# 3.1.10 Hazards by Enhanced UV Irradiation

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*Hazards by Enhanced UV-Iradiation: While UV-C is totally absorbed by the ozone layer, a part of the solar UV-B and total UV-A reach the Earth's surface. In the skin UV irradiation induces a variety of acute effects like tanning, thickening of the skin or reddening and chronic effects like skin ageing. In the worst case UV-irradiation induces skin cancer, the most frequent cancer in the white population world-wide. Following the world-wide trend the incidence of skin cancer (malignant melanoma MM, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)) is continuously increasing in Germany due to a changed social behavior resulting in an enhanced UV-exposure. Nevertheless, thinning of the ozone layer, leading to enhanced UV-B irradiation on the Earth, may still play a role for the skin cancer incidence in future. UV-radiation can induce DNA damage that is repaired very effectively by the skin cells. Furthermore heavily damaged cells will be removed from the body by means of programmed cell death (apoptosis). However, in the case of misrepair mutations can occur that are characteristic for UV-damage (UV-signature mutations). There is increasing evidence that the occurrence of these mutations in epidermal stem cells of human skin characterizes an early step in the multi-step process of skin cancer development, involving tumor suppressor- or proto-oncogenes. Other effects like e.g. deregulation of epigenetic control of cellular functions as well as immunosuppression by UV-radiation also play important roles in the induction and progression of skin cancer. Educational campaigns and balanced information of the public, teaching a reasonable behavior concerning solar UV- or artificial (sunbed) radiation and/or early detection of skin cancer are useful tools to decrease the skin cancer risk as well as morbidity and mortality of skin cancer in the population. However, it is also important to take ecological measures for the protection of the ozone layer to prevent a further enhancement of UV-B irradiation at ground-level.*

*Gefährdung durch verstärkte UV-Strahlung - Während UV-C-Strahlung vollständig von einer intakten Ozon-Schicht absorbiert wird, erreichen Anteile von UV-B- Strahlung und die gesamte UV-A-Strahlung der Sonne die Erdoberfläche. In Haut kann UV-Strahlung akute Effekte wie Bräunung, Haut-Verdickung oder Rötung hervor-rufen, aber auch chronische Effekte, wie die Hautalterung. Im schlimmsten Fall kann UV-Strahlung zu Haut-krebs führen, der weltweit häufigsten Krebserkrankung in der weißen Bevölkerung. Wie auf der ganzen Welt, nimmt auch die Hautkrebs-Inzidenz (malignes Melanom, MM, Basalzellkarzinom, BCC und Plattenepithelkar-zinom, SCC) auch in Deutschland kontinuierlich zu. Dies hat seinen Grund, hauptsächlich, in einem geänderten Sozialverhalten, welches zu erhöhter UV-Exposition führt. Allerdings kann auch eine weitere Ausdünnung der Ozonschicht, welche zu erhöhter UV-B-Einstrahlung bewirkt, für die Hautkrebsinzidenz in der Zukunft eine Rol-le spielen. UV-Strahlung induziert DNA-Schäden, die von der Zelle effektiv repariert werden können. Darüber hinaus werden schwer geschädigte Zellen aus dem Körper durch programmierten Zelltod (Apoptose) entfernt. Im Falle von Fehlreparaturen kann es aber zur Bildung von Mutationen kommen, welche charakteristisch für UV-Schäden sind (»UV-signature mutations«). Es gibt zunehmende Evidenz, dass das Auftreten solcher Muta-tionen in epidermalen Stammzellen der Haut als frühes Ereignis im mehrstufigen Prozess der Hautkrebsent-stehung angesehen werden kann, wobei Tumor-Suppressorgene und Onkogene beteiligt sind. Andere Prozesse, wie z.B. die Fehlregulation der epigenetischen Kontrolle zellulärer Funktionen und die UV-bedingte Immun-suppression stellen ebenfalls wichtige Faktoren für die Induktion und Progression von Hautkrebs dar. Aufklä-rungskampagnen und ausgewogene Informierung der Bevölkerung, welche einen verantwortlichen Umgang mit solarer aber auch künstlicher (Solarien) UV-Strahlung vermitteln und/oder die Früherkennung von Haut-krebs zeigen sich als nützliche Maßnahmen, die das Hautkrebs-Risiko sowie die Erkrankung und Sterblichkeit an Hautkrebs reduzieren können. Trotzdem ist es immer noch wichtig, ökologische Maßnahmen zum Schutz der Ozonschicht zu ergreifen, um eine weitere Zunahme von UV-B-Strahlung an der Erdoberfläche zu verhindern.*

**B**ased on recent estimates in 2012 more than 230,000 new cases of cutaneous malignant melanoma (MM), the induction of which is associated with UV exposure, occur globally each year (FERLAY 2013). It has been furthermore estimated that, additionally, 2-3 million non-melanocytic skin cancers (NMSC,) which are mainly basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are diagnosed each year worldwide (SURDU et al. 2013). Furthermore, 20% of 12–15 million cases of blindness due to damage of the lens (cataract) are supposed to be UV induced (REPACHOLI 1996). The increased incidence of these diseases is to be attributed in particular to excessive sun exposure due to a change in people's recreational and social behavior. In addition, the decrease of the protective ozone layer in the atmosphere - and thus the increase in solar UV radiation on the ground - might also considered as a cause for an increase in skin cancer. However, new results indicate a recovery of the ozone layer (WEATHERHEAD & ANDERSEN 2006). Whether these changes have influences on skin cancer incidence has to be monitored in the future.

The investigation of effects caused from UV irradiation in the biosphere, and especially the estimation of the connected risks for man, require exact knowledge of the contributive quantities and the underlying interaction processes. Accordingly, some basic mechanisms of UV induced skin damage will be described in this chapter and the resulting risk of long term effects (skin cancer) will be pointed out.

## Acute and Chronic Effects of UV Irradiation

When describing biological effects of UV irradiation, the UV spectrum is frequently divided into three spectral bands, UV-A (315–400 nm), UV-B (280–315 nm) and UV-C (100–280 nm).While UV-C is absorbed totally by the upper atmosphere mainly by oxygen and to some degree also by ozone, UV-B is absorbed by ozone (but not totally) and UV-A radiation is mainly scattered by air molecules and a large part reaches Earth surface (*Fig. 3.1.10-1*). In dependence of the wavelength and an associated depth of penetration into the skin, UV radiation induces a variety of effects, based on photophysical and photochemical transformation processes of radiation energy. The most noticeable reaction of the skin to UV exposure is pigmentation. This tanning as well as a thickening of the skin's outermost layers are considered to be protection mechanisms. If UV exposure exceeds a certain, individually different, threshold, an acute damage occurs and several hours after irradiation a reddening of skin (erythema) appears. Additional UV exposure, further exceeding the threshold, leads to the development of blisters and eventually necrosis of the skin surface.

Chronic effects, such as premature aging of the skin, result from cumulative damage induced by years of UV exposure and are associated with irreversible changes like damage of connective tissue and wrinkling (solar elastosis), permanent capillary dilation (teleangiectasia) and enlargement of pores and blackheads (comedos). Furthermore, enhanced sun exposure can induce a disturbance of the keratinization (actinic keratosis), representing a precursor lesion of the squamous cell carcinoma. However, the induction of skin cancer is by far the most fatal result of UV exposure, associated with changes of the genetic material of the skin cells.

## Skin cancer

The incidence of skin cancer has been considerably increasing worldwide during the last decades. Besides malignant melanoma (MM), the main cause of skin cancer death, non-melanocytic skin cancers (NMSC) like basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), which in total belong to man's most frequent malignant tumors, are of importance (DIEPGEN & MAHLER 2002). UV-exposure has been shown to be mainly responsible for these observations (IARC 2012). MM accounts for about 5–10% of all skin cancer, whereas in terms of non-melanoma skin cancer (NMSC), BCC accounts for approximately 80–85% and SCC for about 15–20%. CM derives from pigment (melanin) producing melanocytes, whereas NMSC derives from epidermal keratinocytes (IARC 2012).

UV-A and UV-B from the sun and from UV-emitting devices (e.g. sunbeds) are classified as known carcinogens to humans (IARC Group 1) (IARC 2012). This classification was based on a large number of experimental data, epidemiological studies and meta-analyses thereof. It was concluded that there was sufficient evidence in humans for the carcinogenicity of solar radiation for MM, BCC and SCC. With regards to artificial sources of UVR, it was concluded that there was sufficient evidence for an increased risk of MM and of ocular melanoma, and a positive association was observed for sunbed use and SCC (IARC 2012).

### Skin Cancer Occurrence

Over the last 50 years a steep increase in both MM and NMSC has been documented in Caucasian populations (ERDMANN et al. 2013; LOMAS et al. 2012). Worldwide, highest incidence rates are by far those observed in Australia and New Zealand where fair-skinned populations are exposed to intensive UVR (ERDMANN et al. 2013; LOMAS et al. 2012). Based on estimations for 2012, more than 230,000 new cases of MM occurred

globally, 100,000 alone within Europe (FERLAY 2013). The lifetime risk of getting MM is highest in New Zealand and Australia with 3.6%. Lifetime risk for getting melanoma in Europe countries is ranging from 0.3% to 1.6% (ERDMANN et al. 2013). In Europe particularly high MM incidences are found in Nordic countries, Switzerland, the Netherlands, the Czech Republic and Slovenia. Mediterranean countries tend to have lower rates as well as the Baltic and Eastern European countries (ERDMANN et al. 2013; FERLAY 2013).

Incidence rates NMSCs are difficult to estimate as they are often not or only incompletely registered in cancer registries (LOMAS et al. 2012). However, based on data from few countries with population-based registries (Denmark, Finland, Scotland, Malta, Germany and the Netherlands) age-standardized incidence rates (ASR) of primary BCC are estimated to be 77–158 cases per 100,000 person-years in those regions (DE VRIES et al. 2012). Data from the Cancer Registry of Schleswig-Holstein (Germany) for the year 2011 lead to an estimate of 251.430 new skin cancer cases/year in Germany (MM: 29.450; BCC: 145.570 and SCC: 76.370).

Incidence rates of SCCs are much lower than those reported for BCCs (BIRCH-JOHANSEN et al. 2010; DOHERTY et al. 2010; LOMAS et al. 2012), e.g. 12/19 (f/m) cases per 100,000 person/years among women and 19.1 cases among men in Denmark (world standard) (BIRCH-JOHANSEN et al. 2010), 13.8/36.9 (f/m) in Scotland (DOHERTY et al. 2010), and 20.5/35.4 (f/m) cases among in The Netherlands (per 100,000, European standard) (HOLLESTEIN et al. 2012).

According to recent estimates, 55,500 deaths from melanoma occurred in 2012 worldwide, including 22,200 in Europe (FERLAY 2013). In comparison, mortality from NMSCs is low (< 0.1% of incident cases) (JENSEN et al. 2008; LEWIS & WEINSTOCK 2007). However, due to their high incidence NMSCs contribute to the rising morbidity as well as to a significant oeconomic burden to health services.

The risk of additional induction of basal cell carcinoma and squamous cell carcinoma can roughly be calculated. People with a yearly solar UV dose of 100 MED (MED = minimal erythemal dose, 1 MED corresponds to the lowest UV dose to achieve a reddening of the skin) obtain a 2 fold risk to develop skin cancer if they achieve an additional dose of 100 MED at the age of 35 to 65 years. An additional dose at the age of 15 to 45 years enhances the risk to develop a skin cancer during 75 years of life by a factor of 3.4 (SLAPER 1998).

In accordance with a worldwide trend, the incidence of all skin cancers in Germany is increasing faster than that of all other cancers. This fact is to be attributed in particular to excessive sun exposure due to a change in people's recreational and social behavior. Since sun tanned skin is in general considered beautiful and a sign of a healthy body, sun tanned skin is no longer only an expression of people's outdoor activity and recreation but has become a purpose of itself. This has led to excessive recreational exposure to UV radiation by sunlight or UV tanning devices (solaria). In addition to this changed behavior of large parts of the population, the decrease of the protective ozone layer in the atmosphere - and thus an increase in solar UV radiation on the ground - may also become a cause for a future increase of skin cancer. Based on UV monitoring, data models have been developed correlating the ozone reduction with UV-B increases at the earth's surface, resulting in an enhanced biological effectiveness of solar radiation. For a decrease of 1% of the ozone layer an increase of UV induced skin cancer of 1–3% has been calculated (SSK 1996).

# Biological Effects of UV Irradiation

UVR exposure has been shown to be the main cause of skin cancer, including cutaneous malignant melanoma (MM), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). In 2009, within the IARC monograph program UVR as well as the use of tanning devices was classified as carcinogenic to humans (group 1) (EL GHISSASSI et al. 2009; IARC 2012).

Although UV exposure has been recognized as a main risk factor for the incidence of the skin cancer, the underlying molecular mechanisms have further to be elucidated in more detail. Nevertheless, UV-induced mutations in specific genes, involved in the cell regulation, as well as chromosomal instability have been connected with the development of skin cancer.

UVR is that part of the electromagnetic spectrum emitted naturally from the sun or from artificial sources (e.g. sunbeds) which covers the wavelength-region from 100–400 nm. Historically, this wavelength band has been sub-divided into 3 further wavelength regions, UV-C in the range of 100–280 nm, UV-B in the range of 280–315 nm and UV-A in the range of 315-400 nm. The UV component reaching Earth's surface comprises about 95% UV-A and only 5% UV-B (IARC 2012). Solar UV-C is absorbed by (an intact) stratospheric ozone layer and hardly reaches the Earth's surface (see *Fig. 3.1.10-1*).

UV irradiation can penetrate the skin, interacting with photo sensible components of the cells (DNA, proteins, melanin, and other photo sensible molecules). These interactions cause a series of photophysical and photochemical reactions affecting the nature of biolo-

gical relevant molecules. Due to wavelength specific interactions, the biological effectiveness of UV irradiation decreases with penetration depth, where the shorter wavelength band UV B (280–315 nm) in comparison to UV-A (315–400 nm) is reduced more significantly (*Fig. 3.1.10-1*).

### DNA Damage

The main cellular target for UVR is DNA. A multitude of photoproducts, the ratio of which depends markedly on UV-wavelength, are formed in cellular DNA and can give rise to pre-mutagenic lesions. These photoproducts may be formed via direct (photon absorption in
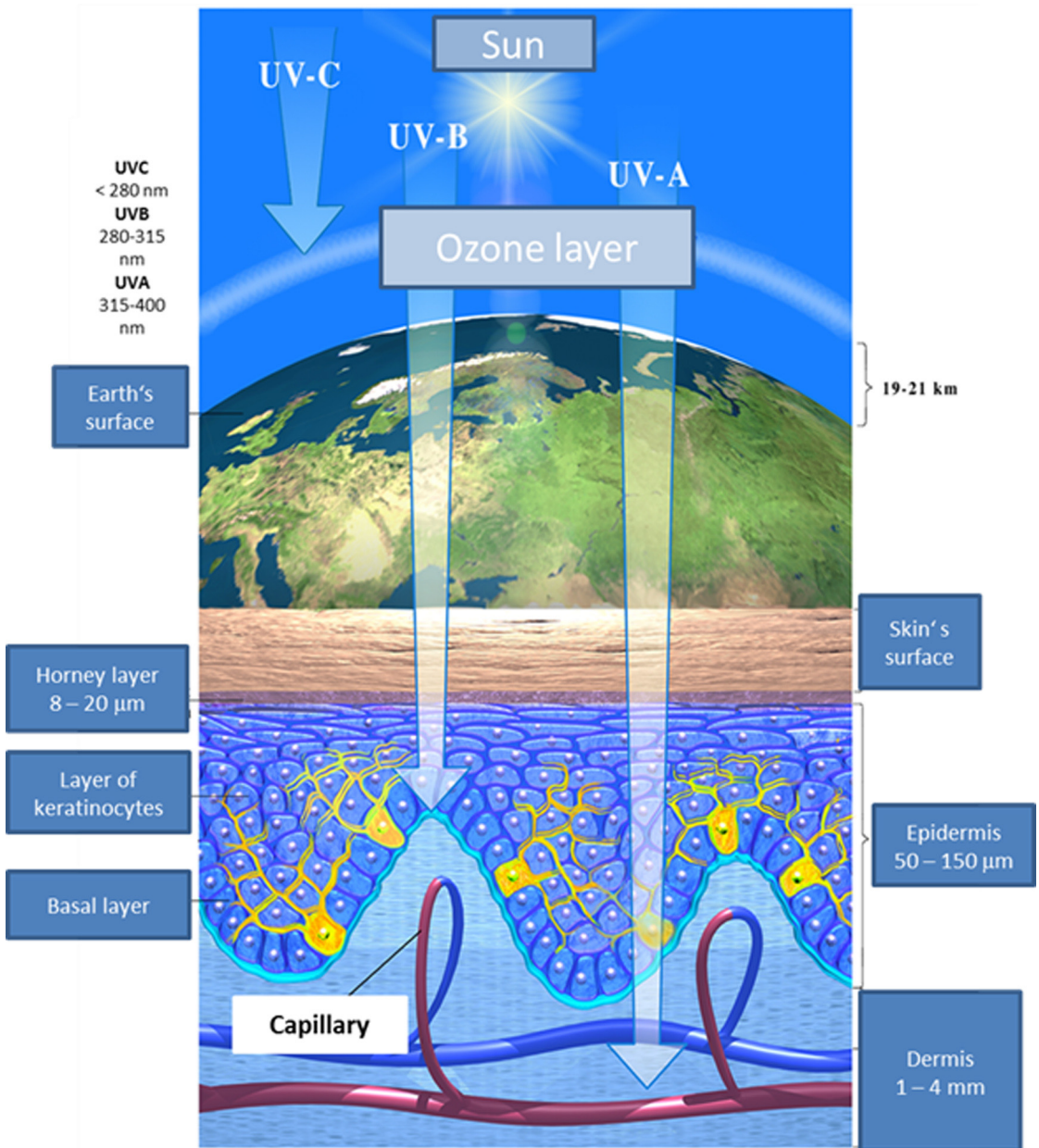


**Fig. 3.1.10-1:** *UV-C is absorbed totally absorbed in the upper atmosphere, mainly by oxygen. Parts of UV-B and most of UV-A can pass the atmosphere. While UV-B-radiation penetrates only into the upper part of human skin (epidermis), UV-A is able to penetrate also in the lower part of human skin (dermis). For this reason, UV-A might be able to damage different types of cells (in the dermis) compared to UV-B (which is able to damage keratinocytes and cells in the basal layer).*

DNA) or indirect mechanisms. Unlike UV-B, UV-A is only weakly absorbed by DNA. DNA-damage induction by UV-A occurs indirectly via absorption of UV-A-photons by endogenous (melanins, porphyrin, flavin groups) or exogenous photosensitizers (e.g. azathioprine, an immunosuppressive drug) (RIDLEY et al. 2009). These photosensitizers absorb in the UV-A range and release, in a complex reaction scheme, reactive oxygen species (ROS), giving rise, e.g. to guanine modifications including 8-oxo-guaninine which is known to be an important pre-mutagenic lesion after UV-A-irradiation (RIDLEY et al. 2009). UV-A is also able to produce reactive nitrogen species like e.g. nitric acid and peroxynitrite which are able to introduce cellular and DNA-damage (DIDIER et al. 1999). UV-A predominantly induces oxidized purines and relatively few oxidized pyrimidines and few (single) strand breaks in DNA (DIDIER et al. 2001; KIELBASSA et al. 1997; POUGET et al. 2000). In vitro, UV-A is also able to introduce DNA double strand breaks in DNA of human keratinocytes and skin fibroblast (GREINERT et al. 2012; WISCHERMANN et al. 2008), rendering a UV-A irradiated genome prone to possible production of chromosomal aberrations. UV-A can also introduce epigenetic changes (gene promotor methylation, histone methylation) in human keratinocytes, after chronic exposure. Via these modifications it can silence tumor suppressor p16 expression (CHEN et al. 2012). UV-A is also able to introduce the main mutagenic lesion, cyclobutane-pyrimidine dimers (CPDs) in the genome of human skin cells; CPDs, not oxidative lesions, were the main type of DNA damage induced in human skin (MOURET et al. 2006; MOURET et al. 2011).

UV-B is more than 1,000 time more effective in producing CPDs (via direct photon absorption in DNA) than UV-A, and is therefore the main source of CPDs in human cells (MOURET et al. 2010). In addition to CPDs, UV-B induces a second pyrimidine-dimer, the pyrimidine (6–4) pyrimidone photoproduct ((6–4)PP), in a ratio of 3:1 (CPD:(6-4)PP) (MITCHELL et al. 1990). Irradiation of human keratinocytes, in-vitro, with UV-B induces hundreds of thousands CPDs in the genome (GREINERT et al. 2000) .

If these CPDs are not repaired by cellular repair systems or repaired error-prone they give rise to C→T or CC→TT transition or tandem mutations which are considered "UV-signature mutations" (MATSUMURA & ANANTHASWAMY 2002). These types of mutations have been found frequently in tumour suppressor genes and oncogenes (e.g. p53, PTCH, p16, RAS) which play important roles in the aetiology of skin cancer. It has been demonstrated that for instance >90% of all SCC detected in the US carry UV-signature mutations in the p53 gene (ORTONNE 2002).

## Programmed Cell Death (Apoptosis)

Under certain circumstances, e. g. the accumulation of UV induced lesions in the cell, it may be favorable for the organism to eliminate the damaged cell from the tissue by destroying it. This programmed cell death (apoptosis) can be induced by UV irradiation by a sequence of complex genetic activation processes and via membrane mediated signal transduction, where UV induced DNA lesions (e.g. DNA strand breaks) as well as protein modifications are most important as initial events. In contrast to necrosis (non programmed cell death) apoptosis starts with a specific fragmentation of the DNA resulting in a fragmentation of the whole cell into membrane wrapped apoptotic bodies that are removed from the tissue without inflammation processes.

Immune cells of the skin (e.g. T-cells) are very sensitive about UV exposure. In contrast to the cells mainly constructing the skin (keratinocytes, fibroblasts) T-cells undergo apoptosis at doses below the threshold for erythema induction. The anti-inflammatory effect of UV-irradiation has been attributed to this phenomenon.

Furthermore, UV overexposure of the skin can induce apoptotic keratinocytes, called »sunburn cells« that are removed from the tissue. Supposing that UV induced mutations occur in genes involved in the programmed cell death (e.g. p53, see paragraph 5), the regulatory function of the apoptosis (removing of damaged cells) fails and subsequent cell divisions can lead to an accumulation of the genetic damage resulting in rising skin cancer risk (DE GRUIJL AND REBEL 2008; ZIEGLER et al., 1994).

## Immunosuppression

UVR causes suppression of certain aspects of the immune system (FISHER & KRIPKE 1977). The development of skin cancer appears to be partly controlled by the immune system. In human skin all necessary cellular requirements are present to induce and elicit anti-tumour immunity (SCHRODER et al. 2006). It has been well documented that patients with organ transplants who receive immunotherapy are very prone to skin cancer (BORDEA et al. 2004). Immunosuppression by solar-simulated UVR in men has been observed at doses three times lower than those required for immunosuppression in women (DAMIAN et al. 2008; IARC 2012). UV-B ultimately suppresses the immune system by inducing the production of immunosuppressive mediators, by damaging and triggering the premature migration of antigen-presenting cells required to stimulate antigen-specific immune responses, by inducing the generation of suppressor cells and by inhibiting the activation of effector and memory T cells (IARC 2012).

For UV-A-induced immunosuppression the pro-

duction of reactive oxygen species and reactive nitrogen species alter the redox equilibrium, target proteins, lipids and DNA. These might modulate immune competent cells resulting in aberrant behaviour and migration of antigen-presenting cells, the inhibition of T-cell activation and generation of suppressor cells (Norval et al. 2008). In experimental systems and in human skin, UVR can induce immunosuppression locally and systemically (IARC 2012). Minimal sun exposure with doses of one MED was found to influence the immunosystem with probably far-reaching consequences. Immunosuppression can have an influence upon carcinogenesis if the detection and elimination of transformed cells by the immunosystem is prohibited. Moreover, immunosuppressive effects are of importance for health policy according to virus and bacteria mediated effects like herpes simplex infection, leprosy and tuberculosis. In particular the progress of the acquired immune deficiency disorder [AIDS] may be aggravated by an additional UV-induced immunosuppression. Accordingly, investigations focused on the mechanisms of UV-induced immunosuppression which in spite of many data are still unclear, are classified by the World Health Organization (WHO) as very important (Kjellström 1996).

### *Ocular Damage*

As an acute effect of intensive sun exposure, inflammation of the cornea (photokeratitis) and the conjunctiva (photoconjunctvitis) can occur. These injuries are most frequently observed in an environment with high reflectance, eg. snow. The most serious sun affection on the eye is manifested as snow blindness. A WHO study indicates that 20% of cataracts (opacity of the lens), the most prevalent cause of blindness in the world (12–15 million cases per year), are induced by UV irradiation (Repacholi 1996). Investigations on the cellular and molecular level (e.g. in human lens epithelial cells) showed that UV-B as well as UV-A induced lesions in DNA and in membranes are responsible for the induction of cataracts. Additionally, a degenerative modification of the conjunctiva (pinguecula) and a wing-shaped overgrowth of the conjunctiva (pterygium), as well as a non-inflammatory affection of the retina, caused by a photochemical injury of the pigmented epithelium and the photoreceptors, are attributed to an enhanced UV exposition.

## Molecular Mechanisms of Skin Cancer Induction

There exists overwhelming evidence from epidemiological studies and basic science that the main environmental risk factor for the three main types of skin cancers (MM, BCC, SCC) is UVR; other risk factors are related to sensitivity to UVR (IARC 2012).

For MM, one of the largest meta-analyses shows that most risk factors are associated with UVR, such as number of acquired nevi (which are UVR-induced), number of atypical nevi, sunburn, intermittent sun exposure, total cumulative sun exposure and presence of actinic tumours (all statistically significantly related with MM) and chronic sun exposure (not statistically significant) (Gandini et al. 2005a; Gandini et al. 2005b; Gandini et al. 2005c). The »intermittent sun exposure«-hypothesis stems from observations showing that certain sun-intensive activities, such as sunbathing, outdoor recreation activities and sun-seeking holidays, generally yielded moderate-to-strong positive associations with MM risk, particularly if exposure occurred at young ages (see below), but that more regular exposure as well as total cumulative sun exposure generally showed weaker, no or even inverse associations (Armstrong & Kricker 2001; IARC 2012). Recent studies show that MM of the head and neck are strongly associated with actinic keratoses (»chronic« UVR-exposure), and MM on the trunk are strongly associated with acquired nevi (»intermittent« UVR-exposure) (IARC 2012; Purdue et al. 2005; Whiteman et al. 2006). About 50–60% of all MM carry mutations in the BRAF-gene, leading to activation of the MAP-Kinase (MAPK-) pathway inducing proliferation of melanocytes and impairment of apoptotic response to metabolic stress. These BRAF-mutations occur more frequently in MM on intermittent UVR-exposed human skin areas compared to MM developing in more chronically exposed parts of human skin (Maldonado et al. 2003), indicating that UVR-exposure patterns are determinants of mutation induction. Although BRAF-mutations only include about 2-3% UV-signature mutations (Hocker & Tsao 2007), results of a melanoma metastasis genome sequencing study showed that about 70% of all mutations had been C-T, CC-TT »UV-signature mutations« (Pleasance et al. 2010).

Important risk factors for NMSC are closely related to individual UV sensitivity, such as skin type (UV-sensitive skin types are at higher risk for the development of BCC or SCC than those with less sun-sensitive skin (Gallagher et al. 1995a; Gallagher et al. 1995b), presence of actinic keratosis (Salasche 2000), a personal history of NMSC (Marcil & Stern 2000), and immunosuppression (Espana et al. 1995; Jensen et al. 1999; Ong et al. 1999).

There is increasing evidence that risk factors for BCC are comparable to CM, partly also dependent on intermittent UVR-exposure such as sunburns (Kricker et al. 1995; Zanetti et al. 2006). Interestingly, UV-si-

gnature mutations have been found in the p53-, PTCH- and smoothened-gene (KIM et al. 2002; RATNER et al. 2001), all involved in BCC development which has been taken as a further indication that UVR plays the important role in the aetiology of BCC.

SCC appear frequently on sun exposed areas of the human body (nose, forehead, ears) and depend to a high degree solely on total cumulative sun exposure (ARMSTRONG & KRICKER 2001). Therefore, SCC are often found in the occupational UVR-exposed populations like in farmers, street workers, or seamen. A well-described p53-dependent model for SCC development exists since several years according to which specific p53 mutations lead to a pre-cancerous skin lesion, actinic keratosis (AK), where one allele of the p53 gene is already mutated. This mutation disturbs the p53-dependent apoptosis of UVR-damaged cells (»sunburn cells«) and favours clonal expansion of AK-cells (ZHANG et al. 2005). If AK-cells are further UVR exposed, this can induce mutation of the second p53 allele leading to a total loss of the »p53 checkpoint« responsible for cell cycle control of skin keratinocytes. This leads to uncontrolled cell division and eventually to development of invasive SCC alongside additional gene mutations (e.g. RAS) (BRASH 2006; BRASH et al. 1996). p53 mutations are found in more than 90% of SCC in-situ cases (Ortonne 2002). These mutations are predominantly of a »UV-signature« type and occur non-randomly in the p53 gene in so called »mutational hot spots« which are located in the gene in certain positions where nucleotide excision repair of pre-mutagenic lesions (CPDs) is hindered (Tornaletti 2009). There is good evidence that SCC in mouse models as well as in human skin originate from inter-follicular epidermal stem cells (WATT et al. 2006) which might not be able to fully repair UVR-induced damage and therefore accumulate persistent DNA lesions (CPD retaining basal cells) (MITCHELL et al. 2001; NIJHOF et al. 2007).

## Concluding Discussion

UV radiation (UV-A and UV-B) reaching the earth's surface can cause cellular and genetic changes in the skin and in the eye, where the induction of skin cancer is by far the most fatal result of UV exposure. The multi-step process of skin cancer induction is attributed to UV induced lesions in the desoxyribonucleic acid (carrying the genetic information), removed incompletely or incorrectly by the cellular repair processes. This error-prone repair can result in the mutation of cell regulating genes, subsequently leading to malignant transformation of the cells. The complex mechanisms of skin cancer induction still have to be elucidated.

In recent decades the incidence of skin cancer has been increasing faster than that of all other cancers. According to this world wide tendency, in Germany an increased incidence is observed for squamous cell and basal cell carcinoma as well as for malignant melanoma. Above all, this fact is to be attributed in particular to excessive sun exposure due to a change in people's recreational and social behavior. Sun tanned skin is in general considered beautiful and a sign of a healthy body, holidays in southern countries have become more frequent. This has led to excessive recreational exposure to UV radiation by sunlight or solaria resulting in an enhanced skin cancer risk. Furthermore, other effects like the UV induced immunosuppression may have far-reaching consequences to health policy activities (e.g. vaccinations).

In addition to the changed recreational behavior of the population the reduction of the protecting ozone layer has to be mentioned as a reason for an enhanced skin cancer risk in future. As a result of the increasing UV-B irradiation on the earth's surface, calculated in models, a further increase of skin cancer incidence could be expected. If this really the case has to be continuously monitored in international UV-networks and by population based (skin) cancer registries.

Nevertheless, the population has to be educated by means of instruction campaigns on reasonable behavior in the sun and on dangers when using solaria (BREITBART et al. 2006; GREINERT et al. 2008). Additionally, the continued development of ecological measures prohibiting a further degradation of the protecting ozone layer is necessary to decrease the incidence of skin cancer and other UV related diseases. Furthermore, early detection (skin cancer screening) of skin cancer has been shown to be effective to reduce the burden of this disease (CHOUDHURY et al. 2012).

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