and skin colour, moles, ancestry, use of sunlamps, eye protection, outside work, fluorescent lighting, southern residence, yr of intense exposure	Series 1: population-based, 197 cases and 385 controls Series 2: not population-based, 337 cases and 800 sibling controls. 140 cases were included in both series. Result for case series 1 also was reported by Ajani *et al.* (1992) using the same numbers but with fewer covariates in the logistic regression model (see below).

Table 2.17 (continued)

Reference, study location and period	Cases	Controls	Exposure assessment	Exposure categories	Relative risk	Adjustment for potential confounders	Comments
Siemiatycki (1991), Montreal, Canada, 1979–85	[33] incident male cases of uveal melanoma, aged 35–70 yr, histologically confirmed; response rate, 69.6%	533 population controls; participation rate, 72%	Personal interview and collection of detailed occupational history	*Occupational exposure to arc welding fumes* No Yes	 1.0 8.3 (2.5–27.1)	Age, family income, ethnicity, respondent type, cigarette and alcohol indexes	4 exposed cases
Ajani *et al.* (1992), USA, 1984–87	197 White patients with uveal melanoma, histologically confirmed, diagnosed during the previous yr, residents of 6 New England States; mean age, 59.2 yr, range 18–88 yr; participation rate, 92%	385 controls selected by random digit dialling, matched 2:1 for age (+/– 8 yr), sex, telephone exchange; mean age, 58.3 yr, range 19–88 yr; response rate, 85%	Telephone interview with occupational history and exposures related to work occurring 15 yr before the interview.	*Exposure to welding arc* No Yes	 1.0 0.99 (0.48–2.05)	Age, ancestry, skin colour, moles, use of sunlamps, past income level	Same population as in study by Seddon *et al.* (1990) in case series 1 using the same numbers but with more covariates in the logistic regression model (see above).
Holly *et al.* (1996), USA, 1978–87	221 male White patients with histologically confirmed uveal melanoma, age 20–74 yr residing in 11 States; participation rate, 93%	447 controls selected by random digit dialling, matched 2:1 by age (5-yr age group) and residential area; interview rate, 77%	Interviewer administered questionnaire with demographic and phenotypic caracteristics, occupational history, exposure to chemicals.	*Welding** No Yes *Years from start of occupation to diagnosis or interview* ≤ 10 11–29 ≥ 30	1.0 2.2 (1.3–3.5) 1.2 (0.2–6.6) 1.5 (0.7–3.0) 2.1 (1.1–4.0)	Age, number of large nevi, eye colour, tanning or burning response to 30 min. sun exposure in the summer noond sun	* Self welding or in proximity to others for > 3 h a wk for > 6 mo

Table 2.17 (continued)

Reference, study location and period	Cases	Controls	Exposure assessment	Exposure categories	Relative risk	Adjustment for potential confounders	Comments
Guénel *et al.* (2001), France 1995–96	50 cases (29 men and 21 women) identified from records of local pathology departments for surgery, and from 2 cancer treatment centres in France; diagnosis confirmed by pathologists or ophthalomogic report; participation rate, 100%	479 (321 men, 158 women) controls selected from electoral rolls, frequency matched by age (5-yr interval), sex and study area; participation rate, 76%	Face-to-face interview, or occasionally telephone interview	*Worked for six mo or more as a welder or sheet metal worker* No Yes *Duration of employment as a welder* Less than 20 yr 20 yr or more	 1.0 7.3 (2.6–20.1) 5.7 (1.6–19.8) 11.5 (2.4–55.5)	Age	Data also included in analysis of Lutz *et al.* (2005). Results shown here for men only; only one woman in this study had worked as a welder and she was a case.
Vajdic *et al.* (2004), Australia, 1996–98	246 White Australian residents, aged 18–79 yr, with histopathologically or clinically diagnosed melanoma originating in the choroid, ciliary body; participation rate, 87% among those eligible	893 controls matched 3:1 by age, sex, residence, selected from electoral rolls; participation rate, 47%	Self-administered questionnaire, and telephone interview regarding sun exposure, sun-protective wear and quantitative exposure to welding equipment and sunlamps	*Own welding* Never Ever *Duration of use* 0.1–4.0 yr 4.1 to 22.0 yr > 22 yr *Lifetime hours of use* 0.1–52.0 52.1–858.0 > 858 *Age at first use* > 20 yr ≤ 20 yr	 1.0 1.2 (0.8–1.7) 0.8 (0.4–1.4) 1.2 (0.7–2.2) 1.7 (1.0–2.7) 1.1 (0.6–1.9) 1.4 (0.8–2.3) 1.1 (0.6–1.9) 1.2 (0.8–1.9) 1.2 (0.7–1.9)	Age, sex, place of birth, eye colour, ability to tan, squinting as a child and total personal sun exposure at 10, 20, 30, and 40 yr of age	

Table 2.17 (continued)

Reference, study location and period	Cases	Controls	Exposure assessment	Exposure categories	Relative risk	Adjustment for potential confounders	Comments
Lutz *et al.* (2005), Denmark, Latvia, France, Germany, Italy, Sweden, Portugal, Spain, and the United Kingdom, 1995–96	292 incident cases of uveal melanoma, identified from ophthalmologic departments, hospital records or cancer registries aged 35–69 yr; participation rate, 91%	2062 population controls selected from population registers, electoral rolls or practitioner, frequency matched by region, sex and 5-yr birth cohorts; participation rate, 61%; 1094 cancer controls randomly selected from colon cancer patients; participation rate, 86%	Questionnaire with face-to-face or telephone interview	*Worked for six mo or more as a welder or sheet metal worker* No Yes *Working with welding* No Yes	 1.0 2.2 (1.2–4.0) 1.0 0.9 (0.6–1.5)		Data from France reported in analysis of Guénel *et al.* (2001). Results shown here for men only; only one woman in this study had worked as a welder and was a case.

d, day or days; h, hour or hours; min, minute or minutes; mo, month or months; wk, week or weeks; yr, year or years

UVA-emitting), the period 1979–91 (mainly after solaria were designed to emit mainly UVA) or the period 1975–87 (covering both categories of solarium) when they were 20–29 years of age. The odds ratios for solarium use in these subgroups were 3.75 (95%CI: 1.73–8.13) for use in 1963–83, 3.19 (95%CI: 1.22–8.32) for use in 1979–91, and 1.28 (95%CI: 0.46–3.60) for use in 1975–87. These results show little difference between those exposed in the earlier and later periods of solarium use. [The Working Group noted that only seven cases of melanoma were observed in each of these periods, and there was little statistical power to see a difference.] A recent meta-analysis of use of artificial tanning devices and skin cancer (IARC, 2007b) reported that the relative risks of melanoma associated with ever use of a sunbed or sunlamp did not vary with year of publication of a study or the first year of a study period, where available. [The Working Group noted that the most relevant time metric would be year of first reported use of a sunbed or sunlamp, rather than the year of publication or first year of study period.]

2.3.3 Use of sunscreens and risk for melanoma

Initially, sunscreens contained only UVB absorbers; more recently they have covered a broader spectrum with the addition of UVA reflectors or absorbers, although many are still less effective against the higher wavelengths of UVA than they are against UVB (see Section 1). Recent meta-analyses of published observational studies of sunscreen and melanoma, each including slightly different subsets of studies, have found meta-relative risks close to unity with highly significant heterogeneity among studies: 1.11 (95%CI: 0.37–3.32) with a *P* value for heterogeneity < 0.001 (Huncharek & Kupelnick, 2002); 1.0 (95%CI: 0.8–1.2) with a *P* value for heterogeneity < 0.001 (Dennis *et al.*, 2003); and 1.2 (95%CI: 0.9–1.6) with a *P* value for heterogeneity < 0.0001 (Gorham *et al.*, 2007). [The Working Group noted that although these observations might be explained by a lack of effectiveness of early sunscreens against higher wavelengths of UVA, there are other possible, and probably more plausible, explanations. First, there is undoubted positive confounding between sunscreen use and sun exposure, and probably also sun sensitivity. Although this confounding can, in principle, be dealt with by adjustment for sun exposure and sun sensitivity in multiple variable models of the association of sunscreen use with melanoma risk, inaccurate measurement of these confounders limits the ability of modelling to control their confounding. Thus, residual confounding could easily explain the lack of protective effect of sunscreens seen in observational studies of melanoma (IARC, 2001). Second, there is clear evidence of adaptation to the use of sunscreens such that people who apply sunscreens before outdoor recreation may increase their duration of exposure to the sun (Autier *et al.*, 2007) so that their dose of erythemal UV radiation may not change. Thus, observed associations of sunscreens with risk of melanoma (or other skin cancers) in observational studies do not provide useful information regarding the relative effects of UVB and UVA on cancer risk.]

2.3.4 UVB phototherapy

UVB phototherapy is used to treat a variety of skin conditions. Lee *et al.* (2005) reviewed the literature and concluded that there was no evidence of an increased risk of skin cancer in those who had received UVB phototherapy as their only form of UV phototherapy. [The Working Group noted that only three cases of melanoma were identified among about 1000 who had received this therapy.]

Lim & Stern (2005) extended follow-up of 1380 patients with severe psoriasis who had been treated with variations of PUVA, methotrexate, UVB, topical tar, and ionizing radiation. In

patients who had less than 100 PUVA treatments, the incidence rate ratio for cutaneous squamous cell carcinoma with ≥ 300 UVB treatments was 0.81 (95%CI: 0.34–1.93) for chronically sun-exposed sites, and 2.75 (95%CI: 1.11–6.84) for rarely to intermittently sun-exposed sites. The corresponding values for basal cell carcinoma were 1.38 (95%CI: 0.80–2.39) for chronically sun-exposed sites and 3.00 (95%CI: 1.30–6.91) for intermittently sun-exposed sites. [The Working Group noted that the possibility that the observed effect required interaction with PUVA or another treatment for psoriasis cannot be ruled out in this study.] Hearn *et al.* (2008) described the results of follow-up of 3867 patients who had received narrow-band UVB phototherapy, a quarter of whom had also received PUVA. In comparison with data from the Scottish Cancer Registry, there were near 2-fold increases in the risk of first squamous cell carcinoma [two observed cases] and of first basal cell carcinoma [14 observed cases] for treatment with narrow-band UVB only, but their 95% confidence intervals included unity. For melanoma, the relative risk was just below 1. For those who had more than 100 UVB therapy treatments, the risks, relative to those who received 25 or less such treatments, were 1.22 (95%CI: 0.28–4.25) for basal cell carcinoma, 2.04 (95%CI: 0.17–17.8) for squamous cell carcinoma, and 1.02 (95%CI: 0.02–12.7) for melanoma. Two previous small studies of narrow-band UVB, of 126 (Weischer *et al.*, 2004) and 484 patients (Black & Gavin, 2006), observed only one skin cancer between them, an in-situ melanoma, in less than 10 years of follow-up.

Given the few cases of skin cancer so far reported in patients given UVB phototherapy as their only form of phototherapy, the statistical power of currently available studies to detect other than a large increase in relative risk of any type of skin cancer with this therapy, and, therefore, of UVB specifically is weak.

2.4 Synthesis

2.4.1 Solar radiation

In Caucasian populations, both basal cell carcinoma and squamous cell carcinoma are strongly associated with solar radiation, as measured by indicators of accumulated solar skin damage (e.g. increasing age, especially for squamous cell carcinoma; and presence of actinic keratoses), and secondarily by recalled episodes of acute solar skin damage (multiple sunburns).

The causal association of cutaneous melanoma and solar exposure is established, this link has become clearer in the last decade or so through the observation of the site-specific heterogeneity of melanoma, the lower-than-average phenotypic risk for skin carcinogenesis among outdoor workers, and the recognition that the different associations of melanoma with sun exposure observed among Caucasian people at different latitudes around the world correlate with marked variations in sun exposure opportunity and behaviour.

Five case–control studies of cancer of the lip have been published. The three earliest studies found apparent increases in risk with outdoor work, but use of tobacco could not be ruled out as an explanation for these associations. The two later studies both took account of possible confounding of outdoor exposure with tobacco smoke. One of them, in women, showed increased risks for cancer of the lip with several measures of exposure, together with strong and moderately consistent dose–response relationships. The other, in men, found no increase in risk with leisure time or holiday sun exposure but a substantial increase in risk with cumulative exposure during outdoor work during the summer months, without any indication of dose–response across four categories. This lack of dose–response suggests bias rather than a causal effect.

Four case–control studies reported at least one result each suggesting that sun exposure is associated with conjunctival intraepithelial neoplasia or squamous cell carcinoma of the eye. Only one study was exclusively of conjunctival squamous cell carcinoma; in this study and another, the relevant exposure variables (office work and cultivating the fields) were only indirect measures of sun exposure. A very large difference between cases and controls in prevalence of conjunctival solar elastosis in another study raised concerns about possible bias. The remaining study reported a strong association of ocular surface dysplasia with solar keratoses and increasing risk with increasing duration of residence at ≤ 30° south latitude. However, only 22% of its cases had conjunctival squamous cell carcinoma.

Two out of three studies that examined the distribution of choroidal melanomas found them to be concentrated in the central area or the macula area of the choroid, which coincides with the estimated distribution of light in the retinal sphere. Of ten case–control studies of ocular melanoma published from 1985 to 2009, four reported statistically significant associations of one or more measures of sun exposure with ocular melanoma. In two studies, these associations were with the latitude of birth or of residence in early life, with some inconsistency between them. In the other two, which were more recent and had better measures of exposure than many previous studies, one study related only to occupational sun exposure and showed a strong association with a dose–response relationship, and the strongest association seen in the other was with occupational sun exposure and showed evidence of a dose–response relationship. These results relate principally to choroid and ciliary body melanomas (the dominant types). Two studies reported results consistent with a positive association of small numbers of iris melanomas with sun exposure. One study with a small number of conjunctival melanomas found no such association.

The associations of sun exposure with several internal cancers have been investigated in case–control and cohort studies, generally with the hypothesis that sun exposure might be protective against such cancers. The cancers investigated included cancer of the colorectum (two studies), of the breast (five studies), of the ovary (one study), of the prostate (four studies), and several cancers of the lymphatic tissue, principally non-Hodgkin lymphoma and Hodgkin disease (15 studies). Exposure metrics used in these studies included residential or occupational ambient solar radiation, recreational or non-recreational sun exposure, recent and lifetime sun exposure, and sun-related behaviour. The results were mostly inconsistent.

2.4.2 Artificial sources of UV

(a) Tanning appliances

Two meta-analyses investigated the association between indoor tanning and skin cancers.

The summary relative risk for ever versus never use of indoor tanning facilities was significantly increased for melanoma, with no consistent evidence for a dose–response relationship. All studies that examined age at first exposure found an increased risk for melanoma when exposure started before approximately 30 years of age, with a summary relative risk estimate of 1.75.

For squamous cell carcinoma, the three available studies found some evidence for an increased risk, especially when age at first use was below 20 years. Studies on basal cell carcinoma did not support an association with use of indoor tanning facilities.

Four case–control studies reported on associations between artificial tanning devices and ocular melanoma. Each observed an increase in risk of ocular melanoma in the highest category of exposure to these devices, and there were

indications of a dose–response relationship in three of the studies. In two studies, the risk was higher in people who began exposure before 20 years of age than those who began after this age. Possible confounding with natural sun exposure was explicitly addressed in two of the studies.

Five studies reported on the association of use of indoor tanning devices with internal cancers, specifically breast cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, and multiple myeloma. Most studies found little evidence of an association. Two studies observed inverse associations between the use of internal tanning devices and non-Hodgkin lymphoma, and one study with Hodgkin lymphoma. Possible confounding with exposure to natural sunlight cannot be ruled out in any of these studies.

(b) Welding

Six case–control studies reported on the association between welding and ocular melanoma. All found evidence of a positive association, which was strong in three studies, each of which related specifically to working as a welder or sheet metal worker (other studies included working in proximity to welding in the definition of exposure). In each of three studies in which it was examined, there was evidence of a dose–response relationship.

2.4.3 UVA, UVB, UVC

Several sources of evidence were examined to see if the carcinogenic effects of UVA and UVB could be distinguished: descriptive studies of skin cancer have shown that the slope of latitude variation in incidence of melanoma is less than that in incidence of squamous cell carcinoma and basal cell carcinoma, suggesting that melanoma incidence is more influenced by UVA irradiance than are squamous cell carcinoma and basal cell carcinoma. Present data on the risk for melanoma associated with the of UV-emitting tanning devices show little evidence that it varies with the relative contributions of UVB and UVA emitted from the devices. There is little or no evidence to suggest that the use of sunscreens that block mainly UVB radiation increased the risk for melanoma. Studies of patients exposed exclusively to UVB phototherapy show weak evidence of an increase in risk of squamous cell carcinoma and basal cell carcinoma, based on a few cases.

3. Cancer in Experimental Animals

The previous *IARC Monograph* on solar and ultraviolet radiation concluded that there was *sufficient evidence* for the carcinogenicity of solar radiation, broad-spectrum ultraviolet radiation, ultraviolet A, ultraviolet B and ultraviolet C radiation in experimental animals (IARC, 1992).

The experimental induction of skin cancers in mice following exposure to a mercury-arc lamp was first reported by Findlay (1928). Initially, haired albino mice were used, but hairless Skh-1 (albino) and Skh-2 (pigmented) immunocompetent mice and eventually immunodeficient nude mice or transgenic mice are now used.

Hundreds of studies have clearly established the carcinogenic activity of UVR in mice. The action spectrum for ultraviolet-induced skin carcinogenesis in albino hairless mice has been determined and shows a peak in the UVB range (280–315 nm) and a steep decrease in the UVA range (315–400 nm). However, while the induction of non-melanoma skin cancer is regularly obtained in mice, the induction of melanoma was exceptional.

Solar radiation was tested for carcinogenicity in a series of studies in mice and rats. Large numbers of animals were studied (600 rats and 2000 rats and mice), and incidences of squamous-cell carcinoma of the skin and of the conjunctiva were clearly increased in most of the surviving mice and rats (Roffo, 1934, 1939; IARC, 1992).

Broad-spectrum UVR (solar-simulated radiation and ultraviolet lamps emitting in the entire UV wavelength range) was tested for carcinogenicity in two large studies in mice (Grady *et al.*, 1943; Blum, 1959; IARC, 1992), several studies in rats, and one study in hamsters and guinea-pigs (Freeman & Knox, 1964; IARC, 1992). Incidences of squamous-cell carcinoma of the skin and of the cornea/conjunctiva were clearly increased in rats and mice. Hamsters developed malignant tumours of the cornea. No eye tumours were observed in guinea-pigs.

In several studies in mice exposed to sources emitting mainly UVA radiation, squamous-cell carcinomas of the skin were clearly induced. Both short-wavelength UVA (UVA2, 315–340 nm) and long-wavelength UVA (UVA1, 340–400 nm) were effective (IARC, 1992).

In several studies in mice exposed to sources emitting mainly UVB radiation, the predominant tumour type was squamous-cell carcinoma of the skin. Skin papillomas were observed in one study in rats and one study in hamsters. Invasive melanomas were induced in two experiments in platyfish-swordtail hybrid fish. In two out of three studies in opossums (*Monodelphis domestica*), squamous-cell carcinomas were shown to develop; in one of these three studies, malignant tumours of the cornea were observed and melanocytic neoplasms of the skin were reported in another one (IARC, 1992).

In some studies in mice exposed to sources emitting mainly UVC radiation, squamous-cell carcinomas of the skin were clearly induced. In one study in rats, keratoacanthomas of the skin were observed. In none of the experiments involving UVC was it possible to exclude completely a contribution of UVB, but the size of the effects observed indicate that they cannot be due to UVB alone (IARC, 1992).

UVR has been studied in protocols involving two-stage chemical carcinogenesis. UVR has been reported to exert many effects on the carcinogenic process, including initiation, promotion, cocarcinogenicity and even tumour inhibition. Chemical immunosuppressive agents have been shown to enhance the probability of developing UVR-induced tumours in mice (IARC, 1992).

Studies released since the previous *Monograph* are summarized below.

3.1 Non-melanoma skin cancer

See Table 3.1

3.1.1 Mouse

Most of the recent studies were not designed to test whether or not the radiation used was carcinogenic per se but to investigate the process of UV carcinogenesis, or to test enhancement or inhibition of photocarcinogenicity by drugs and chemical agents. Methods for testing photocarcinogenicity have been standardized to meet the requirements of regulatory agencies (Forbes *et al.*, 2003; Sambuco *et al.*, 2003).

Recent studies have mainly focused on the mechanisms of UV-induced carcinogenesis and have used specific strains of mice. Sencar mice were derived by selective breeding for susceptibility to chemical carcinogens. They are more sensitive th an other mouse strains to a variety of chemical initiators and promoters (e.g. 7,12-dimethylbenz(a)anthracene (DMBA) and 12-*o*-tetradecanoylphorbol-13-acetate (TPA)) as well as to UV radiation. Sencar mice have been widely used to study multistage skin carcinogenesis. Using these mice, squamous cell carcinomas (SCCs) and malignant spindle cell tumours (SCTs) appeared within 16-18 weeks and 30 weeks of irradiation respectively (Tong *et al.*, 1997, 1998). Tong *et al.* (1997, 1998) have also shown that alterations in the *Tp53* gene are frequent events in SCCs induced by chronic UV exposure in Sencar mouse skin, and that overexpression of H-Ras-p21 in conjunction with aberrant expression of keratine K13 is a frequent event in UVR-induced SCCs in Sencar mouse

Table 3.1 Non-melanoma skin cancers induced in mice and opossum exposed to ultraviolet radiation

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, Sencar (F) up to 60 wk Tong *et al.* (1997, 1998)	63, 10 controls exposed to UVR from Dermalight 2001 sun lamp (3 ×/wk, 8 min each time, for 18 wk). Total UVB dose = 139.2 J/m^2 UVR-induced skin tumours biopsied when 1.5 × 1.5 mm for histological examination, immunohistochemical detection of p53, Hras-p21 and keratin K13 expression, and DNA isolation. Skin biopsies from untreated control mice.	Among all 73 tumours biopsied: 4% papillomas, 54% SCCs, 36% spindle cell tumours (SCT), 6% dermal fibromas and BCCs. *Tp53* mutations (exon 5) in 10/37 (27%) of SCCs and 12/24 (50%) of SCTs Hras-p21 expressed in 24/36 (67%) of SCCs but not in normal skin SCTs or UV-exposed skin. Co-expression with K13 in 47% SCCs.	SCCs begin to appear 18 wk after initiation of UV irradiation. Among the 8 mutations, 3/8 (38%) were C → T changes (codons 146 and 158)-a typical "UV-signature" mutation-and 3/8 (38%) were C → A changes (codons 150 and 193), which is also a frequent mutation pattern induced by UVR.
Mice, Tg.AC (F) 20 wk Trempus *et al.* (1998)	10 animals/group 3 exposures (every other d) on shaved back 2.6 to 43.6 kJ/m^2 (cumulative). FS40T12 sunlamp (60% UVB, 40% UVA, total output 1.6 mW/cm^2)	Papillomas develop from 4 wk in a dose dependent manner, that progress to malignancy in the high UV exposure groups: - 21.8 kJ/m^2: 6/10 (60%) mice with SCC or SCT at 23–30 wk - 43.6 kJ/m^2: 5/9 (55%) mice with SCC or SCT at 18–30 wk	UV-induced tumours harbour few *Tp53* mutations. In contrast, UV-exposed skin show *Tp53* activation in the basal layer.
Mice, PKCε transgenic FVN/B starins 215, 224 sex and duration (NR) Wheeler *et al.* (2004, 2005)	number/group at start (NR) exposed to UVR (2 kJ/m^2) from a bank of 6 Kodacell filtered FS40 sunlamps, 3 ×/wk, up to 38 wk.	SCC develop earlier and more frequently in transgenic mice than in normal littermates. Up to 60% mice developed SCC by 38 wk.	PKCε overexpression sensitizes skin to UVR-induced cutaneous damage and development of squamous cell carcinoma possibly at the promotion step of carcinogenesis, and this is probably accomplished by promoting the enhanced induction and release of specific cytokines such as TNFα.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, Skh-1 (F) 26 wk Rossman *et al.* (2002)	15 animals/group 1.7 kJ/m^2 solar UVR (mostly UVB) 3 ×/wk, ± 10 mg/L sodium arsenite in drinking-water for 26 wk	2.4-fold increase in yield of tumours in mice given arsenite compared with mice given UVR alone. Tumors (mostly SCCs) appeared only in UVR treated mice, and only on the exposed area (backs) of the mice.	Low (non toxic) concentrations of arsenite can enhance the onset and growth of malignant skin tumours induced by a low (non erythemic) dose of UVR in mice. Tumors occurring in mice given UVR plus arsenite appeared earlier (time to first tumour < 60 d *vs* > 80 d after UVR exposure alone) and were much larger than in mice given UVR alone.
Mice, Skh-1 (F) 182 d Burns *et al.* (2004)	Number at start (NR) Mice were fed sodium arsenite continuously in drinking-water starting at 21 d of age at concentrations of 0.0, 1.25, 2.5, 5.0, and 10 mg/L. At 42 d of age, solar spectrum UVR exposures were applied every other d (3 ×/wk) to the dorsal skin at 1.0 kJ/m^2 per exposure until the experiment ended at 182 d.	More than 95% of the tumours were SCCs. Only UVR irradiated mice developed locally invasive SCCs. Mice exposed only to UVR: 2.4 ± 0.5 cancers/mouse at 182 d. Arsenite enhanced the UVR-induced cancer yield in a linear pattern up to a peak of 11.1 ± 1.0 cancers/mouse at 5.0 mg/L arsenite (i.e. peak enhancement ratio: 4.63 ± 1.05). A decline occurred to 6.8 ± 0.8 cancers/mouse at 10.0 mg/L arsenite.	This study was designed to establish dose–response relationship for cancer enhancement in a new mouse skin model using arsenite in drinking-water in combination with chronic topical UVR exposures Arsenite alone and UVR alone induced epidermal hyperplasia, but the combined exposures have a greater than additive effect. 50% cancer incidence occurred at 140 d in the UVR only group, whereas in the highest response group (UVR plus 5.0 mg/L), 50% incidence occurred at 109 d.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, SK1-hrBD (F) 6 mo Uddin *et al.* (2005)	15-30 animals/group Weanling mice were exposed to solar spectrum UVR alone (1 kJ/m^2 3 x/wk) or to UVR + sodium arsenite (5 mg/L in drinking-water) and fed laboratory chow supplemented or not with Vitamin E (α-tocopheryl acetate, 62.5 IU/kg diet) or organoselenium (1,4-phenylene*bis*(methylene) selenocyanate (*p*-XSC), 10 mg/kg diet) for 26 wk.	~95% of the tumours were SCCs. Few papillomas, fibrosarcomas and premalignant hyperplasias were also seen. Average tumour/mouse: UVR–3.60 UVR + Vitamin E–2.53 UVR + p-XSC–3.33 UVR + arsenite–7.0 UVR + arsenite + Vit E–3.27 UVR + arsenite + p-XSC–3.40	The first tumour appeared in mice exposed to UVR + arsenite at 10 wk after beginning UVR exposure, whereas the first tumour in mice exposed to UVR alone appeared after 12 wk of UVR exposure. Mice exposed to UVR plus arsenite exhibited an enhanced tumour yield (1.94-fold) compared with mice exposed to UVR alone. Vitamin E and p-XSC reduce tumour yield in mice given UVR + arsenite (2.1 and 2.0 fold respectively). Vitamin E but not p-XSC reduces tumour yield induced by UVR alone
Mice, SK1-hrBR (F) 182 d Davidson *et al.* (2004)	12-19 animals/group Animals were exposed to: - UVR alone (1.2 kJ/m^2, from 3 FS 20 and 1 F-20T12-BL lamps; 85% UVB, 4% UVA), - K_2CrO_4 alone (2.5 and 5.0 ppm in drinking-water), - or combination of UVR + K_2CrO_4 (0.5, 2.5, and 5.0 ppm). Exposure to UV started 1 mo after the initial chromate exposure, 3 ×/wk (every other d) for the first 3 mo, then 2 x /wk (Monday and Wednesday) for 3 further mo.	No tumour in untreated mice and mice treated with chromium alone. Dose-dependent increase in the number of skin tumours (SCCs > 2 mm) in mice exposed to K_2CrO_4 and UV compared with mice exposed to UV alone: 2.63 and 5.02 tumours/ mouse for 2.5 and 5.0 ppm K_2CrO_4 *vs* 0.8 ($P < 0.05$).	Proportion of malignant tumours per mouse: - UV alone: 0.55. - UVR + 5 ppm K_2CrO_4: 0.73

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, SK1-hrBD (M, F) 6 mo Uddin *et al.* (2007)	10 animals/group Weanling mice were exposed to: - UVR (1.0 kJ/m^2, 3 ×/wk) for 26 wk, - UVR + 2.5 or 5.0 ppm potassium chromate, - UVR + 20, 100 or 500 ppm nickel chloride in drinking-water. Vitamin E or selenomethionine was added to the laboratory chow for 29 wk beginning 3 wk before the start of UVR exposure.	96% of the tumours were SCCs and 4% were papillomas Cancers/mouse: - Male: UVR: 1.9 ± 0.4 UVR + 2.5 ppm K_2CrO_4: 5.9 ± 0.8 UVR + 5 ppm K_2CrO_4: 8.6 ± 0.9 - Female UVR: 1.7 ± 0.4 UVR + 20 ppm $NiCl_2$: 2.8 ± 0.9 UVR + 100 ppm $NiCl_2$: 5.6 ± 0.7 UVR + 500 ppm $NiCl_2$: 4.2 ± 1.0	Chromium and nickel significantly increase the UVR-induced skin cancer yield in mice. Chromate caused a more rapid cancer induction (percentage of mice with cancer) in mice given UVR plus chromate: at 18 wk of UVR exposure, 50% of mice given UVR alone developed at least one cancer compared to 80% of mice given UVR + 2.5 ppm chromate and 100% of mice given UVR + 5.0 ppm chromate. Final cancer incidence: – UVR: 80% - UVR + chromate (2.5 and 5.0 ppm): 100%. Neither vitamin E nor selenomethionine reduced the cancer yield enhancement by chromium.
Mice Skh:HR-1 hairless (F) 232 d Reeve *et al.* (1996)	15 animals/group Animals were: - pre-fed for 4 wk on diets designed to provide 20% by weight of fat, comprising 0.5%, l%, 15% or 20% polyunsaturated sunflower oil (balance: hydrogenated cottonseed oil), - exposed to an incremental SSUV radiation regime for 10 wk, 5 d per wk, cumulative doses 111 J/m^2 UVB and 2 106 kJ/m^2 UVA. Feeding of the prepared diets continued until d 232 from commencement of the UV irradiation, when the experiment was terminated.	First tumours appear - by d 84 in mice fed the highest polyunsaturated fat, - by d 113 in mice fed the lowest polyunsaturated fat. CHS reactions in those groups supporting the highest tumour loads (fed 15% or 20% polyunsaturated fat), were significantly suppressed in comparison with the mice bearing smaller tumour loads (fed 0.5% or 10% polyunsaturated fat).	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Opossum *M. domestica* (M, F) 12–24 mo Sabourin *et al.* (1993), Kusewitt *et al.* (2000)	32-62 animals/group; 31 controls Shaved or unshaved animals exposed to 250–500 J/m^2, 3 x/wk, from a bank of FS40 lamps (280 to 400 nm), rate 4 W/m^2, for ≈1 yr. Immediately after UV irradiation, half of the animals are exposed to visible light (60 or 90 minutes) to remove pyrimidine dimers by photoreactivation. Controls exposed to photoreactivating light. To prevent photoreactivation, animals are maintained under red light.	Corneal tumours develop in nearly 100% animals. 154 tumours examined histologically: - 134 fibrosarcomas, - 18 haemangiosarcomas - 2 squamous cell carcinomas overlaying sarcomas Post-UVR exposure to photoreactivating light delays the onset of eye tumours and reduces overall tumour incidence	The South American opossum *Monodelphis domestica* possesses a photolyase enzyme that catalyses the monomerization of UV-induced pyrimidine dimers in DNA. UVR effects reduced by photoreactivation can be attributed to pyrimidine dimers formation.

BCCs, Basal Cell Carcinomas; CHS, Contact Hypersensitivity; d, day or days; h, hour or hours; min, minute or minutes; mo, month or months; NR, not reported; SCCs, Squamous Cell Carcinomas; SCTs, Spindle Cell Tumours; SSUV, simulated solar UV radiation; TNFα, tumour necrosis factor α; vs, versus; wk, week or weeks; yr, year or years

skin. Using the v-Ha-*ras* transgenic Tg.AC mouse line, sensitive to tumour promoters, Trempus *et al.* (1998) have shown that SCCs and SCTs developed within 18-30 weeks following the initial UVR exposure and that in contrast to other mouse stains used in photocarcinogenesis studies, few *Tp53* mutations were found in Tg.AC UV-induced skin tumours, although all Tg.AC tumours express the v-Ha-*ras* transgene. Other strains of transgenic mice, FVN/B strains 215 and 224, which overexpress protein kinase C epsilon (PKCε) and are highly susceptible to the induction of skin tumours by chemical carcinogens, also show increased susceptibility to the induction of skin tumours by UVR. *PKCε* transgenic mice were observed to be highly sensitive to the development of papilloma-independent metastatic squamous cell carcinomas elicited by repeated exposure to UVR (Wheeler *et al.*, 2004, 2005). In studies using Skh-1 mice, exposure to UVR induced a statistically significant increase in the number of malignant skin tumours per mouse, mainly SCCs when compared to controls (Rossman *et al.*, 2002; Burns *et al.*, 2004; Davidson *et al.*, 2004; Uddin *et al.*, 2005, 2007). Dietary polyunsaturated fat enhances the development of UVR-induced tumours in Skh-1 mice, this enhancement being mediated by a modulation of the immunosuppression caused by chronic UV irradiation (Reeve *et al.*, 1996).

3.1.2 Opossum (*Monodelphis domestica*)

Unlike laboratory rodents, a small marsupial, the South American opossum *Monodelphis domestica* possesses the ability to remove cyclobutane-pyrimidine dimers by photoreactivation, a light-dependent process of enzymatic monomerization. *M. domestica* is sensitive to UVR, and, when photoreactivation is prevented, develops primary tumours of the skin and eye in response to chronic exposure to low doses of UVR. Virtually all *M. domestica* chronically exposed to low doses of UVR develop primary corneal tumours; post-UVR exposure to photoreactivating light delays the onset of eye tumours and reduces overall tumour incidence (Sabourin *et al.*, 1993, Kusewitt *et al.*, 2000).

3.2 Melanoma

3.2.1 Transgenic mice exposed to ultraviolet radiation

See Table 3.2

In the mouse, wild-type animals are resistant to malignant melanoma (MM) development even when exposed to repeated treatments with ultraviolet radiation. Chronic UVR treatment regimens, however, have increased MM penetrance by up to 26% in mice carrying various transgenes capable of inducing spontaneous MM development, or melanocytic hyperplasia.

Inbred lines of transgenic Tyr-SV40E mice, having an integrated recombinant gene comprised of the tyrosinase promoter, expressed in pigment cells, and the simian virus 40 early-region transforming sequences spontaneously develop ocular and cutaneous melanomas (Bradl *et al.*, 1991). UVB irradiation of 2–4-day old Tyr-SV40E transgenic mice of either moderate or low susceptibility lines induce skin melanoma (Klein-Szanto *et al.*, 1994; Kelsall & Mintz, 1998).

The pigment-producing cells in TP*ras* transgenic mice express a mutated human T-24 Ha-*ras* driven by a 2.5 kb promoter region from the mouse tyrosinase gene. The *ras* transgenic mice exhibit an altered phenotype, including melanocytic hyperplasia and a muted agouti coat, indicative of hyperproliferative melanocytes. Topical 7,12-dimethylbenz[*a*]anthracene (DMBA) treatment of TP*ras* mice resulted in a high incidence of melanomas. UV light exposures induced papillomas in TP*ras*-negative littermate and melanomas in some albino TP*ras* mice (Broome Powell *et al.*, 1999). When Hacker *et al.* (2005) treated brown mice (mixed C3H/Sv129 strain background) carrying a melanocyte-specific

Table 3.2 Melanomas induced in transgenic mice exposed to ultraviolet radiation

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, C57Bl/6 Tyr-SV40E, moderately susceptible line 9 (M, F) Duration (NR) Klein-Szanto *et al.* (1994)	19, 11 controls Exposed to 328 mJ/cm^2 UVB (20 min/d) for up to 4 consecutive d.	Melanocytic lesions resembling macules, nevi, or early melanomas gradually appeared in the irradiated mice (not in unirradiated transgenic controls of similar age). 20 wk after irradiation, skin samples containing 26 selected lesions were grafted to low susceptibility line 12 mice. - 10/26 selected lesions in 7 of the grafts gave rise to melanomas - all melanomas had ulcerated and two had metastasized.	Eye melanomas develop before any skin melanomas and are fatal in young mice of the more susceptible lines; less susceptible mice have much later onset eye tumours and longer lives. Skin melanomas were obtained in the absence of advanced eye melanomas by grafting skin from high susceptibility (unirradiated) donors to low susceptibility hosts, thereby greatly prolonging the life of the donor skin.
Mice, C57Bl/6 Tyr-SV40E, low susceptibility line 12 (M, F) Duration (NR) Kelsall & Mintz (1998)	112, 71 controls Exposed on each of 3–10 d to 0.22–0.42 J/cm^2 UV radiation from F40 sunlamps (65% UVB), totaling 1.1–3.7 J/cm^2 (8 protocols) Controls: non transgenic C57BL/6 mice.	14 melanomas in 80 (18%) mice surviving at 4 wk, latency: 37–115 wk, metastases in 5/14 (35%) mice The most favourable protocol (1.9 J/cm^2 total UVR, at 0.38 J/cm^2/d for 5 d starting at 3 d of age) led to the highest incidence of melanoma, 5 of 19 (26%) mice and one of the lowest mortality rates, 2 of 19 (10%).	Among the 80 transgenic survivors, 40% of the mice had from one to four keratoacanthomas on the tail. Most arose 6–8 mo after UVR; one-fifth of the lesions regressed spontaneously in 8–20 mo after detection. Keratoacanthomas also arose on the tails of 4 of the group of 16 surviving C57BL/6 nontransgenic controls treated with UVR.
Mice, TP*ras* (M, F) 45 wk Broome Powell *et al.* (1999)	10 animals/group, 18 controls (TP*ras*-negative littermates) - Irradiated 2 x/wk for 38 wk from FS40T12 UVB lamps (> 90% UVB), - Initial dose 5.6 kJ/m^2, increased twice by 20%, up to a total final dose of 8.06 kJ/m^2.	Melanocytic naevi and melanomas develop in 20% irradiated mice.	The TP*ras* mice that developed melanoma had an albino coat colour
Mice C3H/Sv129, TP*ras* (M, F) Duration (NR) Hacker *et al.* (2005)	10-18, 42 controls Exposed to a single total dose of 8.15 kJ/m^2 from FS40 lamps (UVA 320–400 nm, 2.36 kJ/m^2 UVB 280–320 nm, 5.77 kJ/m^2, UVC 250–280 nm, 0.02 kJ/m^2)	UVR irradiated mice (n = 14) developed in situ cutaneous MM with a penetrance of 57% by 12 mo, none of the untreated controls (n = 42) developed tumours	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice C3H/Sv129 Cdk4/TP*ras* (M, F) Duration (NR) Hacker *et al.* (2006)	2–3 d old *Cdk4*$^{R24C/R24C}$, *Cdk4*$^{R24C/R24C}$/TP*ras*, *Cdk4* $^{R24C/+}$/TP*ras* mice Exposed to a single total dose of 8.15 kJ/m^2 from FS40 lamps	*Cdk4*$^{R24C/R24C}$ mice did not develop melanoma, spontaneously or after neonatal UVR. TP*ras* mice developed neonatal UVR-induced, but not spontaneous, melanomas. 58% of mice homozygous for the *Cdk4-R24C* mutation and also carrying the melanocyte-specific activated H*ras* (*Cdk4*$^{R24C/R24C}$/TP*ras*) developed melanoma spontaneously. UVR treatments increased the penetrance of tumour development to 83% (and from 0% to 40% in *Cdk4*$^{R24C/+}$/TP*ras* mice) and decreased the age of onset compared with untreated animals.	Lesions were mainly dermal melanomas, often multicentric, usually accompanied by epidermal hyperplasia in UVR treated animals. The increased melanoma susceptibility in mice carrying both activated Cdk4 and H*ras* is underlined by their increased propensity to develop multiple primary melanomas. All melanoma-bearing UVR-treated *Cdk4*$^{R24C/R24C}$/TP*ras* animals developed more than one primary lesion, significantly more than untreated *Cdk4*$^{R24C/R24C}$/TP*ras* mice (40%, $P = 0.012$) or UVR-treated TP*ras* mice (16%, $P = 0.001$).
Mice, albino FVB, HGF/SF (M, F) 13 mo Noonan *et al.* (2001)	Number/group at start (NR) UV-irradiated at: – group A, 3.5 d and again at 6 wk; – group B, 6 wk; – group C, 3.5 d; – group D, no UV treatment. Neonatal mice received a single treatment of 9.58 kJ/m^2 from Phillips F40 UV lamps (UV-A, 320–400 nm, 3.31 kJ/m^2; UV-B, 280–320 nm, 6.24 kJ/m^2; UV-C, 250–280 nm, 0.03 kJ/m^2). 6-wk-old mice received a single treatment of 19.16 kJ/m^2.	Only mice from groups A and C developed melanoma. No melanoma in non-transgenic or untreated transgenic mice (observation: 13 mo). Melanoma development in HGF/SF transgenic mice after UV irradiation at both 3.5 d and 6 wk (group A) identical to that seen after only a single exposure at 3.5 d (group C). UV irradiation (group B) was not tumorigenic.	The second UV exposure increased the multiplicity of melanocytic lesions as well as the incidence of non-melanocytic tumours.

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, albino FVB, HGF/SF (M, F) 14 mo De Fabo *et al.* (2004)	Number/group at start (NR) Neonatal HGF/SF-transgenic mice irradiated at 3–5 d of age with a source coupling UV interference or cutoff filters to a 2.5 kW xenon arc lamp, to produce UVB or UVA wavebands or solar simulating radiation (UVB + UVA + visible radiation in proportions approximating sunlight). Neonatal transgenic animals also irradiated with F40 sunlamps, (UVB + UVA radiation and visible light). Total UVvis doses (kJ/m^2): Xenon UVB filter: 14.0 unfiltered F40 lamp: 14.7 solar simulator: 322.1 mylar filtered F40: 14.1 Xenon UVA filter: 150 (UVB and solar simulator doses are equivalent to 23 standard erythemal doses) UVB dose 14.0 kJ/m^2 UVA dose 150 kJ/m^2	Incidence of MM Xenon UVB filter: 10/18 unfiltered F40 lamp: 6/23 solar simulator: 5/29 mylar filtered F40: 1/20 Xenon UVA filter: 0/23	UVB highly effective at initiating melanoma. A further group of animals was irradiated with 4.5 kJ/m^2 of UVB (7 SED), which was also effective at initiating melanoma (not shown). UVA radiation did not initiate any melanomas. Removal of UVB from the broadband F40 source prevented the initiation of melanoma. Median time to first melanoma (d): Xenon UVB filter: 127 unfiltered F40 lamp: 169 solar simulator: 284
Mice XPA (–/–), SCF-Tg 24 mo Yamazaki *et al.* (2005)	Number/group at start (NR) Irradiated 3 x/wk for 10 wk, 5 J/cm^2 UVB (total dose: 150 J/cm^2), from FL.20SE.30; fluorescent lamps (55% radiation within the UVB range (305 nm), 25% and less than 1%, within UVA and UVC, respectively).	55% of UV-treated XPA (–/–), SCF-Tg mice develop melanoma at 70 wk after UVB radiation. Lentigo maligna melanoma appear 4 mo after the termination of UVR exposure. At 6 mo, some mice developed nodular melanoma. No melanoma develop in UV-treated XPA-normal, SCF-Tg mice and non-treated XPA -(–/–), SCF-Tg mice.	

d, day or days; F, female; h, hour or hours; M, male; min, minute or minutes; MM, malignant melanoma; mo, month or months; NR, not reported; SED, standard erythemal dose; wk, week or weeks; yr, year or years

mutant *Hras* (G12V) transgene (TP*ras*), with a single neonatal UVR dose of (8.15 kJ m^2), 57% of the UV irradiated mice developed in situ cutaneous MM by 12 months, whereas none of the untreated controls developed tumours. In another study by the same author, UVR treatment greatly increased the penetrance and decreased the age of onset of melanoma development in *Cdk4*$^{R24C/R24C}$/TP*ras* animals compared with TP*ras* alone (Hacker *et al.*, 2006).

However, murine melanocytic tumours are dermal in origin and lack the epidermal component that characterizes human melanoma. However, the skin of transgenic mice in which a metallothionein-gene promoter forces the overexpression of hepatocyte growth factor/scatter factor (HGF/SF) has melanocytes in the dermis, epidermis and dermal–epidermal junction, and is thus more akin to human skin. Untreated HGF/SF-transgenic mice are already genetically predisposed to late-onset melanoma. Using these transgenic mice, Noonan *et al.* (2001) showed that a single UV irradiation of neonates is sufficient to induce early onset melanoma in the majority of animals, while UV irradiation of 6-week-old mice is insufficient. Using the same model, it was further shown that UVB and not UVA is effective at initiating melanoma (De Fabo *et al.*, 2004).

Xeroderma pigmentosum group A gene-deficient (XPA–/–), stem cell factor-transgenic (SCF-Tg) mice are defective in the repair of damaged DNA and do have epidermal melanocytes. Following chronic UVB irradiation, these mice develop lentigo maligna and nodular melanomas (Yamazaki *et al.*, 2005).

3.2.2 Human melanocytes grafted to immunodeficient mice exposed to ultraviolet radiation

See Table 3.3

Atilasoy *et al.*, have developed an experimental model in which full-thickness human skin is grafted to immunodeficient recombinase activating gene-1 (RAG-1) knockout mice (Atillasoy *et al.*, 1998). Chronic UVB irradiation with or without an initiating carcinogen can induce human melanocytic lesions, including melanoma. It was further shown that overexpression of basic fibroblast growth factor (bFGF) via adenoviral gene transfer in human skin xenografted to severe combined immunodeficiency mice led to black pigmented macules within 3 weeks of treatment, and to melanoma when bFGF was combined with UVB (Berking *et al.*, 2001).

In contrast with experiments using neonatal foreskin, no melanocytic lesions were induced when adult skin was used (Berking *et al.*, 2002). In normal human skin grafted onto severe combined immunodeficient mice (SCID), an increased expression of a combination of three growth factors, bFGF, stem cell factor, and endothelin-3, along with exposure to UVB can transform normal melanocytes into a melanoma phenotype within 4 weeks. Invasion of melanoma lesions was found in skin from newborn donors, whereas melanomas in adult skin were of a non-invasive in situ type only. This suggests that susceptibility of skin to exogenous tumour promoters is dependent on age (Berking *et al.*, 2004).

3.2.3 Opossums

See Table 3.4

Chronic UVB irradiation of suckling young opossums (*M. domestica*) induces nevi and melanoma that progress to metastasis (Robinson *et al.*, 1994, 1998) suggesting that in this species, UVB can act as a complete carcinogen, inducing precursor lesions and driving progression to metastatic melanoma.

3.2.4 Fish

See Table 3.5

Interspecies hybrids and backcrosses of platyfish (*Xiphophorus maculatus*) and swordtails

Table 3.3 Melanomas induced in human melanocytes grafted to immunodeficient mice exposed to ultraviolet radiation

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, RAG-1 (M, F) Duration (NR) Atillasoy *et al.* (1998)	Number/group at start (NR) 8–12 wk old mice grafted with full-thickness human foreskin. 4 groups: after 4-6 wk: no treatment, a single treatment with 7,12- dimethyl(a) benzanthracene (DMBA), UVB irradiation at 500 J/m^2 alone 3 ×/wk, and a combination of DMBA and UVB.	9/40 (23%) of human foreskin grafts treated with UVB only, and 18/48 (38%) of grafts treated with the combination of DMBA + UVB developed solar lentigines within 5 to 10 mo. 73% of of all UVB-treated xenografts develop melanocytic hyperplasia 1 melanoma (nodular type) out of 48 DMBA+UVB treated xenografted mice.	
Mice, SCID (M, F) Duration (NR) Berking *et al.* (2001)	Number/group at start (NR) Human skin xenograft injected intradermally with adenoviral vector bFGF/Ad5, exposed 3 ×/wk for 10 min to 30–50 mJ/cm^2 UVB from FS72/T12 UVB lamps throughout a period of 2 to 10 mo.	1 lentiginous melanoma in an adult abdominal skin graft after 2 mo (7 bFGF/Ad5 injections and 26 UVB irradiations).	
Mice, SCID and RAG-1 (M, F) Up to 22 mo Berking *et al.* (2002)	155 adult human skin specimens grafted onto SCID or RAG-1 mice, irradiated 2–3 ×/wk with 40 mJ/cm^2 UVB over a period of up to 10 mo with or without beforepical application of DMBA.	Only actinic keratoses and 1 squamous cell carcinoma. No melanocytic lesions.	Melanocytes from young individuals may be more susceptible to the transforming effect of genotoxic agents than melanocytes from adults.
Mice, SCID (M, F) Duration (NR) Berking *et al.* (2004)	Human skin xenografts (neonatal foreskin or adult skin) injected intradermally with adenoviral vectors bFGF/Ad5, ET-3/Ad5, SCF/Ad5 exposed 3 ×/wk to 30 – 50 mJ/cm^2 UVB from FS72/T12 UVB lamps throughout a period of 4 wk.	17/50 invasive melanomas in newborn foreskin. in situ melanomas in 45–56% of adult skin grafts exposed to the three growth factors independent from the exposure to UVB.	Lesions regressed upon withdrawal of the growth factor stimulation after 4 wk.

bFGF, basic fibroblast growth factor; d, day or days; ET-3, endothelin-3; F, female; M, male; mo, month or months; NR, not reported; SCF, steam cell factor; wk, week or weeks

Table 3.4 Melanomas induced in South American opossum *M. domestica* exposed to ultraviolet radiation

Species, strain Reference	Number/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
South American opossum (*M. domestica*) Duration (NR) Robinson *et al.* (1994)	- 43 litters of suckling young were irradiated with sunlamps with a spectral emission peak at 302 nm (UVB) to induce melanocytic nevi. Total doses of 0.87–5.0 kJ/m^2 were divided equally among up to 14 exposures during the 19 d from birth. – 13 litters received doses of 125 J/ m^2 of UVB every other d, for up to 19 d after birth, with a maximum total dose of 1.12 kJ/rn^2. - 30 litters received different total doses, up to a total dose of 5.0 kJ/ m^2. Affected animals were then exposed 3 times/wk to 125 J/ m^2 of UVB for up to 45 wk to promote progression to malignancy.	Of 358 sucklings exposed, 217 (60%) survived to weaning, and 22 (6%) possessed a nevus at weaning. Nevi of 8 of the 20 chronically-exposed animals progressed to malignant melanoma with metastases to lymph node(s).	
South American opossum (*M. domestica*) Duration (NR) Robinson *et al.* (1998)	620 suckling young were exposed to ultraviolet radiation (UVR, predominantly UVB: 290–320 nm) to determine an optimal protocol for induction and progression of melanoma (7 protocols).	The lowest dose (175 J/ m^2) administered three times a wk for three wk led to the highest incidence of melanotic lesions with melanoma potential (8.1%) among young (5-mo-old) adults. Among 101 much older animals (> 17 mo at necropsy), 43% showed metastatic melanoma to the lymph nodes and almost one-third of these had progressed to widespread dissemination.	In the opossum, UVR can act as a complete carcinogen for progression to widely disseminated disease and exposure of sucklings can lead, in old age, to widespread metastatic melanoma in this model.

d, day or days; NR, not reported; wk; week or weeks

Table 3.5 Melanomas induced in Platyfish-swordtail hybrids exposed to ultraviolet radiation

Species, strain (sex) Duration Reference	Number/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Platyfish (X. *maculatus*)-swordtail (*X. Helleri*) hybrids (M, F) up to 6 mo Setlow *et al.* (1989)	A total of 5000 fish. Multiple exposures on 5-20 consecutive days beginning on d 5 after birth (150 to 1700 J/ m^2/d) or a single exposure of = 200 J/ m^2/d of $\lambda > 304$ nm from FS-40 sunlamps, filtered by a thin acetate film ($\lambda > 290$ nm), or a thin Mylar film ($\lambda > 304$ nm), or a thick plastic sheet ($\lambda > 360$ nm).	Tumor prevalence: 20% to 40% at 4 mo of age, (background rates: 12% in strain 1, and 2% in strain 2).	Exposure of the fish to visible light after UV exposure reduces the prevalence to background.
Platyfish (X. *maculates*)-swordtail (*X. Helleri*) hybrids (M, F) 4 mo Setlow *et al.* (1993)	Groups of five 6-d-old fish submitted to a single irradiation - from a filtered ($\lambda > 304$ nm) sunlamp - or with narrow wavelength bands at 302, 313, 365, 405, and 436 nm and scored for melanomas 4 mo later.	Single exposures to filtered sunlamp radiation: - up to 42% melanomas for (850 J/m^2). The action spectrum (sensitivity per incident photon as a function of wavelength) for melanoma induction shows appreciable sensitivity at 365, 405, and probably 436 nm.	Only heavily pigmented animals are susceptible to melanoma induction by a single, relatively small exposure to UV.

d, day or days; F, female; M, male; mo, month or months

(*Xiphophorus helleri*) eventually develop genetically determined spontaneous melanoma (the Gordon-Kosswig melanoma). Setlow *et al.* (1989) have developed two strains of these fishes that are susceptible to invasive melanoma induction by exposure to filtered radiation from sunlamps in the wavelength ranges $\lambda > 290$ nm and $\lambda > 304$ nm. Irradiation of these fishes and of *X. maculatus*/*X. couchianus* hybrids with narrow wavelength bands show that the action spectrum for melanoma induction shows appreciable sensitivity at 365, 405, and probably 436 nm, suggesting that wavelengths not absorbed directly in DNA are effective in induction (Setlow *et al.*, 1993).

3.3 Synthesis

Recent studies have mainly focused on the mechanisms of UV-induced carcinogenesis and have used specific strains of mice (sencar mice). Several studies conducted examining the tumorigenic effects of solar radiation, broad-spectrum ultraviolet radiation, UVA, UVB and UVC in experimental animals, since 1992, support and confirm the conclusions of the previous *IARC Monograph*.

Solar radiation causes squamous-cell carcinoma of the skin and of the conjunctiva in mice and rats.

Broad-spectrum UVR causes squamous-cell carcinoma of the skin and of the cornea/conjunctiva in mice and rats.

UVA causes squamous-cell carcinoma of the skin in mice.

UVB causes squamous-cell carcinoma of the skin in mice and opossum and invasive skin melanomas in platyfish-swordtail hybrid fish and opossum.

UVB causes skin melanomas in transgenic mice and skin melanomas in genetically engineered immunocompromised mice grafted with human melanocytes.

UVC causes squamous-cell carcinoma of the skin in mice.

4. Other Relevant Data

4.1 Transmission and absorption in biological tissues

UVR may be transmitted, reflected, scattered or absorbed by chromophores in any layer of tissue, such as the skin and the eye. Absorption is strongly related to wavelength, as it depends on the properties of the responsible chromophore(s) (IARC, 1992).

UVC (200–280 nm) has the highest energy and thus is potentially the most damaging to biological tissues. However, because of its absorption by the ozone layer, its impact on human health is largely theoretical except for occasional artificial UV sources. UVB (280–315 nm) makes up only 5–10% of the UVR that penetrates the ozone layer but because of its ability to directly damage DNA-forming modified bases, understanding molecular and cellular links between UVB exposure and carcinogenesis has continued to be a major focus since the previous *IARC Monograph* (IARC, 1992). The role of non-DNA chromophores in UV carcinogenesis has been extensively studied over the past 15 years in particular in relation to UVA (315–400 nm) exposure. UVA, in addition to inducing a variety of DNA damage, also penetrates the dermis where it interacts with proteins and lipids resulting in skin ageing (for a review, see Ridley *et al.*, 2009).

4.1.1 Eye

The eye is a complex multilayered organ. The retina at the back of the eye receives visible radiation and the intermediate layers attenuate UVR to different degrees, thereby protecting the retina from photodamage. The outermost cornea absorbs UVC (from artificial sources) and a substantial amount of UVB, which is further attenuated by the lens and the vitreous humour in front of the retina. UVA is less attenuated by the cornea than by the internal structures, and

does not reach the retina (for a review, see Young, 2006). Age-related changes in lens crystallins affect their structure and function causing the lens to increasingly scatter light on the retina, and causing the lens to become opaque (for a review, see Sharma & Santhoshkumar, 2009)

4.1.2 Skin

The skin comprises two main layers (for a review, see Young, 2006):

1) the outer acellular and cellular epidermis, and
2) the inner largely extracellular dermis.

Keratinocytes are the main epidermal cell type, which differentiate to create the outermost, non-living, terminally differentiated, cornified and protective stratum corneum. The dividing cell population is located in the innermost basal layer of the epidermis. Dendritic pigment-producing melanocytes and immunocompetent dendritic Langerhans cells are also present in the epidermis. The dermal connective tissue is mostly collagen synthesized by fibroblasts. The dermis contains the skin's vascular supply. Significant differences have been found in the UVA and UVB absorption properties of different skin types (Antoniou *et al.*, 2009).

4.2 Genetic and related effects: consequences of UVR exposure

4.2.1 Photoproduct formation

(a) DNA photoproducts: direct and indirect formation

A multitude of photoproducts, the ratio of which depends markedly on wavelength, are formed in cellular DNA by solar UVR (IARC, 1992). The question of which types of DNA damage are formed by UVA, UVB and UVC has been extensively studied. Unlike UVB, UVA is weakly absorbed by DNA and the primary method of DNA-damage induction by UVA occurs indirectly via photosensitizers, which include endogenous melanins or proteins containing porphyrin, haem or flavin groups. They can also be exogenous, e.g. antibacterial agents such as naladixic acid and fluoroquinolones or the immunosuppresive drug azathioprine (for a review, see Ridley *et al.*, 2009), and 8-methoxypsoralen (methoxsalen) in combination with UVA (PUVA) used for photochemotherapy. These exogenous chemicals absorb in the UVA range and release reactive oxygen species (IARC, 2012), and thus mediate UVA-induced DNA damage. The excited sensitizers may react with DNA directly by one-electron transfer (Type I mechanism) and/or via the generation of singlet oxygen ($^1O_2$) by energy transfer to molecular oxygen (major Type II mechanism), giving rise to guanine modifications including 8-oxoguanine. The excited sensitizer can also transfer an electron to oxygen resulting in the formation of superoxide anion radical (O_2^-) (minor Type II mechanism). Disproportionation of O_2^- can give rise to hydrogen peroxide (H_2O_2), and reactive species formed through the interaction of H_2O_2 with metal ions may induce DNA damage (for reviews, see Ridley *et al.*, 2009 and Hiraku *et al.*, 2007).

In addition to the generation of reactive oxygen species, reactive nitrogen species such as nitric acid and peroxynitrite are formed after UVA exposure. UVA irradiation can also lead to the long-term cellular generation of both reactive nitrogen species and reactive oxygen species (Didier *et al.*, 1999; Valencia *et al.*, 2006), indicating the possibility of a prolonged effect of a single UVA exposure (see Section 4.2.3).

Several studies *in vitro* have shown a predominance of oxidized purines after UVA-induced oxidative damage with relatively few strand breaks or oxidized pyrimidines (Kielbassa *et al.*, 1997; Pouget *et al.*, 2000). However, thymidine-derived cyclobutane–pyrimidine dimer lesions have been detected after UVA exposure in several cell models (e.g. Chinese hamster ovary cells) (Douki

et al., 2003), and in human skin (Courdavault *et al.*, 2004; Mouret *et al.*, 2006), recently reviewed by Ridley *et al.* (2009). Moreover, in human skin after exposure to UVA, cyclobutane–pyrimidine dimer lesions rather than oxidative lesions were the main type of DNA damage induced (Mouret *et al.*, 2006). It has been suggested that UVA may generate cyclobutane–pyrimidine dimer lesions via a photosensitized triplet energy transfer in contrast to formation via direct excitation of DNA by UVB (Douki *et al.*, 2003; Rochette *et al.*, 2003).

(b) Other chromophores

In addition to DNA, many other cellular components absorb and/or are damaged by solar UVR (IARC, 1992). Non-DNA chromophores and targets are particularly relevant at longer wavelengths. For instance *trans*-urocanic acid, a deamination product of histidine, is an important chromophore found in high concentrations in the stratum corneum. *Trans*-urocanic acid undergoes a photoisomerization to *cis*-urocanic acid in the presence of UVR, which has immunoregulatory properties (Norval, 2006).

4.2.2 Mutagenicity

Numerous reports show that sunlight or solar-simulated radiation induces mutations in bacteria, plants, mammalian cells, Chinese hamster ovary and lung (V79) cells, mouse lymphoma cells, and human skin fibroblasts. Studies in bacteria exposed to radiation throughout the solar UV spectrum demonstrate mutagenic activity unambiguously. UVA (320–400 nm) is mutagenic to yeast and cultured mammalian cells; UVB (290–320 nm) to bacteria and cultured mammalian cells; and, UVC (200–290 nm) to bacteria, fungi, plants, cultured mammalian cells, including Chinese hamster ovary and V79 cells, and human lymphoblasts, lymphocytes and fibroblasts. Because wavelengths in the UVC range do not reach the surface of the Earth, they are of no significance as a source of damage in natural sunlight (IARC, 1992).

DeMarini *et al.* (1995) evaluated the mutagenicity and mutation spectra of a commercial tanning salon bed, white fluorescent light and natural sunlight in four DNA-repair backgrounds of *Salmonella*. Approximately 80% of the radiation emitted by the tanning bed was within the UV range (250–400 nm), whereas only ~10% of the sunlight and 1% of the fluorescent light were in the UV range. The tanning bed emitted similar amounts of UVA (315–400 nm) and UVB (280–315 nm), whereas sunlight and fluorescent light emitted, respectively, 50–60 times and 5–10 times more UVA relative to UVB. Based on total dose (UV + visible, 400–800 nm), the mutagenic potencies (revertants × 10^{-3}/J/m^2) of the exposures in strain TA100 were 3.5 for sunlight, 24.9 for fluorescent light, and 100.6 for the tanning bed. Thus, the tanning bed was 29 times more mutagenic than sunlight. The mutagenic potency of the tanning bed was similar to that produced by pure 254-nm UV (DeMarini *et al.*, 1995).

DNA-sequence analysis of the revertants of strain TA100, which is a base-substitution strain, was performed at the doses that produced 10-fold increases in the mutant yields (revertants/plate) compared to the control plates for sunlight and fluorescent light, and a 16-fold increase for the tanning bed. Thus, more than 90% of the mutants analysed were induced by the exposures as opposed to being spontaneous in origin. More than 80% of mutations induced by all three exposures were G:C→A:T transitions, and 3–5% were presumptive or identified multiple mutations. The frequencies of the multiple mutations were increased 38–82-fold in TA100 by the exposures, with 83% (19/23) of these multiple mutations induced by the tanning bed being CC→TT tandem mutations. Thus, DeMarini *et al.* (1995) also showed that a tanning bed produced a mutation spectrum similar to that found in the *TP53* gene in sunlight-associated skin tumours (Dumaz *et al.*, 1994).

4.2.3 Mutation profiles and target genes

The study of the mutation profiles in skin tumours and in particular those from individuals with either a defect in the repair processes that remove UV-induced DNA damage (e.g. xeroderma pigmentosum (XP) patients or other rare syndromes associated with increased skin cancer risk) has allowed the assessment of the relative contribution of bipyrimidine photoproducts and oxidative damage to the mutagenic effects of UVR, and has provided invaluable models to delineate the genes affecting crucial pathways involved in skin carcinogenesis.

Point mutations found in the *TP53* gene in skin tumours from normal individuals and repair-deficient XP patients are mainly G:C→A:T transitions in skin tumours (74% in non-XP, 87% in XP), and also to a lesser extent in internal tumours (47%) where, however, they are mainly located at 5′CG-3′ dinucleotide (CpG; 63%) sequences—probably due to the deamination of the unstable 5-methylcytosine (Dumaz *et al.*, 1994). In XP skin tumours, 100% of the mutations are targeted at pyrimidine–pyrimidine (py–py) sequences and 55% of these are tandem CC→TT transitions. In skin tumours from normal individuals, 14% of the *TP53* mutations are double mutations and, as in XP skin tumours, all these are CC→TT transitions. In contrast, internal tumours rarely contain tandem mutations (0.8%) and, of these, only 2/14 were CC→TT transitions. A similar mutation profile of C→T or tandem CC→TT UV signature transitions, occurring at bipyrimidine sequences, has been found in several other genes including *PTEN* (phosphatase and tensin homologue deleted on chromosome 10; Ming & He, 2009; Wang *et al.*, 2009). *Ras*, *Ink4a-Arf* as well as alterations of the different partners of the mitogenic sonic hedgehog signalling pathway (patched, smoothed, and sonic hedgehog) have also been found in XP tumours and sporadic skin cancers. The majority of mutations are at C→T or tandem CC→TT transitions (Daya-Grosjean & Sarasin, 2005).

Based on the reactivity of different wavelengths of UVR with DNA, these G:C→A:T transition mutations induced at dipyrimidine sites were considered for many years as specifically resulting from UVB-induced cyclobutane–pyrimidine dimers or pyrimidine (6–4) pyrimidone photoproducts, and termed the "UV-signature" or "UV-fingerprint mutations" (Wikonkal & Brash, 1999), and A:T→C:G transversions were considered as UVA "fingerprint mutations" (Drobetsky *et al.*, 1995; Robert *et al.*, 1996). However, the wavelength specificity of these mutations has been challenged based on recent findings in rodent cell models, mouse models, and human skin. The UVA-induced mutation profile in exon 2 of adenine phosphoribosyltransferase (*Aprt)* gene in rodent cells showed a high proportion of mutations recovered opposite thymine–thymine–dipyrimidine damage sites supporting the notion that cyclobutane–pyrimidine dimers are a premutagenic lesion in UVA-induced mutagenesis (Rochette *et al.*, 2003). C→T transition mutations in the *lacZ* transgene have been detected in the epidermis and dermis of UVA-treated mice, corresponding to the formation of cyclobutane–pyrimidine dimers (Ikehata *et al.*, 2008), in the *Tp53* gene of UVA- or UVB-induced skin tumours in hairless mice (van Kranen *et al.*, 1997), in the *TP53* gene of benign solar keratoses and malignant skin squamous cell carcinomas, in humans (Agar *et al.*, 2004), and in UVA-irradiated human skin cells under certain experimental conditions (Courdavault *et al.*, 2004; Rünger & Kappes, 2008).

Another characteristic of mutations in epithelial skin cancers is the preference of their occurrence for a CpG sequence, which is the consensus target motif for epigenetic DNA methylation in vertebrates. Mutation hotspots in such a sequence context within the *Tp53* gene have been identified, and it has been suggested that

their presence could be used as a marker of solar UV exposure (Ikehata & Ono, 2007; Rochette *et al.*, 2009). However, the specificity of dinucleotide mutability in skin cancer is complex. Lewis *et al.* (2008) compared the base-substitution signatures obtained in several mutation assay model systems after exposure to UVB, UVC or simulated sunlight and cancer-specific base substitutions collated in the IARC *TP53* database (IARC, 2006b), for exons 5, 7 and 8 of the *TP53* gene. The UVB, UVC and skin cancer profiles for exon 5 and 8 all showed relatively high levels of G:C→A:T mutations primarily at TC and CC sites, and to a lesser extent at CT sites. However the exon 7 profiles did not group with the skin cancer profiles which showed a relatively high level of G:C→A:T mutations at CpG sites.

Based on these findings, the back-extrapolation from a mutation to an exposure to a single wavelength region of the UVR spectrum is not possible.

The study of syndromes associated with increased skin cancer risk has been instrumental in the identification of genes critical for UV carcinogenesis. Germline mutations in *PTEN* resulting in altered *PTEN* function, detected in patients with Cowden disease and Bannayan–Riley–Ruvalcaba syndrome (Bonneau & Longy, 2000), are associated with an increased risk of basal cell carcinoma, squamous cell carcinoma, and melanoma (Nuss *et al.*, 1978; Camisa *et al.*, 1984; Liaw *et al.*, 1997; Trojan *et al.*, 2001; Ming & He, 2009). Mice with *Pten* deletion and mutation are highly susceptible to tumour induction (Suzuki *et al.*, 1998). Conditional knockout of *Pten* in skin leads to neoplasia (Li *et al.*, 2002; Suzuki *et al.*, 2003; Backman *et al.*, 2004). *Pten* deficiency in mice causes increases in cell proliferation, apoptotic resistance, stem-cell renewal/maintenance, centromeric instability, and DNA double-strand breaks (Groszer *et al.*, 2001; Kimura *et al.*, 2003; Wang *et al.*, 2006; He *et al.*, 2007; Shen *et al.*, 2007), which can enhance susceptibility to carcinogens and the occurrence of secondary genetic or epigenetic alterations that can lead to skin cancer development. Patients with Gorlin syndrome (or basal cell nevus syndrome) suffer with multiple basal cell carcinoma. This syndrome is associated with mutations in the *Patched* (*PTCH*) gene, an essential component in Hedgehog signalling (Epstein, 2008). Aberrant activation of sonic hedgehog homologue (SHH) signalling, usually because of mutations either in the *PTCH* or smoothened (*SMOH*) genes (Reifenberger *et al.*, 2005) or because of hyperactivation of this pathway, is often found in sporadic basal cell carcinomas.

Dysfunctional p53 is likely to affect protective responses to DNA damage and oncogenic signalling. Experiments in both humans and mice have shown that clusters of epidermal cells with mutant p53 occur long before squamous cell carcinoma becomes visible (de Gruijl & Rebel, 2008). Although *TP53* mutations cause genetic instability and facilitate the carcinogenic process, they are not enough to cause basal cell carcinoma or squamous cell carcinoma, and the activation of signalling cascades (normally needed for cell proliferation and homeostasis) is often also involved. Based on the molecular, pathological and functional dissection of such signalling cascades, evidence has accumulated linking an activated receptor tyrosine kinase (RTK)/RAS pathway in combination with dysfunctional p53 to the development of squamous cell carcinoma; activated Hedgehog pathway with possibly dysfunctional p53 to the development of basal cell carcinoma; and in cutaneous melanoma, activated RTK/RAS pathway in combination with inactivation of the inhibitor of cycline-dependant kinase 4 & 6 (*INK4a*) locus (de Gruijl *et al.*, 2001). The Notch signalling pathway has also been identified as a key regulator of epidermal homeostasis and implicated in skin carcinogenesis; aberrrant Notch signalling leads to skin cancer including basal cell carcinoma, squamous cell carcinoma, and melanoma (Okuyama *et al.*, 2008).

4.2.4 Genomic instability, bystander effect, telomere shortening

Another potential mechanism for inducing genomic instability in cells not directly hit by radiation is via the bystander effect. Bystander effects via both gap-junction and extracellular signalling have been observed in cells following UVB treatment (Banerjee *et al.*, 2005, Dahle *et al.*, 2005), and an UVA-induced bystander effect has been reported that can be attenuated by the use of a nicotinamide adenine dinucleotide phosphate (NADPH) oxidase inhibitor, suggesting a possible role of reactive oxygen species in the induction of this effect (McMillan *et al.*, 2008; Whiteside & McMillan, 2009). After UVA exposure, such mechanisms have been extensively investigated partly because of the action spectra of UVA's interaction with DNA. There is an increasing body of evidence that suggests that UVA-induced (and to some extent UVB-induced) damage cannot only remain but also be generated for prolonged periods in the irradiated cell, its progeny, and also in surrounding cells and tissues which were not themselves exposed. The progeny of cells which have survived irradiation show changes in chromosomal structure and copy number, the generation of micronuclei, changes in gene expression and cell survival (Little, 2000; Morgan, 2003), and are all seen as end-points of genomic instability. Such persistent genomic instability defined as the persistent induction of DNA and cellular damage in irradiated cells and their progeny (Ridley *et al.*, 2009) can lead to a hypermutator phenotype where genetic alterations increase generation upon generation in a large proportion of the progeny of the irradiated cells, increasing the risk of malignant transformation. Conversely, another characteristic of persistent genomic instability can be increased cell-kill of the progeny, meaning that the risk of cancer arising from these cells is reduced rather than increased (Ridley *et al.*, 2009).

For instance, instability was observed for several generations in the GM10115 human–hamster hybrid cell line after combined treatment of UVA with bromodeoxyuridine and Hoechst 33258 dye (Limoli *et al.*, 1998). Both UVA and UVB are able to induce delayed mutations in the hypoxanthine-guanine phosphoribosyltransferase (*Hprt*) gene of V79 Chinese hamster fibroblast cells (Dahle & Kvam, 2003), which could be inhibited by reactive oxygen species scavengers (Dahle *et al.*, 2005). Mutations in the *HPRT* gene have shown to be increased 7 days after UVA irradiation in human keratinocytes HaCaT (Phillipson *et al.*, 2002). In the same cell model, UVA treatment led to continued reductions in survival of UVA-treated HaCaT for over 21 days following treatment, and an increase in the number of micronuclei per cell over the same period. The addition of catalase was shown to reverse these effects to near-control levels. A bystander effect was induced in human keratinocytes HaCaT and fibroblasts MRC5 cells treated with UVA radiation but not UVB radiation (Whiteside & McMillan, 2009). One potential mechanism for the generation of reactive oxygen species under such experimental conditions involves the UVA-induction of enzyme activity. One potential target is a NADPH oxidase (Valencia & Kochevar, 2008). This enzyme has been shown to cause increased superoxide generation in response to UVA in mouse, monkey, and human cell lines (Hockberger *et al.*, 1999). The resulting increase in superoxide and its conversion to other reactive oxygen species would lead to increased cellular and DNA damage. Prolonged generation of reactive oxygen species by such mechanisms in the initially exposed cells and their progeny therefore have the potential to enable persistent genomic instability (Ridley *et al.*, 2009).

Another mechanism for inducing persistent genomic instability is via the shortening and loss of telomeres. The shortening of telomeres or the dysfunction of proteins associated with

the telomeres can lead to large scale transfers of sequences between chromosomes, which lead to the amplification or deletion of sequences (Bailey & Murnane, 2006). It has been demonstrated that UVA can increase the rate of telomere shortening (Oikawa *et al.*, 2001; Ridley *et al.*, 2009), therefore suggesting a possible link between UVA irradiation and increasing instability over several generations.

It has also been shown that irradiation with UVA and UVB is able to trigger increased microsatellite instability in radial growth phase melanoma cells (Hussein *et al.*, 2005).

4.2.5 Cell killing – apoptosis and senescence

Apoptosis and premature senescence are protective mechanisms against the presence of unrepaired DNA lesions in the genome that could otherwise induce mutations increasing the risk of carcinogenesis induced after UV irradiation. The fact that nucleotide excision repair (NER)-deficient cells are very sensitive to the cell-killing effect of UV light is a clear indication that unrepaired photoproducts constitute the main apoptosis-triggering signal after UV irradiation (Batista *et al.*, 2009). How these lesions are processed to generate a toxic signal is unclear. While some data suggest transcription blockage is the main reason behind this apoptosis induction, other data suggest that the formation of DNA double-strand breaks during the replication of cyclobutane-pyrimidine dimers-containing DNA is necessary for the commitment to cell death (Batista *et al.*, 2009). UV light (mainly UVA and UVB) is also able to directly activate membrane death receptors that trigger apoptosis independently of DNA damage. Mitogen-activated protein kinases (MAPKs) are also directly activated by UV light and whether this activation is DNA-damage dependent or independent is still unclear.

The hallmark of cellular senescence is the loss of proliferative capacity, with the accumulation of senescent cells in skin leading to skin aging. Once cells have entered into senescence, they undergo a series of morphological and metabolic changes, and gene-expression profiles are altered as has been shown in human skin fibroblasts after exposure to UVB (Chen *et al.*, 2008).

4.3 Genetic susceptibility: host factors modulating the response to UV

4.3.1 DNA repair capacity and single nucleotide polymorphisms (SNPs) in DNA repair genes

Many of the directly formed UV photoproducts are repaired via the nucleotide excision repair (NER) pathway, and those formed indirectly via the modification of DNA by reactive oxygen species and reactive nitrogen species require components of the base-excision repair pathway.

NER operates through two subpathways in the early stages of damage recognition, depending on whether the damage is located anywhere throughout the genome [global genome (GG) repair] or in an actively transcribed gene [transcription-coupled (TC) repair]. GG repair begins with recognition of the damage by the XPC-RAD23B-centrin2 complex, aided in some cases by the UV damaged DNA-binding activity (UV-DDB) that includes the subunits DDB1 and DDB2/XPE. The mechanisms for TC repair are not completely understood; a current model postulates that the pathway is initiated by the arrest of RNA polymerase II at a lesion on the transcribed strand of an active gene, in a process that requires several factors including the Cockayne syndrome A (CSA), CSB, and XPA-binding protein-2 (XAB2) proteins (Sarasin & Stary, 2007; Hanawalt & Spivak, 2008). The recognition events in GG-NER and TC-NER are followed by a common pathway involving the

unwinding of the damaged DNA, dual incisions in the damaged strand, removal of the damage-containing oligonucleotide, repair synthesis in the resulting gap, and ligation of the repair patch to the contiguous parental DNA strand. These steps require the coordinated action of several factors and complexes, including the repair/transcription complex factor TFIIH, and the repair factors XPA, XPG, and excision repair cross-complementing rodent deficiency, complementation group 1 (ERCC1)-XPF, in addition to those required for repair replication and ligation.

The mismatch repair enzyme hMSH2 has also been linked to the NER pathway. This enzyme is a *TP53* target gene and induced by UVB radiation, suggesting a role for mismatch repair in skin cancer development (Rass & Reichrath, 2008).

Defects in NER are associated with three major autosomal recessive disorders, xeroderma pigmentosum (XP), Cockayne syndrome, and trichothiodystrophy. At the clinical level, XP is characterized by a highly increased incidence of tumours in sun-exposed areas of the skin (Stefanini & Kraemer, 2008). In contrast, Cockayne syndrome and trichothiodystrophy are cancer-free disorders characterized by developmental and neurological abnormalities and premature aging, associated in trichothiodystrophy with typical hair abnormalities (Lehmann, 2003). The two genes identified as responsible for the NER-defective form of Cockayne syndrome (*CSA* and *CSB*) are specifically involved in transcription-coupled repair TC-NER. Seven NER-deficient complementation groups have been identified in XP patients (designated XPA to XPG); these XP cases are defective in one of seven genes called *XPA* to *XPG*. An eighth complementation group, the so-called XP variant form (XPV) was latter identified with a defective gene encoding the DNA polymerase ε. This enzyme is required for the replication of the UV-damaged DNA pathway, called translesion DNA synthesis (Stefanini & Kraemer, 2008).

In addition, rare cases have been described showing a complex pathological phenotype with combined symptoms of XP, Cockayne syndrome and/or NER syndrome defects that have been associated with combinations of mutations in *XP*, *CS*, and other unidentified genes (for instance, Itoh *et al.*, 1994; Lehmann, 2003; Spivak, 2005; Nardo *et al.*, 2009).

The rarity of these syndromes associated with mutations in NER genes and compromised repair excludes a direct major public health impact on skin cancer risk, however, suboptimal NER capacity could also result in increased cancer risk. There is increasing evidence that more frequently found genetic variation such as SNPs can also impact on protein expression and function, and thus, potentially cancer risk. It is hypothesized that polymorphisms in genes implicated in the responses to the DNA damage and oxidative stress following exposure to UV constitute genetic susceptibility factors for skin cancers. This has been assessed in many molecular epidemiological studies using either a candidate gene approach or more recently genome-wide association studies (GWAS). SNPs in NER genes have been extensively investigated. For instance, for melanoma, significant associations were found for the NER genes *ERCC1* and *XPF* (which act together in a rate-limiting step in the repair pathway) in a study population of 596 Scottish melanoma patients and 441 population-based controls, with the strongest associations for melanoma cases aged 50 years and under (*ERCC1* OR, 1.59; 95%CI: 1.11–2.27, $P = 0.008$; *XPF* OR, 1.69; 95%CI: 1.18–2.43, $P = 0.003$)] (Povey *et al.*, 2007). Significant associations between melanoma and *XPD* SNPs have also been reported (e.g. Manuguerra, *et al.*, 2006). Variants in genes involved in the signalling cascades activated in response to UVR have been investigated. For instance the *TP53 Arg72Pro* polymorphism, but not *p73* G4C14 → A4T14 and *p21 Ser31Arg*, contribute to the risk of developing cutaneous melanoma (Li *et al.*, 2008).

Over the past few years several groups have assessed the DNA repair capacity in different populations in an attempt to identify "at-risk" subpopulations in the general population (Li *et al.*, 2009). Several DNA-repair phenotypic studies have been developed using cultured blood lymphocytes including the mutagen sensitivity assay, the host-cell reactivation assay, RT–PCR gene expression, microarray for protein expression, and DNA repair capacity. For instance, lower DNA repair capacity measured in a UV-based host-cell reactivation assay has been found in individuals with basal cell carcinoma and cutaneous melanoma (Li *et al.*, 2009), and increased mutagen sensitivity measured as *in vitro* UVB-induced chromatid breaks was found in basal cell carcinoma and squamous cell carcinoma patients (Wang *et al.*, 2005). The underlying molecular basis of this reduced repair capacity remains to be fully determined.

Several studies have reported an age-associated decline in NER (Moriwaki & Takahashi, 2008), which could result in an accumulation of damage, and reduced DNA-repair capacity has been found to be an independent risk factor for basal cell carcinoma and single or non-aggressive squamous cell carcinoma but not for multiple primaries, local aggressiveness, or recurrence of non-melanoma skin cancer (Wang *et al.*, 2007).

Differences have also been reported between keratinocytes and fibroblasts in terms of the lethal effects of UVB and oxidative stress, which could in part be explained by differences in repair capacity and the induction of apoptosis. Keratinocytes have a more efficient NER global genome repair (GGR) subpathway and are characterized by a strong anti-oxidant capacity and a higher susceptibility to reactive-oxygen-species-induced apoptosis than fibroblasts (D'Errico *et al.*, 2005; D'Errico *et al.*, 2007).

Studies following the persistence of DNA photoproducts using high-performance liquid chromatography coupled with tandem mass spectrometry have shown that the rate of removal of UVA-generated cyclobutane-pyrimidine dimers is lower than that of dimers produced by UVB irradiation in human skin using an in-vitro model system (Mouret *et al.*, 2006). The mechanistic basis of these differences in repair capacity remains unknown.

The base-excision repair and single-strand break repair pathways are the main routes for oxidative DNA damage. Attenuation of the repair of 8-oxoguanine via downregulation of the base-excision repair pathway results in hypersensitivity to UVA in a murine cell model (Kim *et al.*, 2002). In humans there is substantial inter-individual variation in 8-oxoguanine repair (Paz-Elizur *et al.*, 2007), and the presence of the *Ser326Cys* SNP in the human 8-oxoguanine DNA glycosylase (*hOGG1*) gene has been shown to impact on its constitutive activity, with the Cys variant protein having a lower enzymatic activity and a greater sensitivity to oxidative stress (Bravard *et al.*, 2009). UVA irradiation induces relocalization of the OGG1 to nuclear speckles where apurinic/apyrimidinic endonuclease-1 (APE1) is also found (Campalans *et al.*, 2007). APE1 is also known as redox factor-1 (REF-1), a redox regulator of multiple stress-inducible transcription factors such as nuclear factor–kappa B (NF-κB). Haploinsufficiency in mice of APE1 increases the apoptotic response to oxidative stress (Unnikrishnan *et al.*, 2009).

4.3.2 SNPs in genes other than those involved in DNA repair

The hypothesis that polymorphisms in genes implicated in the responses to the DNA damage and oxidative stress induced following exposure to UV constitute genetic susceptibility factors for skin cancers has been assessed in many molecular epidemiological studies using either a candidate gene approach or more recently GWAS. For instance, using in a GWAS of 930 Icelanders with basal cell carcinoma and 33117 controls, common variants on 1p36 and 1q42 were found

to be associated with cutaneous basal cell carcinoma but not with melanoma or pigmentation traits (Stacey *et al.*, 2008). SNPs in immune-regulating components such as cytokines may lead to inter-individual differences in immunosuppression response and susceptibility to melanoma. For instance, in the interleukin-6 receptor gene (*IL-6R*), four SNPs (rs6684439, rs4845618, rs4845622, and rs8192284) in linkage disequilibrium were associated with an increased risk of melanoma (Gu *et al.*, 2008). An elevated risk of melanoma was observed in the heterozygous groups of these SNPs with odds ratios of 1.74 (95%CI: 1.07–2.81) for rs6684439; 1.72 (95%CI: 1.04–2.84) for rs4845618; 1.69 (95%CI: 1.03–2.75) for rs4845622; and 1.68 (95%CI: 1.04–2.73) for rs8192284. These associations were not observed in the homozygous variant group with odds ratios ranging from 0.93 to 1.03.

Associations have been found between polymorphisms in the promoter of the vitamin D receptor gene and malignant melanoma (Povey *et al.*, 2007; Barroso *et al.*, 2008; Mocellin & Nitti, 2008) and non-melanoma skin cancer (Gandini *et al.*, 2009).

There is some evidence for a contribution of pigmentation genetic variants, in addition to the melanocortin-1 receptor variants, to variation in human pigmentary phenotypes and possibly the development of skin cancer (Sturm, 2009). A first multistage GWAS of tanning response after exposure to sunlight in over 9000 men and women of European ancestry who live in the USA was recently reported (Nan *et al.*, 2009). An initial analysis of 528173 SNPs genotyped on 2287 women identified with LOC401937 (rs966321) on chromosome 1 as a novel locus highly associated with tanning ability. This association was confirmed in 870 women controls from a skin cancer case–control study with a joint *P* value of 1.6×10^{-9}. However this association was not replicated in two further studies. Several SNPs reaching the genome-wide significance level were located in or adjacent to the loci previously known as pigmentation genes: membrane-associated transporter protein gene (*MATP*), interferon regulatory factor 4 (*IRF4*), tyrosinase (*TYR*), blue eye oculocutaneous albinism type II (*OCA2*), and melanocortin-1 receptor (*MC1R*). These are similar to the hair-colour-related loci detected in the GWAS of hair colour (Han *et al.*, 2008).

4.4 Other effects

4.4.1 Immune response and photoadaptation

The development of skin cancer appears to be controlled in part by the immune system. Within the skin all the necessary cellular requirements are present to induce and elicit antitumoural immunity (Schröder *et al.*, 2006). Almost 30 years ago, Fisher and Kripke were the first to demonstrate that UVR caused suppression of certain aspects of the immune system (Fisher & Kripke, 1977). It has been well documented that patients with organ transplants that are maintained with immunotherapy are very prone to skin cancer (e.g. Bordea *et al.*, 2004). Immunosuppression by solar-simulated UV in men has been observed at doses three times lower than those required for immunosuppression in women (Damian *et al.*, 2008).

The major steps of UV-induced immune suppression have been determined but it should be noted that, in many instances, these details were obtained following a single or a few exposures of a rodent model or human subjects to UVR and that the dose chosen was sufficient to cause burning. In addition, the source used to emit UVR frequently contained more than 50% UVB (wavelength 280–315 nm), considerably more than natural sunlight. In experimental systems, there are differences between what is termed local and systemic immunosuppression. In the former, the antigen is applied directly to the irradiated body site soon after UV exposure. In the latter, following UV exposure of one part

of the body, the antigen is applied to a distant, non-irradiated body site (Applegate *et al.*, 1989).

Following UVB exposure, convincing evidence has been published to indicate that the chromophores for immunosuppression include DNA, urocanic acid (UCA), and cell membranes. Studies by Kripke's team were the first to suggest that DNA (and most likely, the pyrimidine dimer) may be the chromophore for UVB-induced immunosuppression (Applegate *et al.*, 1989), and evidence linking DNA damage with immune modulation has come from studies on XP patients (Suzuki *et al.*, 2001). *Trans*-UCA is a natural component of the strateum corneum, and UV induces a photoisomeric isomerization of *trans*-UCA to *cis*-UCA, which appears to be an initiator of the UV-immunosuppression, although its mechanism of action is still uncertain (Halliday & Rana, 2008; Norval *et al.*, 2008). UVA immunosuppression is likely to involve different chromophores than those required for UVB immunosuppression: molecules like porphyrins have been proposed (Halliday & Rana, 2008).

UVB irradiation triggers the production of various immunomodulatory mediators in the skin. These include cyclooxygenase-2 (COX-2), receptor activator of NF-κB ligand (RANKL), prostaglandins, platelet activating factor, histamine, neuropeptides and cytokines such as tumour necrosis factor (TNF) that modulate the reactivity of the immune cells in the skin (Beissert & Loser, 2008; Halliday & Rana, 2008; Norval *et al.*, 2008). For instance, TNF induces Langerhans cell activation and migration out of the skin into draining lymph nodes, thus limiting the capacity for antigen processing and presentation. Therefore, UVB ultimately suppresses the immune system by inducing the production of immunosuppressive mediators, by damaging and triggering the premature migration of antigen-presenting cells required to stimulate antigen-specific immune responses, by inducing the generation of suppressor cells and by inhibiting the activation of effector and memory T cells. Some of the mechanisms implicated in UVA-induced immunosuppression, such as increased COX-2 activity, are common to those observed after exposure to UVB. In addition, the production of reactive oxygen species and reactive nitrogen species by UVA alters the redox equilibrium and targets proteins, lipids and DNA, and modulates the immune cells resulting in aberrant behaviour and migration of antigen-presenting cells, the inhibition of T-cell activation, and generates suppressor cells (Norval, 2006; Norval *et al.*, 2008, Halliday & Rana, 2008).

The T helper1 (Th1) cytokine response is the main adaptive immune mechanism that offers protection from many infectious diseases. As UVR suppresses this preferentially, while promoting the Th2 cytokine response, there is the potential for UV exposure to increase the severity of infection, to alter viral oncogenicity, to cause reactivation from latency or to decrease the resistance to re-infection. Alteration of immune responses to microorganisms has been shown in rodent models following exposure to UVR (Norval, 2006). In humans, infections by herpes simplex virus (HSV) and human papilloma virus (HPV) are influenced by exposure to sunlight (see IARC, 2007b for details on UV and HPV). UVR is a recognized stimulus of HSV reactivation (Ichihashi *et al.*, 2004) through the suppression of the local immune response as a result of the UV exposure or a direct interaction between the UVR and the virus through modulation of the host transcription factors and the activation of HSV promoters, and hence reactivation of the virus.

There is also some evidence that there are genetic and other differences in the way that individuals respond to vaccination depending on UVR exposure (Norval, 2006). For instance, the findings from a meta-analysis of Bacille Calmette–Guérin clinical trials such as the increase of the efficacy of Bacille Calmette–Guérin vaccination with the

increasing distance from the equator suggested there might be an association between reduced vaccine efficacy and UVR (Colditz *et al.*, 1994).

Human and rodent skins have the capacity to adapt as a result of repeated suberythemal UV exposures. This photoadaption can attenuate the quantity of UVR that reaches the basal and suprabasal cells of the epidermis, and results in an enhanced ability to repair UV-induced DNA damage and an induction of protective enzymes such as superoxide dismutase. Whether photoadaption can lead to photoprotection against the normal downregulation of immunity induced by a high UV dose remains to be established as there are considerable gaps in the knowledge and there are many variables involved, including the acknowledged genetic diversity in the response of individuals to UVR. Evidence for the development of photoadaption is only apparent for epidermal DNA damage, no evidence exists when other parameters were considered such as total urocanic acid content or *cis* isomerization, Langerhans cells and dendritic cell numbers and function, natural killer cell numbers and function, dermal mast cell numbers or contact and delayed hypersensitivity responses (Norval *et al.*, 2008 and references therein). Thus, it is probable that repeatedly irradiating individuals with UVR is likely to continue to result in downregulation of immunity.

4.4.2 Modulation of gene expression

Differential gene expression in a variety of cell types has been demonstrated after exposure to different UV wavebands. For example Koch-Paiz *et al.* (2004) used cDNA microarrays to analyse the responses in human cell line MCF-7 cells following exposure to equitoxic doses of UVA, UVB, and UVC radiation. Under these experimental conditions, 310 of the 7684 genes on the array were UVB responsive, a subset of these to UVC and a subset of the UVB responsive genes also responsive to UVA.

Analysis of the UVR response genes in human melanocytes identified the tyrosine kinase ephrin receptor A2 (EPHA2) as an essential mediator of UVR-induced apoptosis (Zhang *et al.*, 2008).

Chronic UVR exposure can also modulate gene expression. For instance, chronic UVA radiation of human HaCaT keratinocytes results in decreased PTEN expression (He *et al.*, 2006).

MicroRNAs are very small endogenous RNA molecules about 22–25 nucleotides in length capable of post-transcriptional gene regulation. MicroRNAs bind to their target mRNA leading to cleavage or suppression of translation. MicroRNA profiles have been examined in melanomas (and melanoma cell lines) and Kaposi sarcoma (see Sand *et al.*, 2009 and table therein). For instance, the skin specific microRNA miR-203 that represses p63 expression, an important factor in epidermal cell proliferation and differentiation, is downregulated in melanoma lines; miR-221 and miR-222 are linked to melanoma progression through the downregulation of cyclin-dependent kinase inhibitor 1b (p27Kip1/CDKN1B) and the tyrosine kinase c-KIT receptor.

4.5 Synthesis

In addition to what is stated in the summary of Volume 55 of the *IARC Monographs*, it is now known that following exposure to the individual components of UVR, i.e. UVA, UVB or UVC, there is an overlapping profile of DNA damage detectable, in particular for cyclobutane-pyrimidine dimers. However, the proportion of different base-pair changes shows variation depending on the wavelength of radiation and cell type/species. The mechanisms leading to their formation may also be different. Recent experimental evidence in human cells shows that cyclobutane-pyrimidine dimers at cytosine-containing DNA sequences is formed following exposure to both UVA and UVB individually in human skin *ex vivo*.

Human cells have DNA-repair pathways that repair DNA photoproducts: the absence of

these enzymes, as seen in XP patients, leads to an increase risk of developing squamous cell carcinomas and melanomas lending support to a major role of DNA photoproducts in photocarcinogenesis.

UVR exposure gives rise to mutations in several genes in several human cell model systems, and mutations have been detected in several genes in human tumours, for example the *TP53* gene in squamous cell carcinoma and solar keratosis, at DNA bases where known photoproducts could have been formed lending support to a major role of DNA photoproducts in photocarcinogenesis.

Mutations can be detected in human cells exposed to UVA, UVB and UVC: the base-pair changes involved in some of these mutations overlap. In particular, mutations found involving C→T transitions are found in cells treated with either UVA, UVB or UVC. The same situation is found when the base-pair changes, for instance in the *TP53* gene, are analysed in human squamous cell carcinoma and solar keratosis. As C→T transitions are not a specific "fingerprint" for UVA, UVB or UVC, either radiation type could have been at the origin of the exposure initiating the carcinogenic process.

Based on the above mechanistic considerations, UVA, UVB and UVC are carcinogenic in human cells.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of solar radiation. Solar radiation causes cutaneous malignant melanoma, squamous cell carcinoma of the skin and basal cell carcinoma of the skin. A positive association has been observed between exposure to solar radiation and cancer of the lip, conjunctival squamous cell carcinoma and ocular melanoma, based primarily on results observed in the choroid and the ciliary body of the eye.

There is *sufficient evidence* in humans for the carcinogenicity of the use of UV-emitting tanning devices. UV-emitting tanning devices cause cutaneous malignant melanoma and ocular melanoma (observed in the choroid and the ciliary body of the eye). A positive association has been observed between the use of UV-emitting tanning devices and squamous cell carcinoma of the skin.

There is *sufficient evidence* in humans for the carcinogenicity of welding. Current evidence establishes a causal association for ocular melanoma although it is not possible without a full review of welding to attribute the occurrence of ocular melanoma to UV radiation specifically.

There is *sufficient evidence* in experimental animals for the carcinogenicity of solar radiation, broad-spectrum UVR, UVA radiation, UVB radiation, UVC radiation.

Solar radiation is *carcinogenic to humans (Group 1).*

Use of UV-emitting tanning devices is *carcinogenic to humans (Group 1).*

Ultraviolet radiation (bandwidth 100–400 nm, encompassing UVC, UVB and UVA) is *carcinogenic to humans (Group 1).*

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