5. Summary of Data Reported and Evaluation

5.1 Exposure data

Terrestrial life is dependent on radiant energy from the sun. Approximately 5% of solar terrestrial radiation is ultraviolet radiation (UVR), and solar radiation is the major source of human exposure to UVR. Before the beginning of this century, the sun was essentially the only source of UVR, but with the advent of artificial sources the opportunity for additional exposure has increased.

UVR spans the wavelengths from 100 to 400 nm. The biological effects of UVR vary enormously with wavelength; by convention, the ultraviolet spectrum has been further subdivided into three regions: UVC (100–280 nm), UVB (280–315 nm) and UVA (315–400 nm).

Solar UVR that reaches the Earth's surface comprises approximately 95% UVA and 5% UVB: UVC is completely filtered out by the Earth's atmosphere. The amount of solar UVR measured at the Earth's surface depends upon a number of factors, which include solar zenith angle (time of day, season and geographical latitude), stratospheric ozone, atmospheric pollutants, weather, ground reflectance and altitude.

Exposed skin surface is irradiated differently depending on cultural and social behaviour, clothing, the position of the sun in the sky and the relative position of the body. Exposure to UVB of the most exposed skin surfaces, such as nose, tops of the ears and forehead, relative to that of the lesser exposed areas, such as underneath the chin, normally ranges over an order of magnitude. Ground reflectance plays a major role in exposure to UVB of the eye and shaded skin surfaces, particularly with highly reflective surfaces such as snow.

In cutaneous photobiology, radiant exposure is frequently expressed as 'exposure dose' in units of J/cm^2 (or J/m^2). 'Biologically effective dose', derived from radiant exposure weighted by an action spectrum, is expressed in units of J/cm^2 (effective) or as multiples of 'minimal erythema dose' (MED). In cellular photobiology, the term 'fluence' is often used incorrectly as equivalent to radiant exposure.

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

Cumulative annual outdoor exposures may be augmented by exposures to artificial sources of UVR. For example, the use of cosmetic tanning appliances increased in popularity in the 1980s. The majority of users are young women, and the median annual exposure dose is probably 20–30 times the MED. Currently used appliances emit primarily UVA radiation; prior to the 1980s, tanning lamps emitted higher proportions of UVB and UVC.

UVR has been used for several decades to treat skin diseases, notably psoriasis. A variety of sources of UVR are employed, and nearly all emit a broad spectrum of radiation. A typical dose in a single course of UVB phototherapy might lie between 200 and 300 times the MED.

UVR is used in many different industries, yet there is a paucity of data concerning human exposure from these applications, probably because in normal practice sources are well-contained and exposure doses are expected to be low. Acute reactions to overexposure are common among electric arc welders. Staff in hospitals who work with unenclosed phototherapy equipment are at potential risk of overexposure unless protective measures are taken. Individuals exposed to lighting from fluorescent lamps may typically receive annual exposure doses of UVR ranging from 0 to 30 times the MED, depending on illuminance levels and whether or not the lamps are housed behind plastic diffusers. There is increasing use of tungsten–halogen lamps, which also emit UVR, for general lighting.

5.2 Human carcinogenicity data

5.2.1 *Solar radiation*

Subjects with the inherited condition xeroderma pigmentosum appear to have frequencies of nonmelanocytic skin cancer and melanoma that are much higher than expected. Some evidence suggests that the greatest excess occurs on the head and neck.

(*a*) *Nonmelanocytic skin cancer*

The results of descriptive epidemiological studies suggest that exposure to sunlight increases the risk of nonmelanocytic skin cancer. These tumours occur predominantly on the skin of the face and neck, which is most commonly exposed to sunlight, although the distribution of basal-cell carcinomas is not as closely related to the distribution of exposure to the sun as is that of squamous-cell carcinomas. There is a strong inverse relationship between latitude and incidence of or mortality from skin cancer and, conversely, a positive relationship between incidence or mortality and measured or estimated ambient UVR. Migrants to Australia from the British Isles have lower incidence of and mortality from nonmelanocytic skin cancer than the Australian-born population. People who work primarily outdoors have higher mortality from these cancers, and there is some evidence that outdoor workers have higher incidence.

In several cross-sectional studies, positive associations have been seen between measures of solar skin damage and the prevalence of basal- and squamous-cell carcinomas. Measures of actual exposure to the sun have been less strongly associated with these cancers, possibly because of errors in measurement and inadequate control for potential confounding variables. In a study of US fishermen, estimates of individual annual and cumulative exposure to UVB were positively associated with the occurrence of squamous-cell carcinoma but not with the occurrence of basal-cell carcinoma.

Only two population-based case–control studies have been conducted. In one of these, from Canada, the response rate was low and the measures of exposure were crude. In the other study, from Australia, facial telangiectasia and solar elastosis of the neck were strongly associated with the risk for squamous-cell carcinoma, and cutaneous microtopography and solar elastosis of the neck were strongly associated with risk for basal-cell carcinoma. Migrants to Australia had a lower risk of squamous-cell carcinoma than did native-born Australians, and migrants who arrived after childhood had a lower risk for basal-cell carcinoma.

The hospital-based case–control studies that have been conducted suffer from methodological deficiencies, including choice of controls, measurement of exposure and confounding by reaction to sunlight, and are therefore difficult to interpret.

In a cohort study of nurses in the USA, those who spent more than 8 h per week outside without sunscreens had a similar incidence rate of basal-cell carcinoma to those who spent fewer than 8 h per week outdoors. In a cohort study from Victoria, Australia, the rates of both types of skin cancer were increased in outdoor workers, but the effect was not significant after adjustment for reaction to sunlight.

(*b*) *Cancer of the lip*

Cancer of the lip has been related to outdoor occupation in a number of descriptive studies. Migrants to Australia and Israel have lower risks than native-born residents.

Three case–control studies provide useful information about the association between outdoor work, taken as a proxy measure for exposure to UVR, and cancer of the lip. All of them showed a significantly increased risk, although potential confounding by tobacco use was not controlled adequately in any of the studies.

Assessment of the carcinogenicity of solar radiation for the lip is complicated by the fact that carcinoma of the lip as actually diagnosed is a mixture of cancers of the external lip and cancers of the buccal membranes. Use of alcohol and tobacco are known causes of the latter tumours.

(*c*) *Malignant melanoma of the skin*

Descriptive studies in whites in North America, Australia and several other countries show a positive association between incidence of and mortality from melanoma and residence at lower latitudes. Studies of migrants suggest that the risk of melanoma is related to solar radiant exposure at the place of residence in early life. The body site distribution of melanoma shows lower rates per unit area on sites usually unexposed to the sun than on usually or regularly exposed sites.

A large number of case–control studies are pertinent to the relationship between melanoma and exposure to the sun. These include large, carefully conducted population-based studies carried out in Western Australia, Queensland, western Canada and Denmark. Their results are generally consistent with positive associations with residence in sunny environments throughout life, in early life and even for short periods in early adult life. Positive associations are generally seen between measurements of cumulative sun damage expressed biologically as microtopographical changes or history of keratoses or nonmelanocytic skin cancer.

In contrast, the associations with total exposure to the sun over a lifetime or in recent years, as assessed by questionnaire, are inconsistent. This inconsistency may be due to differences in the effects of chronic and intermittent exposure. Chronic exposure, as assessed through occupational exposure, appeared to reduce melanoma risk in three of the large studies, particularly in men; this observation is consistent with the descriptive epidemiology of the condition, which shows lower risks in groups that work outdoors. Several other studies, which were generally smaller or had less detailed methods of exposure assessment, show either no effect or an increased risk associated with occupational exposures.

Assessment of intermittent exposure is complex; nonetheless, most studies show positive associations with measure of intermittent exposure, such as particular sun-intensive activities, outdoor recreation or vacations.

Most studies show positive associations with a history of sunburn; however, this association cannot be easily interpreted, because while it might accurately reflect sunburn it could just as well reflect either the tendency to sunburn, if exposed, or intermittent exposure more generally.

(*d*) *Melanoma of the eye*

There is no latitude gradient among white populations of the incidence of ocular neoplasms, some 80% of which are likely to be ocular melanomas. No effect of southern US birthplace was seen in the two descriptive studies in the USA that examined this aspect.

Four case–control studies, from western Canada and from Philadelphia, San Francisco and Boston, USA, provided information on the association between exposure to solar radiation and ocular melanoma. All of these studies demonstrate an increased risk of ocular melanoma in people with light skin, light eye colour or light hair colour. Two of the studies compared effect of southern US birthplace with birth elsewhere in the USA; a significant difference was seen in the Philadelphia study.

Past residence south of 40 °N latitude was positively associated with ocular melanoma in the Boston study but was not significant in the Philadelphia study after control for southern birthplace. Although several outdoor activities, such as gardening and sunbathing, were associated in the Philadelphia study with ocular melanoma, participation in outdoor activities did not increase risk significantly in Boston or San Francisco.

The lack of consistency of the results of these studies makes their interpretation difficult.

(*e*) *Other cancers*

No adequate study was available to evaluate the role of solar radiation in cancers at other body sites.

5.2.2 *Artificial sources of ultraviolet radiation*

No adequate study was available on nonmelanocytic skin cancer in relation to exposure to artificial sources of UVR.

Two case–control studies, one from Scotland and one from Ontario, with detailed information on use of sunbeds and sunlamps showed positive relationships between duration of use and risk of melanoma of the skin. Several other studies with limited information showed no association.

One case–control study from Sydney, Australia, showed a positive relationship between melanoma of the skin and exposure to fluorescent lights at work among women, but the measurement of exposure was crude and among exposed cases there was a relative excess of melanoma on the trunk, a site likely to be covered at work. A more detailed study from Australia showed no consistent association between cumulative exposure or rate of exposure to fluorescent lights and melanoma. Two other studies had detailed information on exposure. One, from Scotland, showed no such association, while the other, from England, had inconsistent effects depending on the method of ascertainment of information. Another study, from New York, with limited information also showed inconsistent effects depending on the source of information.

Two case–control studies, from Boston and Philadelphia, USA, showed significant positive associations between use of sunlamps and melanoma of the eye. Another case–control study, from San Francisco, showed an increased risk for exposure to 'UV or black light', although the nature of the exposure was not specified.

Two studies, from Philadelphia and Montréal, showed significant positive associations between welding and melanoma of the eye.

5.2.3 *Molecular genetics of human skin cancers*

Base substitutions in a tumour suppressor gene, p53, found in human squamous-cell skin carcinomas that had developed at sites exposed to the sun were similar to those found in experimental systems exposed to UVR, and especially to UVB.

5.3 Carcinogenicity in experimental animals

Solar radiation was tested for carcinogenicity in a series of exceptional studies in mice and rats. Large numbers of animals were studied, and well-characterized benign and malignant skin tumours developed in most of the surviving animals. Although the reports are deficient in quantitative details, the results provide convincing evidence that sunlight is carcinogenic for the skin of animals.

Broad-spectrum UVR (solar-simulated radiation and ultraviolet lamps emitting mainly UVB) was tested for carcinogenicity in many studies in mice, to a lesser extent in rats and in a few experiments in hamsters, guinea-pigs, opossums and fish. Benign and malignant skin tumours were induced in all of these species except guinea-pigs, and tumours of the cornea and conjunctiva were induced in rats, mice and hamsters.

The predominant type of tumours induced by UVR in mice is squamous-cell carcinoma. Basal-cell carcinomas have been observed occasionally in athymic nude mice and rats exposed to UVR. Melanocytic neoplasms of the skin were shown to develop following exposure of opossums and hybrid fish to broad-spectrum UVR.

Studies in hairless mice demonstrated the carcinogenicity of exposures to UVR in the wavelength ranges 315–400 nm (UVA), 280–315 nm (UVB) and $\leq$ 280 nm (UVC), UVB radiation being the most effective, followed by UVC and UVA. UVB radiation is three to four orders of magnitude more effective than UVA. Both short-wavelength UVA (315–340 nm) and long-wavelength UVA (340–400 nm) induced skin cancer in hairless mice. The carcinogenic effectiveness of the latter waveband is known only as an average value over the

entire range; the uncertainty of this average is about one order of magnitude. In none of the experiments involving UVC was it possible to exclude completely a contribution of UVB, but the size of the effects observed indicate that they cannot be due to UVB alone.

No experimental data were available on the carcinogenicity to animals of radiation from general lighting fixtures, including fluorescent and quartz halogen lamps.

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

5.4 Other relevant data

5.4.1 *Transmission and absorption*

Studies of transmission in whole human and mouse epidermis and human stratum corneum *in vitro* show that these tissues attenuate radiation in the solar UVR range. This attenuation, which is more pronounced for the UVB than for the UVA wavebands, affords some protection from solar UVR to dividing cells in the basal layer.

The different components of the human eye act as optical filters for the UVR range. Consequently, little or no UVR reaches the retina in the normal eye.

5.4.2 *Effects on the skin*

UVR produces erythema, melanin pigmentation and acute and chronic cellular and histological changes in humans. Generally consistent changes are seen in experimental species, including the hairless mouse.

The action spectra for erythema and tanning in humans and for oedema in hairless mice are similar. UVB is three to four times more effective than UVA in producing erythema. In humans, pigmentation protects against erythema and histopathological changes. People with a poor ability to tan, who burn easily and have light eye and hair colour are at a higher risk of developing melanoma, basal-cell and squamous-cell carcinomas (see section 5.2).

In humans, acquired pigmented naevi and solar keratoses, indicators of melanomas and squamous-cell carcinomas, respectively, are induced by exposure to the sun.

Xeroderma pigmentosum patients have a high frequency of pigmentary abnormalities and skin cancers on sun-exposed skin. These patients also have defective DNA repair.

5.4.3 *Effects on the immune response*

Relatively few investigations have been reported of the effects of UVR on immunity in humans, but changes do occur. There is evidence that contact allergy is suppressed by exposure to UVB and possibly to UVA radiation. The number of Langerhans' cells in the epidermis is decreased by exposure to UVR and sunlight, and the morphological loss of these cells is associated with changes in antigen-presenting cell function in the direction of suppression; this change may be due not only to simple loss of function but also to active

migration of other antigen-presenting cells into the skin. A reduction in natural killer cell activity also occurs, which can be produced by UVA radiation. These changes are short-lived, and their functional significance is unknown. Pigmentation of the skin may not protect against some UVR-induced alterations of immune function.

Several immune responses are suppressed by UVR in mice and other rodents. Suppression of contact hypersensitivity has received most attention, and this response may be impaired locally, at the site of exposure to radiation, or systemically, at a distant, unexposed site. The two forms of suppression have different dose dependencies—systemic suppression requiring much higher doses—and their mechanisms appear to differ, but the efferent limb of each involves generation of hapten-specific T-suppressor cells that block induction but not elicitation of contact hypersensitivity. Systemic suppression of delayed hypersensitivity to injected antigens can also be produced by exposure to UVB radiation, and several observations suggest that the mechanism of this suppression differs from that of systemic suppression of contact hypersensitivity.

Alterations in immune function induced by exposure to UVR play a central role in photocarcinogenesis in mice. UVR-induced T-suppressor cells block a normal immunosurveillance system that prevents the growth of highly antigenic UVR-induced tumours. It is not known whether this mechanism operates in humans.

5.4.4 *DNA photoproducts*

Solar UVR induces a variety of photoproducts in DNA, including cyclobutane-type pyrimidine dimers, pyrimidine–pyrimidone (6-4) photoproducts, thymine glycols, cytosine damage, purine damage, DNA strand breaks and DNA–protein cross-links. Substantial information on biological consequences is available only for the first two classes. Both are potentially cytotoxic and can lead to mutations in cultured cells, and there is evidence that cyclobutane-type pyrimidine dimers may be precarcinogenic lesions. The relative and absolute levels of each type of lesion vary with wavelength. Substantial levels of thymidine glycols, strand breaks and DNA–protein cross-links are induced by solar UVA and UVB radiation, but not by UVC radiation. The ratio of strand breaks to cyclobutane-type dimer lesions increases as a function of increasing wavelength. In narrow band-width studies, the longest wavelength at which cyclobutane-type pyrimidine dimers have been observed is 365 nm, whereas the induction of strand breaks and DNA–protein cross-links has been observed at wavelengths in the UVB, UVA and visible ranges. Non-DNA chromophores such as porphyrins, which absorb solar UVR, appeared to be important in generating active intermediates that can lead to damage. Solar UVR also induces membrane damage.

5.4.5 *Genetic and related effects*

Measurable DNA damage is induced in human skin cells *in vivo* after exposures to UVA, UVB and UVC radiation, including doses in the range commonly experienced by humans. Most of the DNA damage after a single exposure is repaired within 24 h. The importance of these wavelength ranges depends on several factors. UVB is the most effective, UVC being somewhat less effective and UVA being much less effective, when compared on a per photon basis, probably owing to a combination of the biological effectiveness of the different wavebands and of their absorption in the outer layers of the skin.

Summary table of genetic and related effects of ultraviolet A radiation

Nonmammalian systems														Mammalian systems																											
Prokaryotes		Lower eukaryotes				Plants			Insects					*In vitro*												*In vivo*															
														Animal cells								Human cells								Animals							Humans				
D	G	D	R	G	A	D	G	C	R	G	C	A		D	G	S	M	C	A	T	I	D	G	S	M	C	A	T	I	D	G	S	M	C	DL	A	D	S	M	C	A
	+	+												+[1]	+	+[1]		+[1]				+	+														+[1]				

A, aneuploidy; C, chromosomal aberrations; D, DNA damage; DL, dominant lethal mutation; G, gene mutation; I, inhibition of intercellular communication; M, micronuclei; R, mitotic recombination and gene conversion; S, sister chromatid exchange; T, cell transformation

In completing the tables, the following symbols indicate the consensus of the Working Group with regard to the results for each endpoint:

+ considered to be positive for the specific endpoint and level of biological complexity

+[1] considered to be positive, but only one valid study was available to the Working Group; sperm abnormality, mouse

– considered to be negative

–[1] considered to be negative, but only one valid study was available to the Working Group

? considered to be equivocal or inconclusive (e.g., there were contradictory results from different laboratories; there were confounding exposures; the results were equivocal)

Summary table of genetic and related effects of ultraviolet B radiation

Nonmammalian systems														Mammalian systems																									
Prokaryotes		Lower eukaryotes				Plants			Insects				*In vitro*															*In vivo*											
													Animal cells								Human cells								Animals							Humans				
D	G	D	R	G	A	D	G	C	R	G	C	A	D	G	S	M	C	A	T	I	D	G	S	M	C	A	T	I	D	G	S	M	C	DL	A	D	S	M	C	A
	+							+[1]					+	+	+[1]				+		+	+					+[1]		+							+				

A, aneuploidy; C, chromosomal aberrations; D, DNA damage; DL, dominant lethal mutation; G, gene mutation; I, inhibition of intercellular communication; M, micronuclei; R, mitotic recombination and gene conversion; S, sister chromatid exchange; T, cell transformation

In completing the tables, the following symbols indicate the consensus of the Working Group with regard to the results for each endpoint:

+ considered to be positive for the specific endpoint and level of biological complexity

+[1] considered to be positive, but only one valid study was available to the Working Group; sperm abnormality, mouse

– considered to be negative

–[1] considered to be negative, but only one valid study was available to the Working Group

? considered to be equivocal or inconclusive (e.g., there were contradictory results from different laboratories; there were confounding exposures; the results were equivocal)

Summary table of genetic and related effects of ultraviolet C radiation

Nonmammalian systems												
Prokaryotes		Lower eukaryotes				Plants			Insects			
D	G	D	R	G	A	D	G	C	R	G	C	A
+	+	+		+	+[1]	+	+[1]	+[1]				

Mammalian systems – *In vitro*															
Animal cells								Human cells							
D	G	S	M	C	A	T	I	D	G	S	M	C	A	T	I
+[1]	+	+		+		+		+	+	+	+[1]	+		+	

Mammalian systems – *In vivo*											
Animals							Humans				
D	G	S	M	C	DL	A	D	S	M	C	A
+[1]							+[1]				

A, aneuploidy; C, chromosomal aberrations; D, DNA damage; DL, dominant lethal mutation; G, gene mutation; I, inhibition of intercellular communication; M, micronuclei; R, mitotic recombination and gene conversion; S, sister chromatid exchange; T, cell transformation

In completing the tables, the following symbols indicate the consensus of the Working Group with regard to the results for each endpoint:

+ considered to be positive for the specific endpoint and level of biological complexity

+[1] considered to be positive, but only one valid study was available to the Working Group; sperm abnormality, mouse

- considered to be negative

-[1] considered to be negative, but only one valid study was available to the Working Group

? considered to be equivocal or inconclusive (e.g., there were contradictory results from different laboratories; there were confounding exposures; the results were equivocal)

Solar and 'solar-simulated' radiation and radiation from sunlamps (UVA and UVB) are mutagenic to prokaryotes and plants, induce DNA damage in fish and in amphibian cells *in vitro*, are mutagenic to and induce sister chromatid exchange in amphibian cells, induce micronucleus formation and transformation in mammalian cells *in vitro*, are mutagenic to and induce DNA damage and sister chromatid exchange in human cells *in vitro* and induce DNA damage in mammalian skin cells irradiated *in vivo*.

UVA radiation is mutagenic to prokaryotes and induces DNA damage in fungi. It is mutagenic to and induces DNA damage, chromosomal aberrations and sister chromatid exchange in mammalian cells and induces DNA damage and mutation in human cells *in vitro*.

UVB radiation is mutagenic to prokaryotes and induces chromosomal aberrations in plants. It is mutagenic to and induces DNA damage, sister chromatid exchange and transformation in mammalian cells, is mutagenic and induces DNA damage and transformation in human cells *in vitro* and induces DNA damage in mammalian skin cells irradiated *in vivo*.

UVC radiation induces DNA damage in and is mutagenic to prokaryotes, fungi and plants and induces DNA damage in insects and aneuploidy in yeast. It induces sister chromatid exchange in amphibian and avian cells *in vitro*; it is mutagenic to and induces DNA damage, chromosomal aberrations, sister chromatid exchange and transformation in mammalian and human cells *in vitro*; and it induces DNA damage in mammalian skin cells irradiated *in vivo*.

UVR in the three wavelength ranges can induce or enhance cellular and viral gene expression.

5.5 Evaluation[1]

There is *sufficient evidence* in humans for the carcinogenicity of solar radiation. Solar radiation causes cutaneous malignant melanoma and nonmelanocytic skin cancer.

There is *limited evidence* in humans for the carcinogenicity of exposure to ultraviolet radiation from sunlamps and sunbeds.

There is *inadequate evidence* in humans for the carcinogenicity of exposure to fluorescent lighting.

There is *inadequate evidence* in humans for the carcinogenicity of other sources of artificial ultraviolet radiation.

There is *sufficient evidence* for the carcinogenicity of solar radiation in experimental animals.

There is *sufficient evidence* for the carcinogenicity of broad-spectrum ultraviolet radiation in experimental animals.

There is *sufficient evidence* for the carcinogenicity of ultraviolet A radiation in experimental animals.

There is *sufficient evidence* for the carcinogenicity of ultraviolet B radiation in experimental animals.

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[1]For definition of the italicized terms, see Preamble, pp. 32–35.

There is *sufficient evidence* for the carcinogenicity of ultraviolet C radiation in experimental animals.

Overall evaluation

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

Ultraviolet A radiation *is probably carcinogenic to humans* (Group 2A).

Ultraviolet B radiation *is probably carcinogenic to humans* (Group 2A).

Ultraviolet C radiation *is probably carcinogenic to humans* (Group 2A).

Use of sunlamps and sunbeds *entails exposures that are probably carcinogenic to humans* (Group 2A).

Exposure to fluorescent lighting *is not classifiable as to its carcinogenicity to humans* (Group 3).