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# Dose-response relationship for the association of UV radiation and skin cancer

Statement by the German Commission on Radiological Protection

Adopted at the 323rd meeting of the German Commission on Radiological Protection on the 2/3 February 2023

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**Dosis-Wirkungsbeziehung für den Zusammenhang von UV-Strahlung und Hautkrebs Stellungnahme der Strahlenschutzkommission**

## Preface

Skin cancers such as squamous cell carcinoma, basal cell carcinoma and malignant melanoma are among the most frequent types of cancer in the world, including Germany. Despite this and the fact that ultraviolet radiation (UVR) has been proven to be the main risk factor for the induction of skin cancer, there is still no robust data available to describe a dose-response relationship between the UV dose and incidences of various types of skin cancer. This limited level of knowledge makes it difficult to offer targeted risk communication about UV-induced skin cancers since dose-response relationships as it is common in the context of ionising radiation can help to extrapolate the estimated number of cancer cases among the public resulting from specific types of exposure. Given this situation, the German Commission on Radiological Protection was commissioned to collate the current state of knowledge surrounding dose-response relationships between UV exposure and UV-induced skin cancer, and to propose steps to be taken to improve the current situation, particularly in terms of research.

To prepare a statement with a scientific justification, a working group on dose-response relationship for the association of UV radiation and skin cancer was formed from the non-ionising radiation committee of the German Commission on Radiological Protection, and comprised the following members:

- Dr Rüdiger Greinert (Elbe Klinikum Buxtehude), working group chair,
- Dr Stefan Bauer (Federal Institute for Occupational Safety and Health (BAuA) Dortmund),
- Prof. Thomas L. Diepgen † (Heidelberg University Hospital), member from July 2017 to March 2020,
- Dr Beate Volkmer (Elbe Klinikum Buxtehude),
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The working group was supported by Dr Klaus Kraywinkel (Robert Koch Institute in Berlin) and Timo Heepenstrick (Institute for Occupational Safety and Health of the German Social Accident Insurance (DGUV) in Sankt Augustin).

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# 1 Introduction

Based on the accumulated incidence rates for basal cell carcinoma, squamous cell carcinoma and malignant melanoma, skin cancer is the most common type of cancer in fair-skinned populations worldwide (and Germany) (Leiter et al. 2014). These incidence rates continue to rise globally, except for malignant melanoma in Australia (Erdmann et al. 2013, Helgadottir et al. 2021). The main risk factor for this development has now been demonstraed to be exposure to ultraviolet radiation (UVR) from solar and artificial sources such as solaria (cf. Chapter 2). However, many of the molecular mechanisms involved in UV-induced skin cancer are still not understood. As yet there is no robust data available for the dependency of skin cancer incidence on the underlying UV radiation levels and concomitant dose or exposure measurements. Such data are important to protect against UV radiation and would enable the description of a dose-response relationship for UV-induced skin cancer. At present, there are no risk coefficients available to calculate risk estimates for a specific UV exposure[1], as with ionising radiation.

With a reliable dose-response relationship, UVR protection could be improved in the following areas:

- *Demographic development:*

  Better estimates could be provided for UV-dependent skin cancer incidences that change on account of demographic development in Germany.

  Like with other types of cancer, the incidence rates for most of skin cancers (basal cell carcinoma and squamous cell carcinoma) will increase significantly with age. In the interests of radiological protection and prevention, efforts should be made to better predict this development so that prompt and appropriate action can be taken.

- *Risk groups:*

  To bring UV protection measures into line with changing UV exposure conditions at an early stage, better estimates could be provided for changes to skin cancer incidence in various risk groups, e.g. workers with occupational UV exposure.

  This would enable more reliable recommendations to be issued to the public regarding their leisure-time behaviour, and the setting of UV exposure limits for both professional and private settings.

- *Climate change:*

  Better estimates could be provided with a view to the influence of climate change on UV exposure and skin cancer incidence in Germany.

Efforts should be made to collate data on individual UV exposures and/or to create models that enable predictions regarding the incidence of skin cancers. As UV dose, the central parameter for these dose-response relationships, depends heavily on personal behaviour at work, during leisure time, use of sunscreen, etc., robust dose-response relationships will need to be based on

[1] The term “UV exposure” is used frequently in this statement and reflects usage in international literature. It describes the irradiation of cells, animals or humans with a certain UV irradiance [$J\,m^{-2}\,s^{-1}$], or the fact that exposed cells, animals or humans were exposed to a UV dose [$J\,m^{-2}$] for a certain period of time or have accumulated such a UV dose. However, the term “UV exposure” is also used simply to describe the fact that UV irradiation occurred which, at best, can be characterised by a UV irradiance level or dose.

UV doses measured individually and/or derived from or modelled on other UV exposures. This means that emphasis must be placed on personal dosimetry[2].

The German Commission on Radiological Protection (SSK) has been monitoring the increase in incidence for various types of skin cancer in Germany for several years now, and last compiled its findings about the association of skin cancer and UV radiation in a recommendation of 2016 titled "Protection of man against the hazards of solar UV radiation and UV radiation in solaria" (SSK 2016). This publication also included a series of recommendations to help minimise the risk of developing UV-induced skin cancer. The present recommendation is intended to expound on the 2016 SSK recommendation (SSK 2016), which showed that further insight into dose-response relationships for the association between UV radiation and skin cancer could allow trends to be derived for future skin cancer incidences.

As set out in the advisory mandate issued by the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) dated 13 July 2017, the SSK was asked to advise on the "dose-response relationship for the association of UV radiation and skin cancer". The advisory mandate comprises two main aspects. First, the current level of knowledge should be ascertained, and an analysis conducted to identify deficits in the data and literature. This aspect is covered in Chapter 2 of this statement under the heading "Current state of science". Second, the outcome of compiling and analysing this information should be used as a basis for the statement provided in Chapter 3, which describes measures required to rectify the identified deficits, particularly in the fields of epidemiological, metrological and biomedical research.

# 2 Current state of science

## 2.1 Skin cancer incidence worldwide and in Germany

### 2.1.1 Malignant melanoma

The following estimates on malignant melanoma incidence are based on data from the epidemiological cancer registries maintained by each federal state in Germany (the final state to do so created its register in 2009). On a federal level, the German Centre for Cancer Registry Data has published annual incidence estimates for Germany since 1999 (RKI and GEKID 2019). Cancer registry coverage varies significantly on an international level, with in particular economically weak regions publishing little data. The International Agency for Research on Cancer (IARC) uses registry data and information from other sources to issue regular incidence and mortality estimates for the most frequent types of cancer in every country and region worldwide. However, given that the data sources and methods change over time, these estimates cannot be used for trend analyses.

Based on a current estimate by IARC for 2020, which includes data from population-based cancer registries up to 2016, around 325,000 persons worldwide develop melanoma skin cancer each year, representing about 1.7% of all cancer cases (Ferlay et al. 2020). A little over half of cases (54%) occur in males, with 49% occurring before the age of 65. Incidence rates vary significantly around the world. After factoring out the effect of differing age distributions

[2] Here, personal dosimetry involves measuring a person's individual solar UV exposure on a certain part of their body

among their given population (age standardisation[3] based on the world standard population[4]), the annual incidence rates of around 36 per 100,000 people in Australia and New Zealand are around 100 times higher than that in South and Central Asia (0.3 per 100,000 people) (Figure 1). Northern and Western Europe (which includes Germany according to the WHO definition) has the second-highest incidence rate after Australia, although the rate is around half of that seen in Australia. Taking Europe as a whole, estimates show around 151,000 newly diagnosed cases of skin cancer each year, with some 106,000 annual cases in the EU countries (27 member states). This equates to a 3.7% and 4% share of all cancer types respectively.

[3] Age standardisation: In epidemiology, the term "standardisation" refers to two different methods used to calculate measures permitting meaningful comparisons of populations. Here, a basic distinction must be made between direct and indirect standardisation. Age standardisation involves a standardisation of measures with regard to age structure.
When performing a direct age standardisation, the measures calculated in 5-year age intervals for the population at hand are converted to a standard population. This is typically linked to the age structure from the previous census for the time series of a country. A world standard population is used to draw international comparisons.

[4] World standard population: Standardised world population (see also footnote on age standardisation)

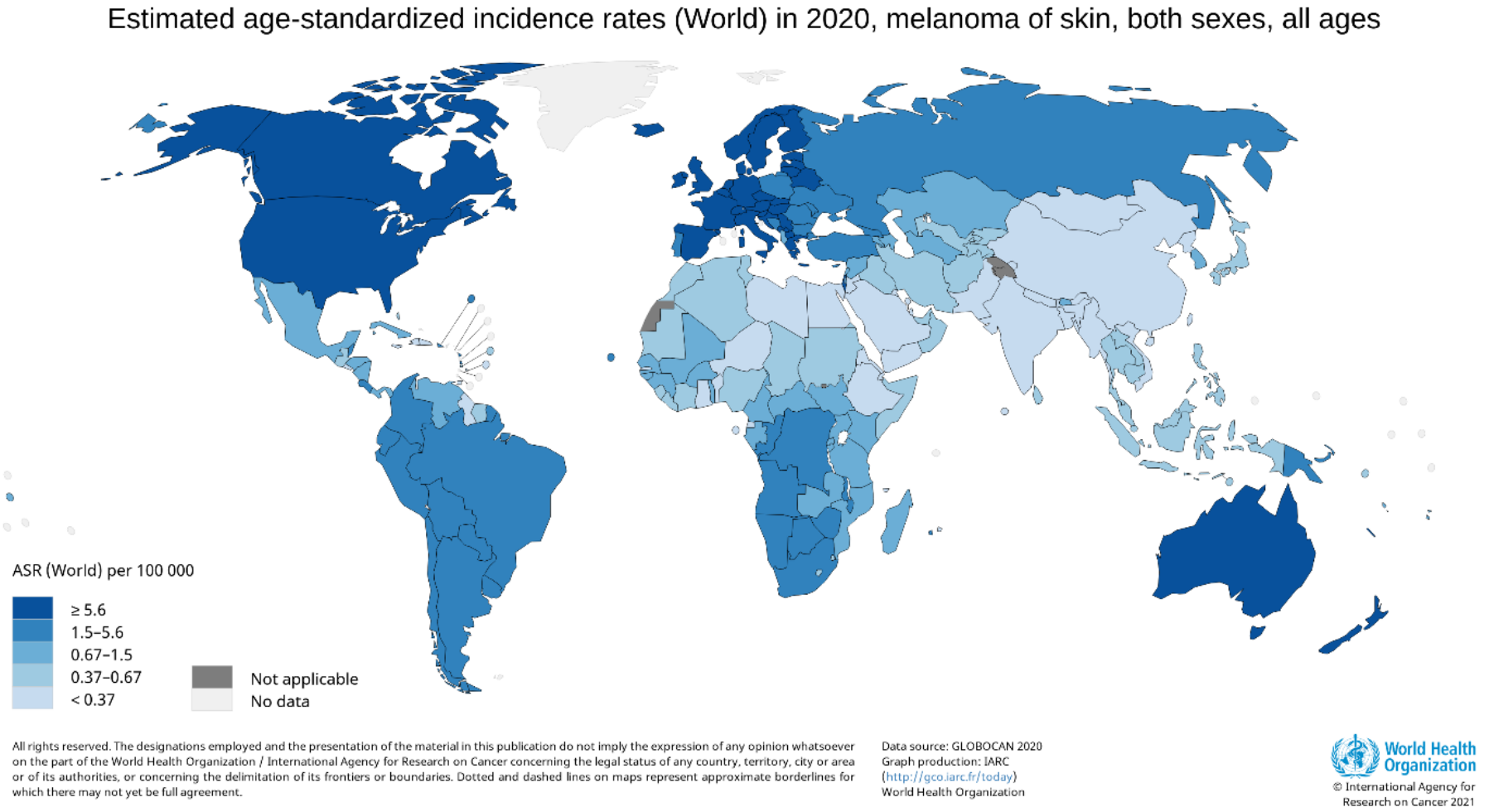


*Figure 1: Estimated age-standardised incidence rates (world) in 2020, melanoma of skin, all sexes, all ages. The lowest annual incidence rates are 0.3 per 100,000 people in South and Central Asia, while the highest annual incidence rates are around 36 per 100,000 people in Australia and New Zealand.*

The high incidence rates in Norway (the highest in Europe), South Africa and, above all, Australia exceed those for countries at a similar latitude, showing that ethnicity and skin type are influencing factors. In US registries this is immediately apparent as from 2012 to 2016, annual incidence among white Americans stood at 26.6 per 100,000 people (2000 US standard population[5]), which is over 25 times higher than the annual incidence of 1.0 per 100,000 people observed among African Americans. This is notable given that a higher share of African Americans live in the southern states of the US and thus have higher UV exposures (SEER 2018b). Annual incidence among people of Asian, Hispanic or indigenous origin is 1.4 to 5.5 per 100,000, which is far lower than the rate among people of European descent. Among populations that are relatively homogenous in terms of ethnicity, latitude and UV exposure at the place of residence also appear to have an influence as incidence is higher the nearer to the equator people live, as reflected in the data for North America (Elwood et al. 1974, Crombie 1979, Lee and Scotto 1993). Various studies, not least from Germany, show a higher risk of skin cancer in areas with a higher average social status, which is not typical for cancer otherwise. Differences in travel and leisure habits are being discussed as possible causes (Hoebel et al. 2018, Singh et al. 2011, Singh et al. 2003, Pearce et al. 2006, Jiang et al. 2015).

IARC estimates do not provide any trend analyses, meaning that other data sources are required for such purposes. The nine US cancer registries within the Surveillance, Epidemiology, and End Results (SEER) Program[6] go back as far as 1975 and show that age-standardised incidence rates have trebled over the past forty years. This increase is particularly evident among higher age groups (SEER 2018a). Scandinavian registries show that incidence rates almost quadrupled during the same forty-year period (Danckert B et al. 2019, Engholm et al. 2010). Irrespective of sex, ethnicity and age, incidence rates in the US have levelled off since 2013, while numbers in Scandinavia continue to rise. Erdmann et al. reported similar findings in their work from 2013 (Erdmann et al. 2013) which analysed data from 39 countries up to the year 2008. The authors found that incidence rates in North America and Australia levelled off, particularly among younger age groups, which was not seen in most European countries. Over the last ten years covered by the data, around two-third of the countries analysed saw annual increases of between 2% and 5%. In most countries, cohort effects[7] (e.g. birth or age cohorts) presented steadily rising rates in generations born up to the end of the 1940s, and sometimes extending beyond that. This could indicate that (behavioural) changes in terms of UV exposure are an important factor among certain age groups, e.g. during childhood and adolescence. In addition, period effects[8] also showed similar increases in different age groups during the same period. Period effects will rather be attributable to changes in exposure that are unrelated to age (e.g. climatic changes), or to increased detection rates because of increased awareness and improved diagnostics.

Malignant melanoma is the cause of around one in 175 of an approximate 57,000 global annual cancer deaths (Ferlay et al. 2020). The incidence of 325,000 referred to above means that one death occurs for every five to six new cases of melanoma worldwide. When used as an estimator of disease-specific survival, the five-year survival rates for the years 2010 to 2014 were over 90% in the US, Australia, New Zealand and some Northern and Western European countries

[5] 2000 US standard population: Population of the United States of America recorded during a census in the year 2000.

[6] https://seer.cancer.gov/

[7] Cohort effect: Differences in disease incidence between different birth cohorts, e.g. irrespective of age, females born after 1960 have a lower risk of developing lung cancer than females born before 1960 due to changes in smoking habits between generations.

[8] Period effect: Unlike the cohort effect, the period effect refers to changes in disease incidence within a certain period of time. An example here would be an increase in thyroid cancer incidence among all age groups 10 years after a reactor accident.

(including Germany), and below 60% in China, Ecuador and Taiwan (Allemani et al. 2018). Correspondingly, differences in melanoma mortality globally were lower than differences in incidence where annual mortality rates ranged from 0.2 per 100,000 people in Eastern, Southern and Central Asia to 3.4 per 100,000 people in Australia and New Zealand (Ferlay et al. 2020).

In Germany, estimates by the Robert Koch Institute (RKI) using data from the Saarland cancer registry and the cancer registry of the German Democratic Republic (GDR) showed a threefold increase in age-standardised incidence rates between 1970 and 1990. According to the Robert Koch Institute, these disease rates then continued to increase at a lower rate until skin cancer screening was introduced in 2008. This led to a major increase of approximately 25% to 30%, which is largely attributable to an increase in diagnosed cases of superficial spreading melanoma with a favourable prognosis (Barnes et al. 2016). This now makes around two-thirds of all new (histologically proven) cases. Between 2009 and 2016, age-standardised annual incidence rates remained largely stable at around 20 per 100,000 for all sexes (old European Standard Population[9]) (RKI and GEKID 2021). However, the influence of screening makes it difficult to evaluate current trends and to extrapolate future incidence rates. According to estimates by the Robert Koch Institute, in 2017 around 22,900 people in Germany (10,900 of whom were female) presented with melanoma for the first time, accounting for 4.7% of all cancer types in all sexes (RKI and GEKID 2021). Based on extrapolations using data from the Schleswig-Holstein cancer registry, an additional 15,800 people in Germany are likely to be diagnosed with the earliest detectable type of malignant melanoma (in situ melanoma) each year (Katalinic 2020).

In Germany, the mean age of incidence for invasive types of melanoma is 60 for females and 68 for males. Some two-thirds of sufficiently documented cases were diagnosed at an early stage (Union for International Cancer Control (UICC)), more frequently in females (73%) than in males (66%). The most often affected part of the body was the torso in males (approximately 41% ) and the lower extremities in females (31%) (RKI and GEKID 2021).

When diagnosed at an early stage (UICC stage I: tumour thickness < 1 mm or < 2 mm without ulceration, neither lymphatic nor systemic metastases), the chance for survival is statistically not impaired compared with the general population, at least in the first five years following diagnosis (100% relative five-year survival rate). At intermediate stages, this value drops to just under 80% for stage II and below 70% for stage III. Survival rates are far worse if metastases are present in other organs at initial diagnosis (stage IV). In such instances, the relative five-year survival rate is only approximately 20% (RKI and GEKID 2021).

In 2019, there were 3,021 melanoma-related deaths in Germany. Between 2009 and 2019, annual age-standardised death rates remained stable for all sexes at 3.0 per 100,000 females and 4.0 per 100,000 males (Germany 2011 standard population) (Destatis 2020). Prior to that, a gradual increase had only been observed in males since the 1970s (Barnes et al. 2016). When drawing comparisons on a European level, IARC estimates that Germany's melanoma mortality for 2020 is approximately 6% lower than the EU average, despite a 52% higher incidence (ECIS 2020).

### 2.1.2 Non-melanoma skin cancer

There is far less epidemiological data available for non-melanoma skin cancers (NMSCs) than for melanoma skin cancer. In many population-based cancer registries, including the US SEER registries, the data for NMSCs is incomplete or fully absent. One likely main reason for this is that non-melanoma skin cancers often are treated on an outpatient basis. Some subtypes like

[9] Old European Standard Population (ESP): Refers to the Old European Standard Population introduced in 1976 which assigned the same age structure to groups of males and females.

basal cell carcinoma are only rarely life-threatening, another reason why they may be under-reported.

Some population-based cancer registries, such as the ones for Scandinavia, at least record squamous cell carcinomas and other rare types of cancer such as Merkel cell carcinoma.

IARC now publishes estimates for non-melanoma skin cancers not including basal cell carcinomas (Ferlay et al. 2020). IARC assumes some 1.2 million cases of non-melanoma skin cancer worldwide in 2018, which accounts for 6.2% of all cancers that year. Males are affected more frequently (60%), with only every fifth case occurring before the age of 65. For every 19 cases there is one death (approx. 64,000 deaths in total per year).

On an international level, non-melanoma skin cancer incidence is similar to that of melanomas, with standardised incidence rates in Australia around 100 times higher than in Southeast and Central Asia. However, unlike melanomas, non-melanoma skin cancer incidence is far lower in Europe than in North America and lower again than in Australia. In Europe, non-melanoma skin cancer incidence is similar to that of melanomas where higher rates were most prevalent in Northern and Western Europe.

Long-term trend analyses are being carried out using data from Scandinavian registries in particular. Age-standardised incidence rates have trebled in males and quadrupled in females since the mid-1970s, and are not set to stabilise for the foreseeable future (Danckert B et al. 2019, Engholm et al. 2010). In the Netherlands, cases increased by an average of 4% annually in males and 6% annually in females between 1989 and 2011. However, a systematic review of 14 European studies across different time periods found comparable trends with an approximate 5.5% annual increase in incidence. In fact, British registry data showed even higher increases (Lomas et al. 2012). In most of the studies, basal cell carcinoma incidence was three to four times higher than squamous cell carcinoma incidence. Australia appears to have by far the world's highest basal cell carcinoma incidence rate (Lomas et al. 2012). However, as described above, the epidemiological data available for basal cell carcinoma is still lacking in terms of robustness.

In the last 10 to 15 years, some German states have made good progress in also recording non-melanoma skin cancers as comprehensively as possible. Based on data from certain German states, the Robert Koch Institute assumes there were 230,000 new cases of non-melanoma skin cancer in 2016, consisting of basal cell carcinomas in around 75% of cases and squamous cell carcinomas in almost 25% of cases. Around 1% of cases are attributable to rare forms of cancer such as Merkel cell carcinoma, a type of neuroendocrine tumour, or sebaceous and sweat gland carcinomas (RKI and GEKID 2019).

Approximately 60% of all malignant non-melanoma skin cancers will at first presentation affect the head, neck or face. In 2016, the mean age of occurrence was 73 for females and 75 for males, with squamous cell carcinoma generally occurring somewhat later than basal cell carcinoma. Trends over time can only be interpreted from around 2006. Similar to melanoma, the introduction of skin cancer screening in 2008 led to a major rise in basal cell carcinoma and squamous cell carcinoma diagnoses. The age-standardised incidence rates appear to have stabilised between 2011 and 2016. Nevertheless, it must be assumed that absolute incidence will continue to increase solely due to demographic change. Also, all of the figures provided only include first occurrences of basal cell carcinoma or squamous cell carcinoma, regardless of de-novo skin tumours[10] or recurrences[11].

[10] De novo skin tumour: Occurrence of an additional tumour without any prior tumour.
[11] Recurrence: Refers to the recurrence of a skin tumour.

According to official causes of death statistics, 1,076 people in Germany died from non-melanoma skin cancer in 2019. This figure is likely to rise, both in absolute numbers and in age-standardised rates (Destatis 2020). Whereas the prospects of survival with basal cell carcinoma are not limited, compared with the general population of the same age, around six out of 100 persons with squamous cell carcinoma will die of their tumor within the first five years and even three in every 10 with Merkel cell carcinoma (Eisemann et al. 2016).

## 2.2 UV-induced skin cancer

There is no longer any doubt that UV radiation is carcinogenic for humans and that there is a direct causal relationship between the initiation, promotion and progression of skin cancer. This is supported by various in vitro studies (also on human cells, tissues, etc.) and animal models, which provide an abundance of molecular biological evidence about dose-response relationships for specific biological endpoints.

With this in mind, the present statement does not include a detailed description of the radiobiological processes involved in UV-induced skin cancer. Further details about this are provided in the SSK recommendation titled "Protection of man against the hazards of solar UV radiation and UV radiation in solaria" (SSK 2016). A brief overview of that recommendation is provided in Annex 1.

## 2.3 Measurement and evaluation of UV exposure

Solar UV spectra measurements have been taken around the world for several decades, with the data subsequently collated and evaluated in terms of biological effectiveness on humans. Here, a wide range of different measuring instruments and methods are being used, e.g. personal radiation dosimeters that measure individual exposure and stationary measuring stations that detect ambient UV radiation. Satellite data are also used, but not covered in this statement. In spite of these metrological options, it is difficult to compare data from literature because measuring instruments have different spectral characteristics, and both individual and group-specific exposure patterns also vary.

### 2.3.1 Metrology

#### 2.3.1.1 Quantities

The term "dose", which is well-known within the realm of ionising radiation (x-ray, alpha, beta and gamma radiation), cannot meaningfully be employed to quantify UV radiation, yet it is nevertheless used to denote the product of irradiance and time (see below). With ionising radiation, the absorbed dose is defined as the absorbed energy per mass (expressed in $J\,kg^{-1}$ = Gy) where, in principle, energy can be absorbed by any component of a cell, meaning that every atom and molecule of a cell can be ionised or excited. With UV radiation, atoms and molecules can only be excited as the photon energy present is insufficient for ionisation to take place. Absorption occurs selectively in certain molecules (chromophores), while other cellular substances remain largely unaffected by this type of radiation. However, important chromophores, particularly DNA, are not distributed evenly within a cell. Also, as mentioned in Annex 1.1, UV radiation penetrates tissue to a varying extent, meaning that the energy absorbed by each layer of skin varies significantly. In view of these variations, this statement focuses on the ambient radiation field rather than tissue energy absorption.

The ambient radiation field is generally expressed by the irradiance, $E$, in $W\,m^{-2}$, which refers to the radiation flux received by a surface per unit area (e.g. the skin), or by the radiant exposure, $H$), in $J\,m^{-2}$, which refers to irradiance of a surface integrated over time of irradiation. As

mentioned above, this is often referred to as the UV dose. In some instances, it may be important to account for the direction of incident radiation and to state the irradiance from a certain part of the sky. In that case, the term radiance, *L*, is used and refers to the irradiance per solid angle (steradian, sr), in W $m^{-2}$ $sr^{-1}$.

Irradiance, radiant exposure and radiance are radiometric quantities that do not take into consideration spectral biological effectiveness, e.g. on human skin. Here, weighting functions (action spectra) can be applied to a mathematical convolution to turn a radiometric quantity into a photobiological one (see Equation 1 in Section 2.3.2.1).

#### 2.3.1.2 Measurement methods

When performing certain radiometric measurements only intended to detect the received energy, non-selective detectors can be used to measure independently of wavelength. This means, for instance, that a thermocouple can be used to measure the temperature increase of an irradiated black surface and then calculate the irradiance. Pyranometers like this typically measure a broad wavelength range of UV, visible and infrared (IR) radiation. Edge filters can then be used to select specific spectral ranges, in turn enabling radiometric quantities for certain spectral ranges, such as the entire UV range or even just the UVA or UVB range. However, given that biological effectiveness of UV radiation depends upon the wavelength quite strongly, such purely radiometric information is of limited benefit when it comes to establishing a dose-response relationship for UV-induced skin cancers. Instead, spectral measurements are needed for narrow, non-overlapping but contiguous bands within a spectrum.

These measurements can be taken with instruments that combine wavelength discrimination (by a monochromator) with a wavelength-independent measurement. However, a monochromator's design may mean that its bandwidth or transmittance depends on the wavelength, in turn requiring a correction of the measured data to calculate the spectral distribution of the received energy. As solar irradiance is highly dependent on wavelength at a range of between 290 nm and 310 nm, instruments such as double monochromators should be used, which reduce scatter radiation by a factor of $10^8$. Instruments with a single monochromator are lighter and less expensive, but only reduce scatter radiation by a factor of $10^4$ (Diffey 2002).

When performing measurements of the radiation exiting the monochromator, a photoelectric sensor is typically used rather than a thermocouple. A photoelectric sensor uses a photocell (external photoelectric effect) or a photoresistor/photodiode (internal photoelectric effect with and without a layer of resistive material). Both of these components are selective sensors whose detection responsivities depends on the wavelength and need to be taken into consideration as well. Modern spectral radiometers detect optical radiation using one or more series of sensitive photodiodes rather than a monochromator with wavelength discrimination as it significantly reduces the time needed to take measurements, while often achieving a level of scatter suppression comparable to that of double monochromators.

Instruments which perform such spectroradiometric measurements, often contain a unit that applies computer-aided weighting of the various ranges of the spectrum to account for the biological effectiveness of solar UV radiation. Alternatively, various integrated systems are used whose detector responsivities are calibrated in accordance with a biological weighting function. Systems which measure in a wavelength-dependent manner include photoelectric sensors such as the Robertson-Berger (RB) meter and its derivatives. There are, however, various other options available, such as polysulphone films (PSFs) which measure the UV dose using a pre-calibrated radiation-induced absorbance change at 330 nm, and detector systems where spores are rendered inactive by UV radiation and the subsequent transmission of cultivated samples measured to calculate the UV dose.

As is the case with all of these measurement methods, it is important to determine whether they are to be used for stationary, local UV monitoring of ambient UV radiation, or for personal dosimetry. While large, high-resolution systems such as double monochromators are used for local solar radiation measurements, small portable monitoring equipment can be used for personal dosimetry purposes. It is understandable that the individual exposure pattern of a person whose personal UV exposure is to be assessed may lead to an individual UV dose that differs by several orders of magnitude compared with extrapolations based on local measurements.

### 2.3.2 Photobiological evaluation of UV radiation

#### 2.3.2.1 Weighting functions and detector responsivities

In an industrial setting and for the purpose of describing technical processes, it is often sufficient to characterise UV radiation using (unweighted) radiometric quantities. However, the biological effect of UV radiation depends on the wavelength, which largely reflects DNA absorption (and its associated damage). As a result, the relative spectral effectiveness of pyrimidine dimer formation, $S_{\mathrm{py}}(\lambda)$ (Freeman et al. 1989), declines by around four orders of magnitude from a maximum of 296 nm to 366 nm (see Figure 2(a)).

To account for the fact that the biological effectiveness of UV radiation depends on the wavelength, the observed spectral physical quantity, typically irradiance $E$, requires convolution with a weighting function $S_{\mathrm{biol}}(\lambda)$ (or action spectrum) at wavelengths of $\lambda_1$ to $\lambda_2$ (DIN 5031-10:2018-03):

$$E_{\mathrm{biol}} = \int_{\lambda_1}^{\lambda_2} E_\lambda(\lambda)\, S_{\mathrm{biol}}(\lambda)\, \mathrm{d}\lambda. \qquad \text{Eq. 1}$$

$S_{\mathrm{biol}}(\lambda)$ represents a general biological effect with specific consequences and can take different forms for various biological endpoints.

The resulting photobiologically effective irradiance, $E_{\mathrm{biol}}$, is better suited to describing the extent of potentially damaging effects from UV radiation than its unweighted (radiometric) counterpart. Figure 2 (a) presents some selected weighting functions associated with biological endpoints that are relevant for humans. The data refer to in vitro, in vivo and ex vivo studies and animal studies.

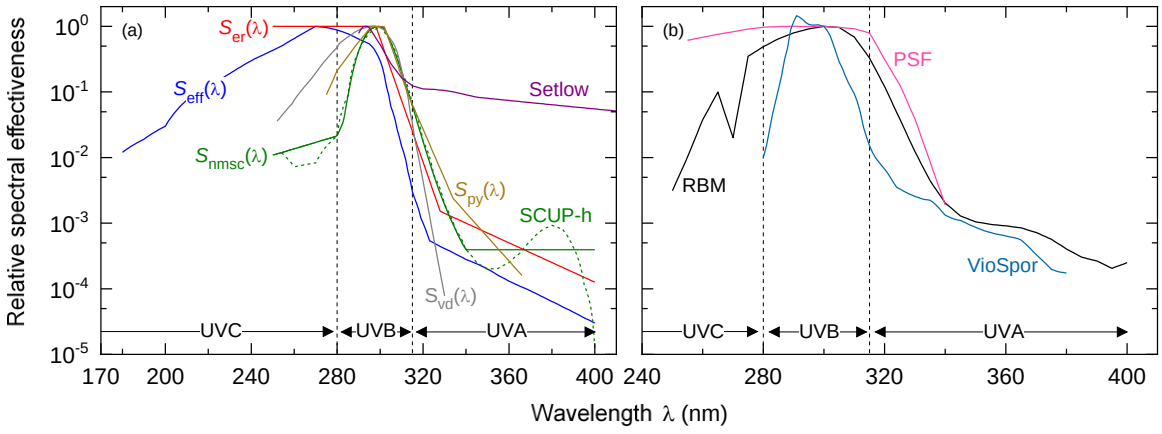


*Figure 2: Semi-logarithmic plot of selected weighting functions and detector responsivities. Figure 2 (a) plots the following relative spectral effectiveness:*

- *$S_{\mathrm{er}}$: erythema formation,*

- *$S_{nmsc}(\lambda)$: photocarcinogenesis of non-melanoma skin cancer,*
- *$S_{vd}(\lambda)$: previtamin $D_3$ synthesis,*
- *$S_{py}(\lambda)$: pyrimidine dimer formation,*
- *SCUP-h: calculated Skin Cancer Utrecht Philadelphia action spectrum,*
- *$S_{eff}$ : combined spectral UV effectiveness for the human eye and skin recommended by the International Commission on Non-Ionizing Radiation Protection (ICNIRP)*
- *Action spectrum proposed by Setlow*

*Figure 2 (b) plots the spectral detector responsivities of*

- *a Robertson-Berger (RB) meter,*
- *a polysulphone film (PSF), and*
- *a VioSpor personal dosimeter*

.

Most of the plotted action spectra are based on a multitude of individual studies. The biological effect of UV radiation depends on the UV sensitivity of epidermal and dermal target cells, with the transmission and absorption parameters of the given skin layers also having a major influence (Meinhardt et al. 2008). In view of this, weighting functions only provide mean relative spectral sensitivity values, with the underlying averaging process typically only including data for fair-skinned people.

The standard curve for the relative spectral sensitivity of human skin to UV-induced erythema, $S_{er}(\lambda)$, proposed by the International Commission on Illumination (CIE curve) (McKinlay and Diffey 1987, CIE 1999) starts at 250 nm and is initially set to 1.0. Starting from 298 nm, it declines exponentially in two stages (ISO/CIE 17166:2019):

$$S_{\mathrm{er}}(\lambda) = \begin{cases} 1.0 & 250\ \mathrm{nm} \le \lambda \le 298\ \mathrm{nm} \\ 10^{0.094(298-\lambda)} & 298\ \mathrm{nm} < \lambda \le 328\ \mathrm{nm} \\ 10^{0.015(140-\lambda)} & 328\ \mathrm{nm} < \lambda \le 400\ \mathrm{nm} \end{cases} \qquad \text{Eq. 2}$$

All action spectra presented in Figure 2 show a comparably strong decline in relative spectral sensitivity from around 300 nm reflecting, above all, the UV radiation absorbed by DNA or, in a very similar way, by the vitamin D precursor 7-dehydrocholesterol. One exception here is Setlow's proposed action spectrum for melanoma induction (Setlow et al. 1993, Setlow 1999) which is determined by both DNA and melanin absorption.

On a practical level, occupational health and safety attaches importance to the $S_{er}(\lambda)$ function and, above all, to the International Commission on Non-Ionizing Radiation Protection (ICNIRP) $S_{eff}(\lambda)$ function or $S_{uvh}(\lambda)$ spectrum. The latter was derived as an envelope of spectral curves plotting threshold levels at which acute UV effects are triggered in the eyes and skin, and includes UV-induced photokeratitis (inflammation of the cornea) and UV-induced photoconjunctivitis (inflammation of the conjunctiva) as well as UV-induced erythema (ICNIRP 2004). Unlike $S_{er}(\lambda)$, a reduced sensitivity can already be observed at shorter wavelengths. In addition, $S_{eff}(\lambda)$ is the only weighting function provided that takes into consideration significant UVC radiation present at wavelengths of 250 nm to 180 nm. German occupational health and safety law has enshrined $S_{eff}(\lambda)$ based on the ICNIRP's exposure limit recommendations.

However, the weighting function for photocarcinogenesis, i.e. UV-induction of non-melanoma skin cancer (NMSC), $S_{nmsc}(\lambda)$, indicates a shift of the decline in UVB sensitivity to longer wavelengths. Also, unlike $S_{er}(\lambda)$ and $S_{eff}(\lambda)$, $S_{nmsc}(\lambda)$ has a pronounced maximum at 299 nm. As laid down in the NMSC action spectrum, UVC and UVA have less influence on UV-induced

non-melanoma skin cancer than UVB. $S_{nmsc}(\lambda)$ is based on the Skin Cancer Utrecht Philadelphia action spectrum for humans, SCUP-h (de Gruijl and Van der Leun 1994), which in turn is based on a mouse model. However, $S_{nmsc}(\lambda)$ represents a simplified form of this, e.g. by assuming a constant relative spectral effectiveness of for $\lambda < 280$ nm and for $\lambda \gtrsim 340$ nm.

More recent findings show that UVA radiation can also induce cyclobutane pyrimidine dimers (CPDs) in the skin (see Annex 1.1.1.2), in turn confirming the UVA spectral range's photocarcinogenic effect observed in the action spectra (Cadet and Douki 2018).

The significance of previtamin $D_3$ synthesis resulting from exposure of human skin to UV is also often discussed in the context of UV-induced skin cancer. Figure 2 (a) shows the corresponding weighting function, $S_{vd}(\lambda)$ (CIE 2006), i.e. the relative spectral sensitivity of previtamin $D_3$ synthesis from provitamin 7-dehydrocholesterol in the epidermis.

The weighting functions considered up to this point present a markedly different spectral sensitivity to that of Setlow's action spectrum for melanoma induction (Setlow et al. 1993, Setlow 1999). This action spectrum is based on a limited set of data for melanoma induction in fish and required correction factors to account for the different transmission and absorption parameters of human skin. With a relative effectiveness of around 0.12 to 0.02 for UVA and visible radiation up to 550 nm (the latter is not plotted in Figure 2), it is the only action spectrum where both spectral ranges contribute significantly to cell damage. In the UVB spectral range, Setlow's action spectrum can largely be explained by the relative spectral sensitivity of pyrimidine dimer formation, $S_{py}(\lambda)$, whereas with UVA radiation, this can be attributed to melanin absorption. Concerns about these Data have been raised, e.g. Fabo et al. (2004) and Mitchell et al. (2007), who carried out experiments involving transgenic mice. By contrast, other studies involving a different strain of transgenic mice whose skin is more similar to that of humans do support the assumption that melanin absorption significantly facilitated melanomagenesis (Noonan et al. 2012).

The above action spectra describe relative spectral sensitivities for certain biological endpoints. As shown in Equation 1 above, spectroradiometric measurements can be convoluted with these action spectra to calculate weighted irradiances. However, a multitude of other measurement methods detect UV radiation integrally, meaning that their spectral detector responsivity mimics an action spectrum (typically that of the CIE erythema curve).

The spectral detector responsivity of the RB meter, which was typically used to evaluate solar UV radiation at the end of the 20th century (DeLuisi et al. 1992), is fundamentally similar to the $S_{nmsc}(\lambda)$ function, although it is much broader at the UVB spectral range and its biological effects include UVC and UVA contributions. Polysulphone films (PSFs) are similar in spectral sensitivity to an RB meter. However, PSFs have a much flatter sensitivity curve at UVB and UVC spectral ranges compared with that of a RB meter, so that its overall shape is more similar to the CIE standard erythema curve. In the past, PSFs were predominantly used in personal dosimetry, but are now used less frequently due to the complicated calibration and data acquisition processes they entail.

Individual UV exposure can also be measured using, e.g. VioSpor dosimeters, where a film of bacterial spores is damaged when exposed to UV radiation. Calculations for a number of solar spectra show that detector responsivity is congruent with $S_{er}(\lambda)$. As a result, VioSpor sensors can mimic the erythema response quite reliably, in turn rendering them suitable for personal dosimetry readings. Recently developed semiconductor detectors are now able to achieve a similarly high congruence between erythema-weighted doses and the results of accumulating measurements (Heydenreich and Wulf 2019). Zölzer and Bauer (Zölzer and Bauer 2021) provide a comparison of the measurement methods described in this section along with various other measurement methods.

When comparing differently weighted irradiances, $E_{biol}$, it is important to consider the underlying weighting functions and monitoring equipment used, as the weighted UV irradiances and doses may vary significantly for the same solar spectrum.

#### 2.3.2.2 Photobiologically effective solar spectrum

At times, the weighting functions described in Section 2.3.2.1 exhibit major differences which are reflected in the biologically effective irradiances calculated using Equation 1. By way of example, Figure 3 provides a summer and winter solar spectrum weighting for evaluation purposes, with the accompanying radiometric and photobiologically effective irradiances given in Table 1.

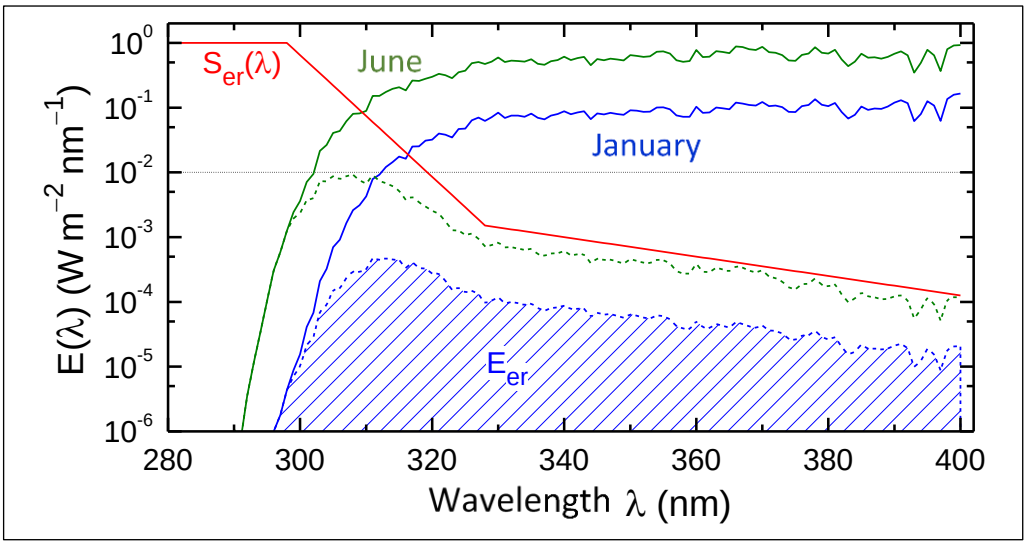


*Figure 3: Example of a summer and winter solar spectrum using the erythema weighting function $S_{er}(\lambda)$. The dotted lines represent product $E(\lambda) \times S_{er}(\lambda)$, while the blue shaded region shows $E_{er}$. The erythema weighting function is plotted via the y-axis despite it being dimensionless.*

The UVB edge of the solar spectrum shows a clear shift towards shorter wavelengths as the minimum solar zenith angle decreases (January → June). As presented in Table 1, this shift and the higher spectral irradiance led to a summer solar spectrum around 7 times "more intense" than the winter solar spectrum. However, this is only a single example, and it is important to note that numerous other factors such as zenith angle, cloud coverage and ozone level may influence the outcome. It is also important to point out that Figure 3 is a semi-logarithmic plot, as a linear plot would have made it difficult to clearly present the minor differences in the weighted solar spectra. This underlines the importance of accurate spectral measurements since the majority of the convolution occurs in the short wavelength region of the UVB edge.

*Table 1: Comparison of radiometric and photobiologically effective irradiances of two solar spectra examples for January and June (values are rounded). Exact irradiances are used to determine the factor for the whole year.*

| | **January** | **June** | **Factor** |
|---|---|---|---|
| $E_{rad}$ | 7.3 W m$^{-2}$ | 51 W m$^{-2}$ | 7 |
| $E_{er}$ | 10 mW m$^{-2}$ | 163 mW m$^{-2}$ | 16 |
| $E_{eff}$ | 2 mW m$^{-2}$ | 39 mW m$^{-2}$ | 19 |
| $E_{nmsc}$ | 20 mW m$^{-2}$ | 360 mW m$^{-2}$ | 18 |
| $E_{vd}$ | 11 mW m$^{-2}$ | 300 mW m$^{-2}$ | 27 |
| $E_{py}$ | 48 mW m$^{-2}$ | 661 mW m$^{-2}$ | 14 |
| $E_{Setlow}$ | 557 mW m$^{-2}$ | 4 W m$^{-2}$ | 7 |
| $E_{RBM}$ | 87 mW m$^{-2}$ | 1.2 W m$^{-2}$ | 14 |
| $E_{PSF}$ | 191 mW m$^{-2}$ | 2.3 W m$^{-2}$ | 12 |
| $E_{VioSpor}$ | 11 mW m$^{-2}$ | 188 mW m$^{-2}$ | 17 |

When analysing the photobiologically effective irradiances, the solar spectrum for June has much higher values across all weighting functions than the January spectrum, with factors of around 14 to 18 for the weighted irradiances for skin damage, $E_{er}$, $E_{eff}$, $E_{nmsc}$, and for pyrimidine dimer formation, $S_{py}(\lambda)$. For the RB meter, the weighted solar spectra ratio of 14 is congruent with the erythema weighting. By contrast, when it comes to previtamin $D_3$ formation, the summer solar spectrum is 27 times more biologically effective than the winter solar spectrum, while with Setlow's action spectrum for melanoma induction it is only 7 times more biologically effective.

Many of the studies cited in this SSK statement investigated correlations between UV exposure and skin cancer incidence using erythema-weighted irradiances or irradiances detected using RB meters. The results of these two measurement methods are comparable, at least in terms of relative change (with factors of 16 and 14 separating summer and winter), despite there being major differences in absolute values (see Table 1).

#### 2.3.2.3 Weighting issues

Problems will be encountered when comparing experimental data from various studies due to the major differences in absolute irradiance values between the differently weighted solar spectra, but also because of the significant uncertainties associated with the weighting itself. In general, weighting functions are determined with monochromatic radiation, meaning they do not account for any potential combination effects at different optical wavelength ranges. As is the case with $S_{py}(\lambda)$, most of the relevant studies only provide a few sampling points from experimental data to determine weighting functions in a discrete way, with values for wavelengths in between interpolated by partially different schemes (linear, quadratic, logarithmic, exponential, spline, etc.) (CIE 2014).

With $S_{eff}(\lambda)$, the interpolation rule prescribes three equations (ICNIRP 2004), resulting in a deviation of around 50% at 320 nm when compared with the discrete sampling points (not given) from experimental data. In addition, weighting functions are often only envelopes which,

as is the case with the $S_{\mathrm{eff}}$ function, still requires partially wavelength-dependent safety factors, thus not reflecting the actual spectral effectiveness present at the given wavelength.

Significant contributions to the photobiologically effective irradiance are only seen at a spectral range of around 300 nm to 320 nm when the solar spectrum is multiplied by a weighting function (see Figure 3). However, this may be just the spectral range where solar spectral irradiance changes by several orders of magnitude. Consequently, calibrating spectral radiometers with bandwidths which are too broad may lead to major errors when determining spectral irradiance, weighting and, in turn, photobiologically effective irradiance.

Various works are available that use the UV index (UVI) to establish a dose-response relationship for skin cancer induction (Hu et al. 2004, Eide and Weinstock 2005, Liu-Smith et al. 2017) despite it not being entirely suited to the purpose. In fact, the UV index was primarily developed to communicate erythema-weighted solar irradiances to the general public. It is defined by

$$\mathrm{UVI} = 40 \times E_{\mathrm{er}} = 40 \times \int_{250\,\mathrm{nm}}^{400\,\mathrm{nm}} E_{\lambda}(\lambda)\, S_{\mathrm{er}}(\lambda)\, \mathrm{d}\lambda \qquad \text{Eq. 3}$$

(WHO 2002). The multiplication factor of 40 has the unit $\mathrm{m^2\,W^{-1}}$ so as to be able to describe the UVI as a dimensionless number with a value of 1 (low) to 12 (high). A UVI of 12 corresponds to $40\ \mathrm{m^2\,W^{-1}} \cdot 0.3\ \mathrm{W\,m^{-2}}$ at a maximum erythema-weighted irradiance of $0.3\ \mathrm{W\,m^{-2}}$ at noon with a clear sky at the equator. One argument against using the UVI as a substitute for ambient[12] irradiance is that providing the UVI in whole numbers typically constitutes an excessive loss of information because, for example, all $E_{\mathrm{er}}$ values between $113\ \mathrm{mW\,m^{-2}}$ and $137\ \mathrm{mW\,m^{-2}}$ are represented by a UVI of 5. However, when developing dose-response relationships between UV irradiance, irradiation and skin cancer incidence in the future, it should be considered whether the "mistakes" involved in using the UVI for the "irradiation-part" are not similar or even trivial when compared with the uncertainties associated with collecting data on skin cancer incidence. In any case, the UVI could be used for an initial approximation of irradiance (cf. Qureshi et al. 2008).

### 2.3.3 Parameters influencing the effect of UV dose and exposure

When reviewing parameters influencing the biological effect of UV exposure, a distinction must be made between physical parameters, genetic and specific (acquired) risk factors, and, above all, individual leisure time behaviour as a function of ambient UV radiation. Interaction may occur with all of these parameters.

It is important to take these parameters into account when evaluating dose-response relationships for skin cancer incidence as many epidemiological studies lack information about to which extent exposed persons have taken physical measures to protect themselves against UV radiation, in which body position they were exposed to UV (lying down, standing, on the move, at rest, averaged across all possible options, etc.) and which risk factors were relevant to a specific cohort. This is significant as many studies on skin cancer incidence and UV exposures were performed retrospectively, which makes it difficult to subsequently estimate the contribution of the aforementioned parameters.

#### 2.3.3.1 Physical parameters

*Spatial orientation of exposed areas of the skin (exposure to UV radiation)*

[12] ambient, e.g. ambient UV radiation

Irradiance $E$ on an area of skin depends on the irradiation angle. If a surface oriented perpendicularly to the ray receives the irradiance $E$, the irradiance received by a surface titled by the angle $\alpha$ will be $E_\alpha = E \cos \alpha$ (Lambert's cosine law).

The orientation of the exposed area is important for two reasons: Each local part of the skin's surface is at a slightly different angle to the sun, and is not only irradiated directly by the sun, but also by other parts of the sky. The relative proportion of UV radiation is higher in diffusely scattered sky radiance than in direct sunlight (Sandmann and Stick 2014). Integration over all solid angles is required to calculate total UV irradiance from all directions, i.e. direct radiation + diffusely scattered sky radiance. Simulation calculations for solar exposure in the Swiss municipality of Payerne showed that when averaged over the course of a year, direct radiation (from noon summer sun) only contributes 15% to 25% of erythemally effective UV radiation, both on horizontal and vertical areas of the body. In other words, 80% of erythemally effective UV radiation typically comes from diffusely scattered sky radiance (Vernez et al. 2012). Solar exposure measurements conducted at the Dead Sea as part of an Israeli study produced very similar results, with 83% of erythemally effective UV radiation originating from diffusely scattered sky radiance in summer, and 95% in winter (Kudish et al. 2011). It therefore comes as no surprise that simulation calculations from the same study show that sunshades and other similar solar protection measures fail to offer a sufficient level of protection against erythemally effective UV radiation. Depending on the distance from the edge of the shadow, the distance of the sunshade from the ground, and the extent to which materials in the vicinity (e.g. light sand) reflect sunlight, horizontal areas of the skin may receive over 50%, and vertical areas 20% to 40% of UVB present outside of the shadow (Kudish et al. 2011). A study on the protective effect of sunshades in Valencia in Spain resulted in much the same conclusion, with diffusely scattered sky radiance estimated to contribute 60% of erythemally effective UV radiation, i.e. somewhat less than that observed in the Israeli study (Utrillas et al. 2010). Simulation calculations thus produce correspondingly lower specific relative exposures in the shade, namely around 34% of erythemally effective UV radiation on horizontal areas, 16% on vertical areas facing north, and 12% on vertical areas facing south. These values were confirmed by way of spectroradiometric measurements with an erythema weighting (Utrillas et al. 2010). The authors of the Israeli study explain that their results differ from those gleaned in Spain because the Dead Sea is around 400 metres below sea level, meaning that light travels through the atmosphere for longer, in turn increasing solar radiation diffusion. Based on this logic, the share of solar radiation diffusion from the Swiss study (450 metres above sea level) should be expected to be even lower, but this was not observed in the results of the study by Vernez et al. (Vernez et al. 2012). However, the light paths there are longer due to the higher latitude and lower solar elevation. Other factors such as aerosol concentration in the air may also have an impact.

Particularly worthy of mention here is that the Swiss study (Vernez et al. 2012) calculated exposures for various parts of a standing person's body. The shoulders were found to have the highest values, followed by the neck, torso and thighs (daily exposures of 34.5; 22.2; 17.5 and 15.3 standard erythema doses – 95th percentile). In an Austrian study, personal dosimetry readings were taken, i.e. UV measuring devices were attached to a full-body suit and the relative exposures of multiple parts of the body measured when in various positions and in motion. The highest values for a standing person were again seen with the shoulders, followed by the forehead, arms and torso. Exposures for a person sitting or lying down were distributed differently, with the thighs in particular experiencing higher exposure levels while sitting. When lying down, the shoulders were of secondary importance (Weihs et al. 2013). The authors cite a number of other studies where volunteers were measured during occupational and leisure time activities. However, they also point out that only one or two measuring devices were attached

to each person and in different places with each study, meaning that the results are not comparable in most cases (see also Section 2.6.3 for information about occupational exposure).

The studies show that a person's spatial orientation has a major influence on individual UV dose, adding to the complexity of personal UV dosimetry and requiring due consideration when modelling individual UV exposure (see also Section 2.6.2)

*Textile solar (UV) protection*

Conventional textiles and special textiles with an ultraviolet protection factor (UPF) can both reduce the amount of UV radiation reaching the body, in turn reducing its damaging effect. For instance, textiles made of cotton, wool or silk have a UPF of 30 to 50+ (Gawish et al. 2016), while special textiles with UV-reflective fibres can reach a UPF of 80+. Solar protection in the form of wearing textiles can significantly reduce the accumulated UV dose. As a result, the "textile solar (UV) protection" parameter must be taken into account when determining "actual" (personal) doses to provide meaningful dose-response relationships for skin cancer incidence (in the future).

*Protection through the use of sunscreen*

Studies show that the correct and consistent use of sunscreen helps to reduce the risk of skin cancer (Green et al. 2011, Ghiasvand et al. 2016) as it can significantly reduce the individual UV dose resulting from a certain UV exposure. However, sunscreen is often used for a planned, prolonged period of time spent in the sun. UV exposure increases when sunscreen is not used correctly, e.g. by not applying enough or failing to reapply sunscreen after bathing. This phenomenon may explain why some studies indicate an increased risk of melanoma among people who use sunscreen (Autier 2009). As a result, the "(correct) use of sunscreen" parameter must also be taken into account when determining "actual" (personal) doses to provide meaningful dose-response relationships for skin cancer incidence (in the future). However, this is difficult to ensure in real-life situations.

#### 2.3.3.2 Influence of genetic (constitutional) factors

The present statement does not provide a detailed description of the genetic risk factors involved in UV-induced skin cancer. Further details are provided in the SSK recommendation title "Protection of man against the hazards of solar UV radiation and UV radiation in solaria" (SSK 2016).

Skin type, i.e. genetically determined sensitivity to UV radiation, has been proven to influence the risk of UV-induced skin cancer. To this end, human skin is categorised into different types (I to VI) based on sensitivity to developing sunburn (Fitzpatrick 1988). However, a number of genetic and cellular changes already occur before sunburn (well below the erythema threshold for the given skin type) which are responsible for an increased risk of UV-induced skin cancer (Narbutt et al. 2009, Mouret et al. 2006, Seité et al. 2010). As a result, further investigation is required into whether only erythema-inducing UV doses should be used to estimate the risk of developing skin cancer, and, if so, to what extent. The number of hereditary, particularly large and very large pigmentations are posited as being an additional hereditary risk factor associated with malignant melanoma (DeDavid et al. 1997, Greeley et al. 1965, Grob et al. 1990, Hendrickson and Ross 1981, Illig 1986).

#### 2.3.3.3 Acquired risk factors for UV-induced skin cancer

Acquired risk factors for non-melanoma skin cancer include chronically UV-damaged skin (Moon and Oh 2001), the presence of actinic keratoses (Dodson et al. 1991), a previous case of BCC or SCC (past medical history) (Marcil and Stern 2000), immunosuppression (e.g. in the context of an organ transplant) (Berg and Otley 2002, Dantal et al. 1998, España et al. 1995,

Jensen et al. 1999, Otley 2002, Preciado et al. 2002) or skin damaged by radiation therapy (Karagas et al. 1996, Lichter et al. 2000, Travisand Arndt 1986.)

The main acquired risk factors for malignant melanoma include the number of acquired pigmentations (Bataille et al. 1996, Breitbart et al. 1997, Gandini et al. 2005, Naldi et al. 2000), the number of clinically atypical pigmentations (Gandini et al. 2005, Halpern et al. 1991), a previous history of developing malignant melanoma (Tucker et al. 1985) and a direct relative (parent, child) developing malignant melanoma (Ford et al. 1995, Hemminki et al. 2001).

#### 2.3.3.4 Behavioural factors influencing the (individual) effects of UV exposure

Exposure to ambient solar UV radiation largely depends on a person's individual behaviour. Behavioural exposures should be investigated with a view to their photobiological effects based on the measurements and assessments of exposure conditions provided in Sections 2.3.1.1 to 2.3.1.3 (see, e.g. Schmalwieser 2020). When considering the individual dose from a certain ambient solar UV exposure, it is important to note whether textile solar protection and sunscreen were used. The dose also depends on individual behaviour, whether the sun was "used" intensively or whether shade was sought, and on individual behaviour in the workplace and during leisure time, be it deliberate or not. This brief list clearly shows that personal dosimetric data are required to describe and prepare dose-response relationships for skin cancer incidence, and that models and methods will need to be developed to extrapolate individual doses from ambient UV exposure values.

## 2.4 In vitro data on UV dose-response relationships – transferability to humans

It is not possible to use in vitro data for dose-response relationships for skin cancer because the complex process of inducing skin cancer, ranging from initiation to promotion and progression cannot be (sufficiently) simulated in an in vitro setting.

Nevertheless there are in vitro substitute experiments that account for certain biological endpoints associated with UV-induced skin cancer. To this end, studies often investigate UV-induced damage (CPD, oxidative damage, strand breaks, etc.) or UV-induced mutations. Examinations on dose-response relationships for the respective endpoints are scarce, however, or appear as a not initially planned endpoint. Instead, studies typically only involve selected UV doses (or just a few different doses). Below is a list of a few publications[13] that focused on the dose-response relationship for the investigated biological endpoint.

In 2014, Sproul et al. (Sproul et al. 2014) published dose-response relationships for CPD induction in a cell line of normal human fibroblasts. This study is noteworthy in that CPD induction was quantified (in CPD per megabase pair (Mbp)) by way of a radioimmunoassay (RIA). The study investigated the induction of damage from exposure (directly after irradiation lasting minutes or hours, depending on the options available within the scope of the experiment) to UVC, UVB, UVA+UVB (solar simulated). The authors observed considerable differences in the dose-response relationships for the different irradiation types manifested in the different slopes of the dose-response curves calculated by linear regression (see Table 2).

[13]These publications were selected from a non-systematic literature search of around 500 publications listed in pubMed with keywords such as "dose effect and UV", "dose effect and skin cancer (incidence)" for in vitro studies, animal model studies, and in epidemiological works.

*Table 2: Slope (in $Mbp^{-1}$ $J^{-1}$ $m^{-2}$) for linear dose-response relationships of CPD induction after irradiation with different UV types (compiled from Sproul et al. 2014). The authors did not provide a standard deviation for linear adjustment of the data.*

| **Radiation type** | **Pitch in CPD $Mbp^{-1}$ $J^{-1}$ $m^{-2}$** |
|---|---|
| UVC | 34 |
| UVB | 0.121 |
| UVA+UVB | 0.0094 |

*CPD = Cyclobutane pyrimidine dimers, Mbp = Megabase pairs*

The results for UVB-induced CPD align with measurements from Mouret et al. in their 2006 work (Mouret et al. 2006), which primarily focused on CPD induction from UVA radiation, but showed a 0.2 CPD $Mbp^{-1}$ $J^{-1}$ $m^{-2}$ increase in the linear dose-response relationship for UVB radiation.

In 2015, Cadet et al. published a review (Cadet et al. 2015) that included values for dose-dependent CPD induction in human fibroblasts, keratinocytes and human skin after UVA irradiation, and quoted values of 0.0164 CPD $Mbp^{-1}$ $J^{-1}$ $m^{-2}$, 0.0049 CPD $Mbp^{-1}$ $J^{-1}$ $m^{-2}$ and 0.006 CPD $Mbp^{-1}$ $J^{-1}$ $m^{-2}$ from literature (Courdavault et al. 2004, Mouret et al. 2006).

As far back as 2000, Greinert et al. (Greinert et al. 2000) described a dose-response relationship for CPD induction after UVB irradiation of HaCaT cells (spontaneously immortalised cell line). They described a saturation curve for the dependency of CPD induction on the UVB dose at a range of 0 J $m^{-2}$ to 2,400 J $m^{-2}$, expressed for analytical purposes as 1-exp(-α*H*) (where *H* = UV dose in J $m^{-2}$), when using CPD immunofluorescence staining with subsequent calibration to determine the absolute number of CPD (via RIA: number of CPD per genome and per cell). At a range of 0 J $m^{-2}$ to 600 J $m^{-2}$, the dose-response curve is roughly linear, with an induction of approx. 1 CPD $Mbp^{-1}$ $J^{-1}$ $m^{-2}$.

Sproul et al. (2014) moreover showed in their work that UV-induced mutations (number of mutations per $10^6$ of surviving cells) was also dependent on the dose in the hgprt gene of a human fibroblast cell line. Linear dose dependencies were observed with UVC (254 nm) and UVA+UVB (Sproul et al. 2014).

Kappes et al. (Kappes et al. 2006) also studied UV-induced mutations. The authors observed a linear dependency of the mutation frequency (number of mutations per $10^6$ in colony-forming cells) in the hgprt gene when irradiating primary neonatal human fibroblasts with UVB of 0 J $m^{-2}$ to 600 J $m^{-2}$. With UVA of 0 kJ $m^{-2}$ to 150 kJ $m^{-2}$, the mutation frequency barely changes compared with the spontaneous mutation frequency, but rises steeply when the dose increases (up to 300 kJ $m^{-2}$).

In 2014, Marionnet et al. (Marionnet et al. 2014) described a linear dose-response relationship for an additional key biological endpoint, the production of reactive oxygene species (ROS), in 3D skin equivalents from human fibroblasts and keratinocytes after UVA1 phototherapy (320 nm to 340 nm) with an energy of 0 kJ $m^{-2}$ to 400 kJ $m^{-2}$.

When reviewing the solar spectrum, a measurement taken on a clear summer's day in Germany when the sun is at its highest showed a UVB dose of approx. 760 J $m^{-2}$ and a UVA dose of approx. 25 kJ $m^{-2}$ after 10 minutes. This shows that the UVA doses involved are extremely high at times. However, it should be noted that the UV radiation sources used in experiments do not correspond with the solar spectrum.

Despite the extremely important findings gleaned from in vitro experiments on the mechanisms of UV-induced DNA damage, cellular changes and the underlying mechanisms of photocarcinogenesis, the multitude of available data – with only a small proportion of the data cited here covering dose dependencies – does not allow conclusions to be drawn about the (UV) dose-response relationship for UV-induced skin cancer. This is due to the complex circumstances involved in determining (individual) doses from UV exposure (cf. also Section 2.3.3) and because of the many stages of reaction involved in the induction of skin cancer, both of which are difficult or impossible to replicate with an in vitro model.

## 2.5 Data from animal models on UV dose-response relationships for skin cancer – transferability to humans

While there is no animal model for basal cell carcinoma, there are mouse models available (immunocompetent hairless SKH1 (albino) and SKH2 (pigmented)) for the induction of squamous cell carcinoma (Benavides et al. 2009, de Gruijl and Forbes 1995). There is also a fish model (killifish, Xiphophorus hybrids) for malignant melanoma that is well-suited to genetic studies, although the tumour histology differs markedly from human melanoma (Ha et al. 2005, Ley 2002). Several studies on UV-induced melanomagenesis were performed on South-American grey short-tailed opossum (monodelphis domestica) (Kusewitt et al. 1996, Ley 2002). In terms of photoreactivation, it should be noted that monodelphis possess a specific repair process for UV-induced DNA damage that human skin does not have, and there are no genetically identical inbred strains. Mice do not develop malignant melanoma after only receiving UV irradiation, i.e. without an additional chemical carcinogen. There are, however, transgenic mouse models available for malignant melanoma where, for instance, there is a driver mutation in the RAS-RAF signalling pathway (Day et al. 2017). In addition, there is a transgenic mouse model (HGF/SF) available in which malignant melanoma can be induced by neonatal UV irradiation. Many stages within this model's histology can be well-aligned with human melanoma (Ha et al. 2005). Nevertheless, it is difficult to draw comparisons between animal models and human skin due to the differences in structure, e.g. skin thickness and pigment cell distribution. This in mind, there is insufficient data available to describe a dose-response relationship in the animal model for the induction of malignant melanoma and basal cell carcinoma. Below, three works are presented which describe squamous cell carcinoma induction after chronic UV irradiation in various mouse models.

Willis and Menter (Willis and Menter 1983) delivered chronic UV exposure (40 days of irradiation, five days per week) and variable UVB wavelengths to Sk-1 mice (hairless, albino) to study the effect of a depleting stratospheric ozone layer on squamous cell carcinoma induction. A xenon solar simulator was used as a source, with UVB wavelengths varied using corresponding filters. The mice were exposed to an initial dose of 0.5 to 0.9 minimum erythemal dose (MED)[14] each day. Depending on the filter used, the MEDs ranged from approx. 7 to approx. 26 J $m^{-2}$, with the dose increased by 20% each week.

This investigation showed that shortwave UVB wavelengths play a key role in tumour induction. Comparing chronic irradiation with an initial dose of 0.5 to 0.9 MED presented a complex picture which the authors posited as being tumour induction with simultaneous protection mechanisms (skin thickening) and tumour-suppressing processes (immune reactions) occurring during irradiation. However, under all of the irradiation conditions, the tumours all presented 15 to 18 days after the start of the irradiation process, irrespective of the

[14]Minimum erythemal dose is the dose which induces a "perceptible" erythema in albino mice 24 hours after irradiation. MED was originally used in dermatology to characterise individual sensitivity of human skin to UV radiation. People with a sensitive skin type (type II) have a MED of 250 to 400 J $m^{-2}$.

dose. Based on the described irradiation record, with an initial dose of 0.5 MED tumours occurred after an accumulated UV dose of 9 to 11 MED, while with an initial dose of 0.9 MED a UV dose of 16 to 21 MED was accumulated before tumours occurred. The authors interpret the data such that time is the limiting factor for tumour development once initial damage has occurred. However, the authors hold that the simultaneous occurrence of carcinomas, albeit at a lower initial dose of 0.5 MED and a lower total dose of 9 to 11 MED, could be indicative of complex (protection) mechanisms occurring faster with a higher initial dose.

Lerche et al. (Lerche et al. 2017) studied the impact of exposure pattern and dose response of solar spectrum UV radiation on the induction of squamous cell carcinoma in an immunocompetent, hairless, pigmented mouse strain (C3.Cg/TifBomTac) irradiated for a total of 500 days. To investigate differences in exposure pattern, 6 x 2 standard erythema doses (SED; 1 SED = 100 J $m^{-2}$), 4 x 3 SED, 3 x 4 SED or 2 x 6 SED were administered each week. The irradiation groups developed different pigmentations, yet this had no influence on the time until initial tumour induction, with 50% of the mice in all irradiation groups developing tumours after 155 to 169 days. This shows that tumour induction started much later than in the above study by Willis and Menter. It should be noted, however, that different mouse strains and different UV irradiation sources were used, and lower UV doses were administered in the Lerche et al. study. The mice were irradiated three times per week to determine the dose-response relationship, with doses of 1.8 to 12 SED administered each week. Here, tumours occurred earlier in conjunction with a weekly increase in dose. However, the same number of tumours per mouse was observed at a lower total dose (sum of weekly doses) with smaller weekly administered doses (despite prolonged irradiation until initial tumour induction) than with higher weekly administered doses (where tumours occurred much sooner). The authors assume that this effect is attributable to pigmentation induced by irradiation along with other protective effects such as UV-induced skin thickening (hyperkeratosis), as was already described for the mouse strain used (Lerche et al. 2009).

De Gruijl and Forbes (de Gruijl and Forbes 1995) reviewed extensive studies on the induction of squamous cell carcinoma in the hairless albino mouse strain SKH-1 using UV lamps, largely emitting 280 nm to 370 nm ($\lambda_{max}$ = 310 nm), as irradiation sources. The mice were irradiated daily with a dose just below the minimum erythemal dose (MED). Under these conditions, the first tumours developed after around 40 days. A reduction in daily dose, or premature termination of daily irradiation after 19 days, led to delayed induction of tumours. However, the tumours all presented with the same induction kinetics. Again, time appears to play a pivotal role, as Willis and Menter (Willis and Menter 1983) had observed previously (see above). Based on the assumption that both UV-dependent and UV-independent processes are involved in tumour induction, the authors express the number of induced tumours per mouse ($Y$) as a function of UV exposure ($H$) and exposure time ($t$) with the following formula:

$$Y = \left(\frac{H}{H_0}\right)^{p1} \left(\frac{t}{t_0}\right)^{p}. \qquad \text{Eq. 4,}$$

The quantity designated "UV exposure ($H$)" by the authors is the erythemally weighted total dose J $m^{-2}$ accumulated in total exposure time $t$, while $H_0$ and $t_0$ represent constants that depend, e.g. on the spectrum of the radiation source used. Exponent $p$ describes the influence of time and is intended to correspond to the number of steps involved in tumour induction. An additional exponent, $p1$, is a measure of the UV-dependent steps. With the aforementioned mouse model, this resulted in the values $p = 7.2 \pm 0.8$ and $p1 = 4.3 \pm 0.5$.

The authors postulate that by changing constants $1/H_0$ and $1/t_0$ correspondingly, the equation can be adapted to epidemiological data and then used as a dose-response model for squamous cell carcinoma and basal cell carcinoma in humans. Assuming that UV exposure is constant,

exposure time *t* in the formula can be replaced by age, and UV exposure *H* can be replaced by the UV dose received by human skin.

An evaluation of incidence data from the Netherlands (Coebergh et al. 1991) and the US (Scotto and Fears 1982) is provided in Table 3. Incidence data for humans were equated to the number of tumours, assuming that multiple tumours only occurred in a small percentage of cases. In contrast to the US data, a parameter for UV dependency ($p1$) could not be provided for the Dutch population because the small geographical size of the Netherlands precludes any differences in ambient UV radiation, meaning that it is not possible, for instance, to describe how skin cancer incidence changes as a function of UV dose. As stated in Table 3, in terms of squamous cell carcinoma, adaption parameter $p$ for the Dutch population is similar to the parameter given in the mouse model. With the US data, parameters $p$ and $p1$ are well below the values determined by the mouse model. The authors pointed out that this discrepancy may be attributable to uncertainties in the incidence data for humans, e.g. migration and multiple tumours, along with key physiological differences between mouse and human skin. In the US data, the parameters defined for basal cell carcinoma incidence data are lower than those for the squamous cell carcinoma data, particularly when it comes to UV dependency ($p1$). Despite these discrepancies, the authors postulate that this model can be used to estimate the risk of developing skin cancer (SCC and BCC) as a result of increased UV exposure.

*Table 3 Values for which powers (p) and ($p_1$) associated with time and UV exposure were given in relation to the number of skin tumours (for mice used in the study and for population cohorts from the Netherlands (NL) and the US according to de Gruijl and Forbes 1995; using data from mouse studies (de Gruijl and van der Leun 1993) and from Dutch (Coeberg et al. 1991) and US population cohorts (white population) (Scotto and Fears 1982).*

| | Squamous cell carcinoma | | Basal cell carcinoma | |
|---|---|---|---|---|
| | $p$ | $p1$ | $p$ | $p1$ |
| Mice | 7.2 ± 0.8 | 4.3 ± 0.5 | - | - |
| NL males | 6.6 ± 0.4 | | 5.4 ± 0.1 | |
| NL females | 8.9 ± 0.7 | | 4.8 ± 0.1 | |
| US males | 4.7 – 6.4 | 2.6 ± 0.7 | 4.5 – 5.0 | 1.5 ± 0.5 |
| US females | 5.4 – 6.5 | 2.6 ± 0.8 | 4.6 – 5.0 | 1.3 ± 0.4 |

## 2.6 Epidemiological data on UV dose-response relationships for skin cancer

### 2.6.1 Theoretical models based on epidemiological data on ambient UV exposure

As far back as the 1970s, data from cancer registries or official causes of death statistics, chiefly from North America, showed a statistical correlation between decreasing latitude, i.e. increasing proximity to the equator, and incidence or mortality of melanoma and non-melanoma skin cancer (Elwood et al. 1974, Swerdlow 1979, Crombie 1979, Lee and Scotto 1993, Moan et al. 2012, Wallingford et al. 2013).

In 2015, Moan et al. (Moan et al. 2015a) published a study in which they plotted skin cancer incidence for squamous cell carcinoma, basal cell carcinoma and malignant melanoma as a function of ambient annual UV dose and then used various models to analyse the relationship

between UV exposure and incidence of skin cancer. Here, they correlated incidence rates from the Norwegian cancer registry with erythemally weighted annual UVR doses from the Norwegian UV-monitoring network. The age-standardised incidence rates (per 100,000 inhabitants) were then converted to the number of tumours per body part (relative tumour density - RTD[15]) and plotted against the mean annual erythemally weighted dose.

The association between RTD and dose was analysed in three different models:

Power model: ln(RTD) vs. ln(dose)

Exponential model: ln(RTD) vs. dose

Linear model: RTD vs. dose

The power model produced the best fit to the collected data (incidence vs. dose) when calculating a regression line in a log-log plot. This was particularly the case for basal cell carcinoma and squamous cell carcinoma, and less so for malignant melanoma.

The underlying power law can be expressed as follows:

$$\ln(\mathrm{RTD}) = A_b \ln(H_{\mathrm{ery}}) + \mathrm{const.} \qquad \text{Eq. 5}$$

($H_{\mathrm{ery}}$ = *erythemally weighted UVR dose*)

This power law reflects traditional formalism according to which the biological amplification factor $A_b$ (Moan et al. 1989, Moan et al. 1999) can be determined as follows:

$$A_b = \frac{\mathrm{dRTD/RTD}}{\mathrm{d}H_{\mathrm{ery}}/H_{\mathrm{ery}}} \qquad \text{Eq. 6}$$

At first approximation, $A_b$ expresses the percentage, or the factor, by which the skin cancer incidence rate increases per percentage, or factor, increase in UV exposure, e.g. annual erythemally weighted UVR dose.

In this first approximation, $A_b$ thus represents the intended measure for describing dose-incidence relationships for skin cancer. In keeping with their analyses, Moan et al. (Moan et al. 2015a) provided the following values for amplification factor $A_b$:

- Malignant melanoma in the throat and neck area: $A_b = 1.29$ for males,
- Malignant melanoma in the torso: $A_b = 1.93$ for females,
- Basal cell carcinoma in the throat and neck area: $A_b = 1.86$ for males,
- Basal cell carcinoma in the torso: $A_b = 2.29$ for females,
- For squamous cell carcinoma, $A_b$ values of 2.27 and 3.13 resulted in female and male torsos respectively.

Even though the above study and its derived $A_b$ values "only" refer to data from Norway, they still show that (ambient) UV exposure data can be used to derive estimates for skin cancer incidence data as a function of the dose.

A study using UV exposure data from 12 different countries (with markedly different annual ambient UV doses) to investigate the association between UV dose and skin cancer incidence also arrived at a similar outcome (Moan et al. 2013).

[15]Relative tumour density (RTD): Age-standardised incidence rate of malignant melanoma, basal cell carcinoma or squamous cell carcinoma in a given body site (e.g. torso) divided by the proportion of the total surface area of the body site covered by the tumour (e.g. torso: 20%). The greater the RTD, the greater the number of tumours per unit area of skin.

In another study, Xiang et al. (Xiang et al. 2014) estimated the proportion of variability in population-based non-melanoma skin cancer (NMSC) incidence arising from differences in ambient UV radiation without taking account of individual solar exposure patterns. The authors pointed out that a series of past studies had already established differences in NMSC incidence rates owing to latitude. However, these studies largely involve comparisons of two different latitudes, for instance, and only cover one country, Australia (Giles et al. 1988, Holme et al. 2000, Marks et al. 1993, Staples et al. 1998, Stern 1999).

The study by Xiang et al. (2014) is a compilation of incidence data for basal cell carcinoma and squamous cell carcinoma published by various authors worldwide between January 1978 and December 2012. Where possible, the published incidence data were correlated with UV doses at the location of the collected incidence values. The mean daily ambient erythemally weighted UV dose based on satellite measurements was used as a measure of the dose (the satellite measurement data sources are described in Xiang et al. 2014), where the resolution (one grid cell) of the satellite data was 1° latitude and 1.25° longitude. The studies used covered a number of different countries with a broad spectrum of latitudes and UV doses.

The data studied by Xiang et al. (2014) show that more than 80% of the differences in basal cell carcinoma and squamous cell carcinoma incidence can be expressed by way of modelling (Poisson regression), which considers the mean daily ambient erythemally weighted UVR dose, day-to-day variability of UV exposure, age groups, sex and study year. This modelling showed an exponential increase in NMSC incidence with increasing UV dose ($H$) (ln(incidence) = x$H$ + const).

In summary, an erythemally weighted UV dose increase of 1 kJ $m^{-2}$ is linked to a 67% increase in basal cell carcinoma incidence and a 95% increase in squamous cell carcinoma. These effects were more evident at lower latitudes, while incidence rates were higher among males and were correlated with increasing age for both sexes.

When plotting data from this publication in the same way as Moan et al. (Moan et al., 2013), i.e. by using a log-log plot, the linear adjustment results in an amplification factor ($A_b$) of around 2.1 (see example for squamous cell carcinoma in females aged 30 to 44 in Figure 4), whereas in the Moan study $A_b$ = 3.3 (Moan et al. 2013, cf. Figure 4). Accounting for the multitude of factors that can influence the amplification factors, such as differences in determining skin cancer incidence and differences in measuring and calculating local UV doses, a similar trend can be seen among the various studies: a 1% increase in annual ambient UV dose leads to a 2% to 3% increase in tumour frequency.

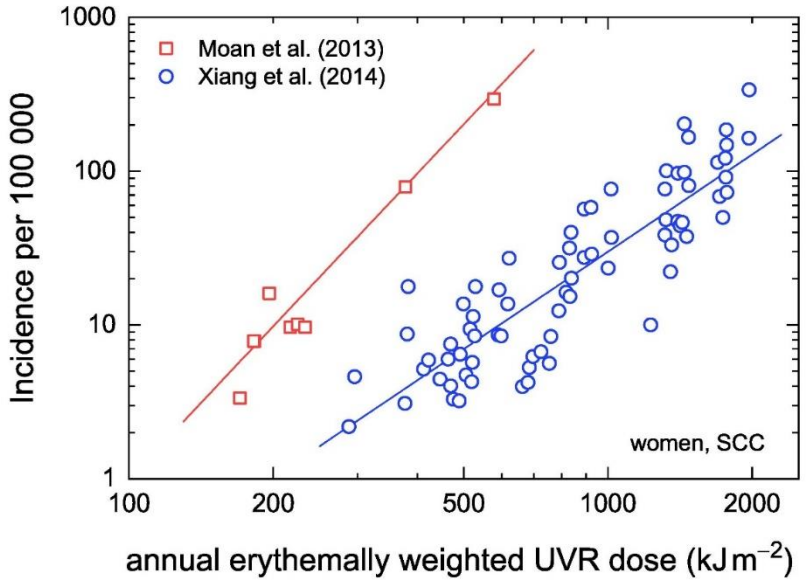


*Figure 4: Increase in incidence of squamous cell carcinoma (SCC) in females calculated using data from two different studies (Moan et al. 2013, Xiang et al. 2014). The data for the mean **annual** erythemally weighted UV dose used here was derived from data in the Xiang et al. (2014) study by multiplying the mean **daily** erythemally weighted UV dose by 365. The data points represent the squamous cell carcinoma incidence rates reported in locations at different latitudes with a different annual erythemally weighted UV dose. The UV exposures were determined using different measurement methods such as satellite data and/or model calculations. The regression lines produce increases (amplification factors, $A_b$, cf. Equation 6) of 3.3 (Moan et al. 2013) and 2.1 (Xiang et al. 2014).*

The authors posited that their analysis is not based on personal dosimetric data, but noted that the mean individual UV exposure in various different populations is around 3% of the ambient UV exposure (Godar 2001, 2005).

Studies on the dependency of skin cancer incidence on latitude suggest an association between UV and skin cancer risk, but there are several reasons why these studies are not suited for proving a causal relationship or modelling a dose-response relationship. First, when recording the latitude at the time of diagnosis, the actual UV exposure is only very roughly approximated (migration and other changes of life circumstances in volunteers are not accounted for). Second, in such (ecological) studies it is extremely difficult to conduct reviews that adequately account for confounders. Consequently, in terms of leisure activities (including holiday), occupational exposure, clothing and protection against the sun, residents of regions with high UV exposure are likely to behave differently to people in regions with low UV exposure. This can skew the outcome significantly in both directions. The distribution of ethnic groups and skin type may also differ from North to South.

As a result, studies involving volunteers recruited individually are expected to deliver a higher level of evidence. However, the cost and effort involved in performing individual long-term exposure measurements, the long latency period, and the high number of cases required impose limitations on this approach. An alternative approach would be to include the question in larger cohort studies, as was the case in the Nurses' Health Study conducted in 1976 among over 120,000 predominantly white female nurses aged between 20 and 55 living in 11 different US states (Qureshi et al. 2008). While it was not possible to measure UV exposure on an individual level, regular surveys were conducted to record individual skin type, moves to other regions, and outcome (occurrence of the three main types of skin cancer). All self-divulged information

regarding melanoma and squamous cell carcinoma was validated, while information about basal cell carcinoma was not. When analysing exposure based on this information, a distinction was made between place of residence at birth, aged 15 and aged 30. An additional evaluation limited the cohort to females living in the same US state at all three points in time. One limitation here was that exposure was only measured roughly by dividing US states into three classes based on the UV index. This analysis was limited to around 80,000 women recruited from 1984 and monitored until 2002. A total of almost 9,000 skin cancer cases were recorded, including 400 cases of melanoma and 800 cases of squamous cell carcinoma. These results show a clear association between the UV index at the place of residence and the occurrence of squamous cell carcinoma. The skin cancer risk for females living in US states with a high UV index was roughly double that of inhabitants living in regions with a low UV index, while results for the middle group were somewhere in between. Less clear, yet statistically significant and with a clear slope in terms of consistent dose-response relationship, were the results for basal cell carcinoma which showed a 30% increase in risk for the group with the highest exposure. The risk of malignant melanoma increased significantly, around 30%, in females living in regions with a medium UV index at birth or aged 15 when compared with females from regions with a low UV index. The results for regions with a high UV index were 20% higher than those for the reference region, but the difference was not significant while the confidence intervals were wider.

The largest study involving individual data is a retrospective Canadian cohort study that links postal codes in data gleaned from almost 2.4 million participants in a 1991 Canadian census survey to modelling for mean individual UV exposure in the summer months (Pinault et al. 2017). During the follow-up period (1992 to 2009), the data were linked to the Canadian cancer registry and resulted in some 8,900 cases of first-time melanoma. Participants who moved to the respective region within the past ten years were excluded. Information queried by the survey included age, sex, migration status, profession (including outdoor work), family status, income and education. Taking the action spectrum for UV-induced vitamin D production (cf. Section 2.3.2.1 Figure 2) into account, the authors describe a modelled mean daily UV exposure in summer, depending on place of residence, of between 2,678 J $m^{-2}$ and 7,290 J $m^{-2}$, with a mean of 6,176 J $m^{-2}$ (the authors provide no error margins for the mean UV exposure values (the low population density in Northern Canada results in a skewed distribution of exposure values)). After adjustment for covariables, the results showed an almost linear relationship between the natural logarithm of the relative risk of skin cancer and a (linear) increase in UV exposure. The risk of skin cancer increased by 22% for a UV exposure that was more than a standard deviation (446 J $m^{-2}$ or 7%) higher than the mean for the total study. The association between UV exposure and melanoma risk was more pronounced among males, people working outdoors, and people with low income and/or low education. Other than UV exposure, higher social status was associated with a higher skin cancer risk, which may be attributable to outdoor leisure activities and travel. By contrast, migrants and unmarried people tended to exhibit a lower risk. The studies encountered limitations in that a lack of individual measurements prevented an analysis of whether intermittent exposure has different effects on various skin cancer types when compared with continuous exposure.

In summary, the aforementioned studies confirm the results of previous ecological studies and indicate a dose-response relationship between UV exposure and skin cancer risk. Due to its higher statistical significance and more accurate exposure estimate, the Canadian study not only statistically confirmed this relationship for melanoma, it also enabled the identification of effect-modifying factors including sex, social and migration status, while also modelling a plausible dose-response curve. The results of the Nurses' Health Study in the US suggest that the dose-response relationship for basal cell carcinoma is qualitatively, yet not quantitatively, similar to that for melanoma, while the association between UV exposure and squamous cell

carcinoma appears to be much clearer. The studies by Moan et al. 2015b and Xiang et al. 2014 suggest a similar difference between basal cell carcinoma and squamous cell carcinoma.

*Table 4: Summary of the studies mentioned in the text*

| Initial author, year | Region | Time period | Exposure | Endpoint |
|---|---|---|---|---|
| Elwood, 1974 | US/Canada | 1950-1967 | Latitude, UV radiation | Mortality: malignant melanoma, non-melanoma skin cancer (NMSC) |
| Swerdlow, 1979 | England/Wales | 1962-1970 | Latitudes, hours of sunshine | Malignant melanoma incidence |
| Crombie, 1979 | Europe/North America | approx. 1970 | Latitude | Malignant melanoma incidence |
| Lee, 1993 | US | 1974-1987 | Latitude | Malignant melanoma incidence and mortality |
| Moan, 2012 | Norway/Sweden | 1997-2007 | UVA/UVB | Incidence: malignant melanoma, squamous cell carcinoma |
| Wallingford, 2013 | England | 1996-2006 | Latitude, regions | Malignant melanoma incidence |
| Moan, 2015 | Norway | 1997-2007 | Latitude, UV dose | Incidence: malignant melanoma, squamous cell carcinoma, basal cell carcinoma |
| Qureshi, 2008 | US | 1984-2002 | US states divided into 3 groups (by UV index) | Incidence: malignant melanoma, squamous cell carcinoma, basal cell carcinoma |
| Pinault, 2017 | Canada | Exposure: 1980-1990 outcome: 1992-2009 | UV exposure modelling | Malignant melanoma incidence |
| Xiang, 2014 | Systematic review of published studies from Europe, North America, Australia and New Zealand | 1978-2012 | Regional UV exposure modelled from satellite data | Incidence: squamous cell carcinoma, basal cell carcinoma |

### 2.6.2 Studies involving individual UV dose estimates

This section explores the extent to which the literature already offers theoretical models where epidemiological data can be used to derive relationships for skin cancer incidence as a function of (individual) UV dose. Here, particular emphasis will be placed on how additional modelling based on ambient UV exposure data can be used to derive a personal dose.

Irrespective of any existing dose-response relationship, Merrill et al. (Merrill et al. 2015) point out the paradox of outdoor workers having a lower malignant melanoma incidence despite accumulating an annual UV dose three to ten times higher than that of indoor workers. The corresponding odds ratios are twice as low as those for indoor workers. The authors deem this to be an indication that factors other than cumulative UV dose, e.g. intermittent UV exposures, play a key role in malignant melanomagenesis. In addition, the authors used published data (IARC) on melanoma incidence from different European countries spanning the years 1960 to

2000. This resulted in an exponential increase in melanoma incidence rate over time, both for females and males (cf. Figure 5).

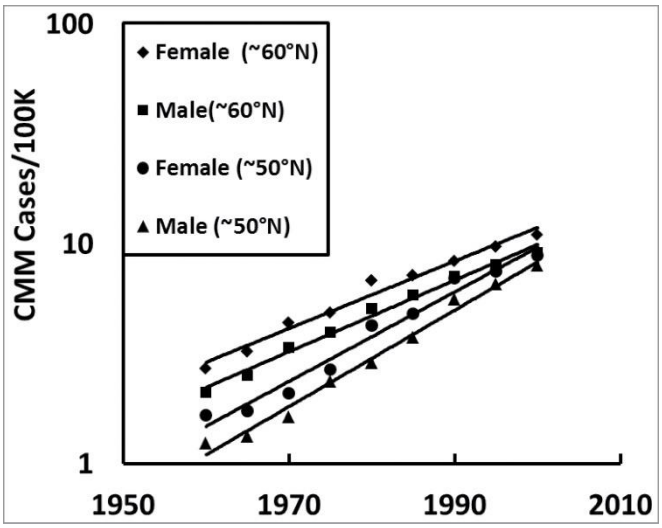


*Figure 5: Melanoma incidence rate among females and males at ~60°N and ~50°N in Europe between 1960 and 2000 (Merrill et al. 2015)*

Together with annual personal UV dose estimates, malignant melanoma incidence rates collected for eight European countries between 1960 and 2000 showed that the malignant melanoma incidence rate decreased as the UV dose increased, at least for the period 1980 to 2000 (cf. Figure 6).

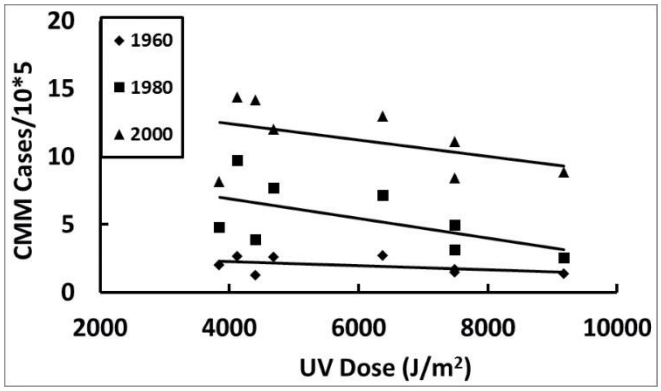


*Figure 6: Melanoma incidence rate plotted for eight European countries across the mean annual UV dose range for the years 1960, 1980 and 2000 (Merrill et al. 2015)*

The authors used multiple linear regression to adjust the data points, resulting in $R^2$ and p values of 0.98 and $10^{-7}$ respectively for the increase in melanoma incidence over time (cf. Figure 5). To express the dependency of melanoma incidence on UV dose, p values of $< 10^{-30}$ were provided for the dependency on the year (1960, 1980, 2000) and $< 2 \times 10^{-7}$ for the dependency on the dose. The authors deemed this analysis to be truly remarkable, speculating that their calculations show that intermittent UV exposures with a decreasing UV dose (and thus decreasing vitamin D production) are a key risk factor for malignant melanoma incidence. The authors also surmise that viral infections (HPV) are a second major risk factor. However, they

do not provide any data to confirm this, instead drawing on the literature to speculate a possible involvement of the human papillomavirus in the aetiology of malignant melanoma. This work does not, however, cover the potential influence of different ethnic groups and skin types of people in Northern, Central and Southern European countries. Nevertheless, the work shows that there are approximation methods available to estimate personal dosimetric data which can be correlated with skin cancer (malignant melanoma) incidence data to provide a dose-response relationship. Here, the mean annual erythemally weighted personal UV dose, $H_{\text{personal}}$, was estimated by converting measured values for a planar exposure (ambient UV) (Pope and Godar 2010) to a cylindrical exposure (substitute for a person standing up). The following approximation formula was used:

$$H_{\text{personal}} = -280X + 22{,}000\ \text{J m}^{-2} \qquad \text{Eq. 7}$$

Here, 22,000 J m$^{-2}$ is the UV dose calculated at the equator, while $X$ [J m$^{-2}$] is the UV dose for a person at a latitude North of the equator (where the skin cancer incidence rate was also determined) (Merrill et al. 2015). The authors point out that the approximation formula (Equation 7) is also applicable to the Southern hemisphere because, for instance, the annual mean UV doses (before conversion of ambient values to cylindrical exposure, see above) are 29,000 J m$^{-2}$ at 34°S in Australia and 28,000 J m$^{-2}$ at 34°N in the US, thus making them comparable (Godar et al. 2017).

In summary, these and the other studies presented above (Merrill et al. 2015, Xiang et al. 2014, Pinault et al. 2017) show that it is indeed possible to use ambient dose collection methods to deliver initial insights into the form and magnitude of dose-response relationships for skin cancer incidence. However, it should be noted that the analysis by Merrill et al. (2015) is the only one to report a decrease in melanoma incidence rate as the annual UVR dose increases. Nevertheless, it is important to bear in mind that the dose values were from measurements taken in eight European countries, meaning there may be major differences in the measured populations.

Other studies show that it is possible to use ambient UV exposure measurements to estimate personal dosimetric data or body site data and then use said data to determine a dose-response relationship for skin cancer incidence. Downs and Parisi published a study (Downs and Parisi 2009) in which they used polysulphone film dosimeters to measure UV irradiation horizontal to the Earth's surface (as a substitute for ambient UV irradiation) and evaluate it against dose measurements performed on various parts of a whole body phantom. This allowed them to calculate the relative share, *ER*, of exposure from the ratio of erythema averaged doses on a certain part of the body to the horizontally administered dose:

$$ER = \frac{E_{\text{body site}}}{E_{\text{horizontal}}} \qquad \text{Eq. 8}$$

This resulted in a percentage (*ER*) of the horizontal UV radiation (as a function of three solar zenith angle (SZA) ranges, cf. Table 5) for the face, neck, arm, hand and leg.

*Table 5: Relative exposure depending on the body site and solar zenith angle*[16]

| Body site | ER (SZA 0°-30°) | ER (SZA 30°-50°) | ER (SZA 50°-80°) |
|---|---|---|---|
| Face | 26% | 39% | 48% |
| Neck | 23% | 36% | 39% |
| Arm | 13% | 17% | 41% |
| Hand | 30% | 35% | 42% |
| Leg | 12% | 23% | 47% |

Schmalwieser and Siani (Schmalwieser and Siani 2018) arrived at a similar conclusion in a more recent review of the development of personal UV dosimetry over time. It showed that a concept can be created to estimate personal UV exposure *PE* as a function of a person's activity (act) (sitting, boating, shopping, fishing, etc.), body site (*BS*) and solar elevation (*se*):

$$PE_{\text{act, } BS\,(se)} = H_{\text{amb}} \cdot ERTA_{\text{act, } BS(se)} \qquad \text{Eq. 9}$$

Here, $H_{\text{amb}}$ = ambient exposure [J m$^{-2}$] and *ERTA* = exposure ratio to ambient.

The authors provide a comprehensive list of the *ERTA* value (in percent) for different times of the day and year to facilitate a personal dosimetry estimate for different body sites (Equation 9) (Schmalwieser and Siani 2018).

Schmalwieser (Schmalwieser 2020) conducted a study that presented other ways to estimate personal UV exposure data from ambient UV radiation measurements. These methods have improved considerably in recent years. Today, 3D computer models of the human body surface based on medical imaging procedures known as voxels can be used to divide the surface of the body (during various activities, such as sport, standing, walking, sitting) into tens of thousands of patches, with each patch defined as a polygon with an accompanying normal vector pointing in a perpendicular direction away from the body. However, to be able to use these models to estimate personal exposure (*PE*, cf. Equation 9), exact estimates (or measurements) of the ambient UV irradiance are required.

Schmalwieser (Schmalwieser 2020) describes three ways of determining exposure:

- Measure the ambient UV irradiance independently of the irradiation angle (on a horizontal surface) and use it in 3D models,
- Measure the ambient UV irradiance dependent on the incidence angle (measured separately) using UV sensors with different alignments,
- Use model calculations for UV irradiance from all directions in radiative transfer models.

The authors point out that defining personal exposure to the entire body "perfectly" is possible by way of a difficult and complex estimate of the irradiance from all directions on all body surface patches.

[16]Solar zenith angle is the angle between the sun and the vertical.

### 2.6.3 Studies involving personal UV dosimetry from workers with occupational exposure

In contrast to malignant melanoma (see Section 2.6.2), incidence analyses conducted in the 1980s showed that outdoor workers have a higher risk of developing basal cell carcinoma and squamous cell carcinoma (Beral and Robinson 1981). Since then, numerous studies have confirmed this increased cancer risk (e.g. among ferrymen, as described in Vitasa et al. 1990). However, indoor workers exposed to artificial UV radiation still have a much higher skin cancer prevalence (e.g. welders, as described in Heltoft et al. 2017). Taking into account the number of outdoor workers (14.5 million in the European Union, with around two to three million in Germany), special protective measures are required for these occupational groups to minimise the number of cases.

Findings on increased UV-related non-melanoma skin cancer risk (basal cell carcinoma and squamous cell carcinoma) include four major meta-analyses conducted around ten years ago (Schmitt et al. 2011, Schmitt et al. 2010, Bauer et al. 2011, Radespiel-Tröger 2011). In a comprehensive analysis of 18 studies (6 cohort studies and 12 case-control studies) regarding the association between squamous cell carcinoma occurrence and work-related UV exposure, outdoor workers with high UV exposure (e.g. seafarers, agriculture, forestry and construction workers) were found to have double the relative squamous cell carcinoma risk (Schmitt et al. 2011) compared to indoor workers (or workers with low occupational UV exposure) or the general population. Sixteen of the eighteen studies found a positive association of occupational UV exposure and squamous cell carcinoma. Statistical significance was reached in 12 studies and interpreted such that it adequately proves the association of occupational solar UV exposure and squamous cell carcinoma and its precursor, actinic keratosis (Diepgen et al. 2012, Fartasch et al. 2012).

For basal cell carcinoma, a meta-analysis of 24 studies (five cohort studies and 19 case-control studies) also showed evidence of a significant association of outdoor work and UV-related basal cell carcinoma risk with a pooled odds ratio (OR) of 1.43 and a confidence interval (CI) of 1.23-1.66) (Bauer et al. 2011). However, the observed study results were less consistent than those seen in the risk assessment for squamous cell carcinoma, and the described effects were not as pronounced. In this analysis, eleven of the studies indicated a significant positive association, while five studies showed non-significant increases and five other studies produced a non-significant risk decrease. However, the amount and level of data available have improved considerably in recent times (see below).

The ICNIRP issued a recommendation for outdoor workers that they should not exceed occupational UV exposures of 1.3 SED of an erythemally weighted UV radiation dose during an eight-hour working day (ICNIRP 2010). In general, past studies showed that this exposure limit is easily surpassed in Australia, New Zealand, Canada, Spain and the US with daily exposures of 5.5 to almost 10 SED (Gies and Wright 2003, Hammond et al. 2009, John et al. 2016, Peters et al. 2019). Studies conducted in France and Denmark where annual UV exposure was measured in SED confirm this trend (Boniol et al. 2015, Thieden et al. 2004, Grandahl et al. 2018).

A recent project involving outdoor workers (GENESIS-UV) showed that annual exposures of 500 SED and more occur very frequently (IFA 2020). In this project, electronic data-logging dosimeters were used to measure the integral erythemal UV dose every second. Almost 1,000 test subjects wore such an electronic dosimeter on the left upper arm each day from April to October. The project ran from 2014 to 2019 and included 95 different occupations. Thanks to a motion sensor and measurements recorded every second, it was possible to determine whether or not a dosimeter was being worn at any given time. The test subjects kept a diary to record

the various tasks being carried out within the scope of their occupation. Taking measurements directly on a person's body allowed individual exposures to be recorded for multiple occupations and tasks within those occupations, which is not possible with ambient measurements. According to these measurements, builders are exposed to around 500 SED each year, while harvest workers are exposed to over 600 SED per year.

Studies by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA) show that on the whole, outdoor employees have higher UV exposures than the thresholds and limits laid down in international guidelines. Consequently, discussions are ongoing at international level as to the occupational UV exposure risk threshold above which employers and legislators are required to take action. This applies in particular to recognising a certain illness as being an occupational disease. In Germany, occupational diseases are defined in section 9 (1) of the German Social Code, Book Seven (SGB VII) as diseases which, based on findings from medical science, are caused by hazardous agents to which certain groups of the population are exposed to a far greater extent than the general population. German law typically assumes that this criterion is met in the event of a doubling of risk (Schönberger et al. 2010).

Older epidemiological estimates for a number of major US cities showed that the incidence rate of squamous cell carcinoma doubled when plotted as a function of the UV dose depending on the latitude with a 40% increase in annual (ambient) UV dose (Armstrong and Kricker 2001). In Germany, this led to squamous cell carcinoma and multiple forms of actinic keratosis being recognised as an occupational disease (BK 5103) if it can be proven that occupational UV exposure was at least 40% higher than the 130 SED annual reference exposure for the German population outside of occupationally insured working hours (BMAS 2013). To accurately estimate this additional exposure, the Wittlich formula was developed which introduces factors to increase or decrease a reference value. These factors include temporal, geographical and personal parameters that influence individual exposure in the workplace (Wittlich et al. 2016).

In terms of the dose-response relationship for skin cancer incidence, a more recent study provided initial insights into basal cell carcinoma (Schmitt et al. 2018a). This multicentre case-control study involved 836 patients with first incident basal cell carcinoma whose lifetime UV exposure was estimated by trained investigators at eight different dermatological research centres. To differentiate occupational from non-occupational UV exposure, the Wittlich formula mentioned above was used. Subsequently, individuals with high levels of occupational UV exposure were seen to be at significantly increased risk of developing basal cell carcinoma when compared to individuals with a small or moderate UV exposure (OR = 1.84 or 1.97). Non-occupational UV exposure was not independently associated with basal cell carcinoma risk. The authors of the study proceeded to generate dose-response relationships for the odds ratios of basal cell carcinoma risk based on total (occupational and non-occupational) UV exposure, or occupational and non-occupational UV exposure separately. This showed that the lifetime occupational UV dose leading to a doubling in basal cell carcinoma risk is 7,945 SED. However, despite observing an increase in odds ratios at doses of 6,000 SED to 20,000 SED, it was not possible to establish a doubling dose for total UV exposure and non-occupational UV exposure. In view of this, the authors derived that the UV-related basal cell carcinoma risk was largely attributable to occupational UV exposure.

# 3 Statement

As presented in Chapter 2, a thorough literature review showed that it is currently not possible to evaluate dose-response relationships for skin cancer research.

This is because results from in vitro studies and animal model studies are difficult to transfer to dose-response relationships for skin cancer in humans. People accumulate UV doses over the course of several decades, often receiving very different doses on account of individual behaviour. It is not possible to simulate such scenarios by way of in vitro experiments and it is extremely hard to replicate in animal studies.

In addition, epidemiological studies only occasionally consider accumulated UV doses in people who recently developed skin cancer, meaning there is little robust data available about dose-response relationships for skin cancer. In the few studies which can be drawn upon here, it was not possible to determine any individualised dose data, e.g. from personal dosimetric measurements. Instead, it was only possible to determine ambient UV irradiances (to calculate (mean) monthly or annually accumulated doses from satellite data or based on latitudes or model calculations). However, there are a few studies available where personal dose estimates and/or modelling was performed in the basis of ambient UV dose measurements, and the results were correlated with skin cancer incidence. These studies can indeed be used to estimate a risk coefficient from the increase in dose-response relationship without having to be based on personal dosimetric data.

Recent suggestions include ways to convert ambient UV irradiance to a personal dose or UV dose accumulated in certain parts of the body (cf. Section 2.6.2). These models and calculations also include certain behaviours (moving, sitting, lying down, etc.). This would allow personal doses to be set in relation to incidences for the three types of skin cancer and skin cancer localisations, in turn enabling dose-response relationship estimates.

Future studies must show whether, given an adequate number of volunteers and sufficient accuracy, personal dosimetric UV dose measurements can be correlated to skin cancer incidence values, or whether model calculations based on ambient UV exposure measurements can be used to create such a dose-response relationship between the measured or modelled personal dosimetric UV dose and skin cancer.

Here, it is essential to record new cases of skin cancer comprehensively and in a standardised manner.

Based on this analysis, the SSK provides the following statement on how the breadth and depth of data could be improved to prepare and evaluate the dose-response relationship for the association of UV radiation and skin cancer:

- Individual UV exposures, ideally from spectral personal dosimetric measurements, should be used to create a dose-response relationship. If this is not possible, additional indirect calculations of individual UV exposure, e.g. simulation calculations, should be performed.
- Epidemiological surveys should be conducted to collect individual dosimetric measurements over a prolonged period and then collated with skin cancer incidence data. Ideally, these studies should be set up prospectively.
- Alternatively or additionally, existing epidemiological data on skin cancer incidence and ambient UV irradiance in places with different UV irradiances should be used in model calculations to extrapolate realistic personal doses and, in turn, the dose-response relationship accounting for individual behaviours.
- If personal dosimetric measurements and/or modelling permit a dose-response relationship for skin cancer incidence, they should be used to specify the risk assessment for UV-induced skin cancer.

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# Annex

## A-1 UV-induced skin cancer

### A-1.1 Influence of UV radiation type

Ultraviolet (UV) radiation consists of an electromagnetic wavelength ranging from 100 nm to 400 nm (see Figure A-1). There are differing definitions for the UVB and UVA boundaries (315 nm or 320 nm) and for the UVA and visible light boundaries (380 nm or 400 nm). The values provided in Figure A-1 follow those set out in the "International lighting vocabulary" issued by the International Commission on Illumination (CIE 1987).

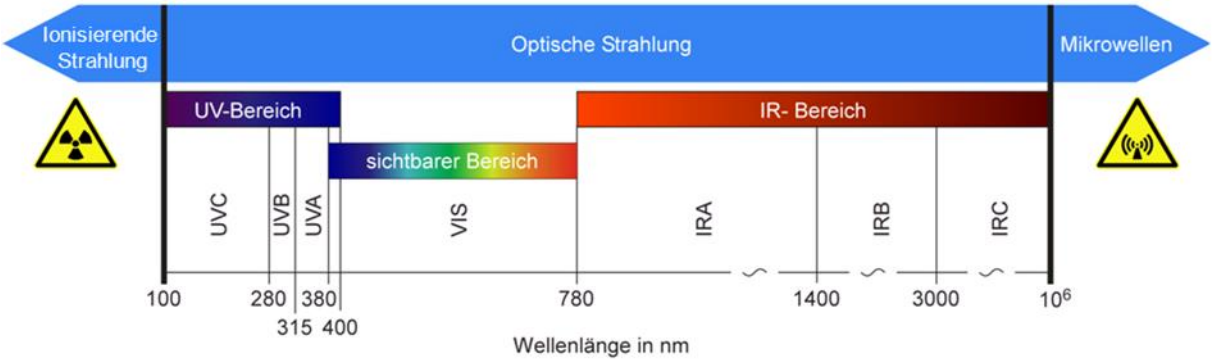


*Figure A-1: UV range as part of optical radiation within the electromagnetic spectrum (BMAS 2015)*

The penetration depth of UV radiation depends on the wavelength (see Figure A-2) and is influenced by the absorption behaviour of so-called chromophores (light-absorbing molecules) as well as reflection in the tissue. The penetration depth increases as the wavelength increases. At 250 nm (UVC, only emitted by artificial UV radiation sources), around 82% of the radiation is absorbed in the first 20 µm. At 297 nm (UVB), around 90% of the radiation is absorbed in the first 40 µm. At 365 nm, UVA radiation penetrates a depth of more than 20% of the epidermis. Within the transition range between UVA and visible light, around 60% of the radiation reaches the cutis (epidermis and dermis). Around 1% reaches the subcutis (Bruls et al. 1984). Skin thickness and thickness of the individual skin layers vary significantly and depend, among other things, on where the area of skin under consideration is located. As a result, in vivo transmission for the various skin layers can only ever be approximated.

Figure A-2 shows the penetration depth of UV radiation into the skin for various wavelengths. UVB radiation may penetrate the epidermis to the basal cell layer (border cell layer between the epidermis and dermis). UVA radiation penetrates deeper into the skin and can reach the dermis (subcutis). Only a very small percentage of UVC radiation reaches the Earth's surface as it is almost completely absorbed by the ozone layer. However, if UVC does reach human skin, e.g. when using artificial UVC radiation sources, it can only penetrate as far as the upper epidermal layer which consists of keratinocytes that have lost their core and DNA due to constant skin renewal.

UV radiation may be absorbed by a range of different chromophores whose absorption spectra are within the UV range. These also include cellular components such as proteins and intracellular photosensitive molecules like flavins or porphyrins (Cadet et al. 2012). However, the absorption of UV photons by the DNA molecule is of key importance here (see Section 2.2.2.).

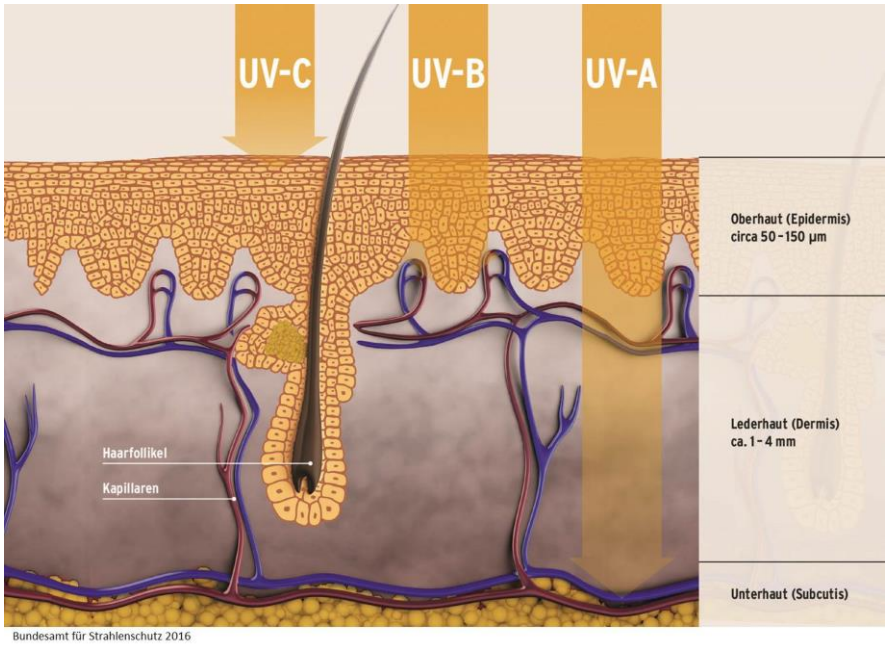


*Figure A-2: Penetration depth of UV radiation into the skin (graphic from the Federal Office for Radiation Protection (BfS))*

## A-1.1.1 DNA damage

### A-1.1.1.1 Induction - Direct reaction path (mainly UVB)

With this reaction path, primarily UVB photons are absorbed directly by the DNA molecule, and the absorbed energy is used for a photodimerisation reaction of neighbouring pyrimidine bases. Two UV-specific photoproducts generally occur as a result of this: cyclobutane pyrimidine dimers (CPD) and pyrimidine-pyrimidone (6-4) photoproducts (6-4PP). As can be seen in the action spectrum for the production of CPDs, $S_{py}$, UVB radiation is around 1,000 times more effective than UVA radiation (Mouret et al. 2012). CPDs are induced at a ratio of 3:1 when compared with 6-4PP (Mouret et al. 2006)**_ENREF_76**. When irradiating cell cultures, a UVB dose that may trigger sunburn (solar erythema) in humans with skin type II is enough to generate several 100,000 CPDs in the genome of human keratinocytes in vitro (Greinert et al. 2000).

### A-1.1.1.2 Induction - Indirect reaction path (mainly UVA)

UVA radiation mainly develops its damaging effect on the DNA molecule via indirect reaction paths. Here, the energy from UVA photons is absorbed by endogenous cellular photosensitive chromophores (photosensitisers) such as riboflavins and the oxidised form of nicotinamide adenine dinucleotide (NADH). In an excited electronic (triplet) state, they can then interact with molecular oxygen via so-called type I and II photoreactions to form reactive oxygen species such as superoxide anions, $H_2O_2$, OH radicals or singlet oxygen. These reactive oxygen species may then lead to DNA single-strand breaks (SSB), DNA double-strand breaks (DSB), DNA protein crosslinking, alkali labile sites (ALS) or base modifications such as UVA-specific 8-oxoguanine (Matsumura and Ananthaswamy 2002).

UVA radiation is also in a position to produce CPDs (even if there is a smaller yield than UVB radiation) (Cadet et al. 2012, Mouret et al. 2012). The mechanisms leading to the occurrence of CPDs following UVA exposure are yet to be fully established. However, premutagenic CPDs

are the most common cause of UVA-induced DNA damage in human skin (Mouret et al. 2006). Given that 95% of solar UV radiation is within the UVA spectrum, this finding is of particular importance when assessing the risk of solar UV radiation.

### A-1.1.2 Repairing UV-induced DNA damage

In mammal cells, bulky lesions such as CPD and 6-4 PP can be eliminated from the genome by means of nucleotide excision repair (NER). This is a complex interaction involving a number of proteins (up to 30) that are responsible for detecting damage, unravelling DNA, cutting DNA, processing DNA and the like. In the end, the damage is enzymatically cut out of the double helix in a 28 to 31-nucleotide long, single-strand DNA section before the resulting gap is filled again (with the opposite strand as a matrix) (Lagerwerf et al. 2011, van der Wees et al. 2007).

UV-induced oxidative damage such as 8-oxoguanine and other oxidative DNA damage may, depending on the kind of damage and its processing, be eliminated from the genome by a number of enzymatic repair paths (Peterson and Cote 2004), including base excision repair (BER) (Dianov and Parsons 2007, Robertson et al. 2009), DNA single-strand break repair (SSB repair) (Dianov and Parsons 2007, Horton et al. 2008, Wilson 2007), DNA double-strand break repair (DSB repair) (Shrivastav et al. 2008, Valerie and Povirk 2003, Wolf et al. 2016), mismatch repair (Skinner and Turker 2005, Slupphaug et al. 2003) as well as nucleotide excision repair (NER) (Lindahl 1993, Satoh et al. 1993, Wang 2008).

Overall, these briefly outlined repair systems are able to effectively eliminate DNA damage from the genome (within a period of minutes through to days, depending on the kind of damage and quantity of induced damage). However, taking into account the fact that minimum erythemal dose generates several 100,000 CPDs per genome of each individual exposed cell (Greinert et al. 2000), it becomes clear how effective, e.g. NER, works and how dysfunctions (non-repair) can occur, as is the case with overloading, deficiency and/or limited repair, which can then lead to mutations.

The DNA repair mechanisms are determined genetically. Xeroderma pigmentosum is a genetic disorder that leads to the affected person being much more sensitive to UV radiation and up to 1,000 times more at risk of developing skin cancer (Emmert et al. 2011, Kraemer et al. 2007, van Steeg and Kraemer 1999).

### A-1.1.3 UV-specific mutations

If UVA-induced or UVB-induced CPDs in a cell's genome are not rectified by cellular repair mechanisms, they lead to the occurrence of C→T or CC→TT transition mutations known as UV signature mutations because they, among the spectrum of all potential DNA mutations, generally only occur as a result of UV radiation (Matsumura and Ananthaswamy 2002, Pfeifer and Besaratinia 2012, Sage et al. 2012). The majority of mutations identified in skin tumours are UV-specific (Aszterbaum et al. 1999, Benjamin and Ananthaswamy 2007, Brellier et al. 2004, de Gruijl et al. 2001, Pleasance et al. 2010). Mutations occur in a range of tumour suppressor genes and oncogenes (e.g. CDKN2A, NRAS, TP53), which play a key part in particular in the aetiology of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). CPDs represent the main UV-induced DNA damage in terms of skin cancer. In addition, UVA-specific DNA lesions can contribute to the occurrence of mutations such as T→G transversions as a result of 8-oxoguanine, which can be made responsible for the development of skin cancer (de Gruijl et al. 1993, Dumaz et al. 1997, Matsumura and Ananthaswamy 2002).

The past ten years have continued to show that epidermal (interfollicular) stem cells with UV damage (and mutations) and stem cells in the outer root sheath of the hair follicle are responsible for the occurrence of skin cancer as a late effect of past UV exposures (Blanpain 2013).

## A-1.2 Types of skin cancer

### A-1.2.1 Malignant melanoma of the skin

Malignant melanoma generally involves a pigmented skin tumour that is responsible for around 90% of all mortalities from skin cancer. This is due to the high incidence of metastasis (25%) in all cases (depending on the stage of melanoma) (Garbe and Lasithiotakis 2006). The association between UV exposure and induction of malignant melanoma in the skin is regularly called into question as malignant melanoma also occurs in parts of the body that are not generally exposed to UV. However, most cases of malignant melanoma (94%) occur in parts of the body that may be regularly or intermittently exposed to UV radiation (face, other parts of the head, neck, chest, back, upper arm, lower arm, hand, thigh, lower leg, foot). There are a number of indications that malignant melanoma occurs as a result of intermittent UV exposure and severe sunburn during childhood and as adolescents (Armstrong and Kricker 2001, Dulon et al. 2002, Levine et al. 2013, Blum et al. 2004).

### A-1.2.2 Basal cell carcinoma

Basal cell carcinoma is a tumour that grows slowly and generally starts out as a small nodule that destroys local tissue and only metastasises in a very few exceptional cases. It is assumed to originate in the epithelium of hair follicles and generally occurs in the head and throat region which is constantly exposed to UV radiation. It can, however, also occur in other parts of the body normally covered by clothing. Basal cell carcinoma has no precursor. Depending on its localisation, the consequences can be severe and may have a substantial impact. The risk of developing basal cell carcinoma is influenced both by the lifetime dose of UV radiation and by intermittent UV exposures such as holidays in southern countries and sunburn which occurred during childhood or as adolescents.

### A-1.2.3 Squamous cell carcinoma

In over 90% of cases, squamous cell carcinoma occurs in skin that has been chronically damaged by UV, such as the face, ears, lower lip and back of the hand. For squamous cell carcinoma aetiology there is a relatively well described model in which early UV-specific mutations in the p53 gene during tumour initiation favour the development of a precancerous precursor of SCC, actinic keratosis. Squamous cell carcinoma is an invasively growing tumour which can quickly gain in size. This invasive growth may metastasise after a prolonged period of time.

### A-1.2.4 Influence of exposure pattern on UV-induced skin cancer

Alongside the influence of various radiation types (UVA vs. UVB) on genomic and cellular damage which can lead to skin cancer after exposure to UV radiation, it is increasingly apparent that the exposure pattern of UV radiation (chronic vs. acute exposure) plays a role in different types of skin cancer. Back in 1996, Armstrong and Kricker (Armstrong and Kricker 1996) were able to derive from epidemiological studies that squamous cell carcinoma incidence increases with the cumulative lifetime dose, whereas malignant melanoma incidence increases with brief intermittent UX exposures (e.g. sunburn). In this context, basal cell carcinoma is somewhere in-between as it can depend upon both cumulative and intermittent exposures. In recent years, the the rising incidence of squamous cell carcinoma from occupational UV exposure has been shown to depend upon the cumulative lifetime dose (Schmitt et al. 2018b).

New in vitro data from experiments involving human dermal fibroblasts also exhibit molecular changes that depend upon the UV exposure pattern. A study from 2017 showed that chronic pre-stimulation of dermal fibroblast with low doses of UVB radiation modified the cellular

response to DNA damage to such an extent that it enhanced CPD repair capacity, induced a cell cycle delay and increased the residual unrepaired cyclobutane pyrimidine dimers (Drigeard Desgarnier et al. 2017).