Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

Preliminary Opinion on

Biological effects of ultraviolet radiation relevant to health with particular reference to sunbeds for cosmetic purposes

The SCENIHR approved this Opinion for public consultation at their plenary on

3 December 2015

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They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCENIHR

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All Declarations of Working Group members and supporting experts are available at the following webpage:
http://ec.europa.eu/health/scientific_committees/emerging/members_wg/index_en.htm

ABSTRACT

Introduction

In 2006, the Scientific Committee on Consumer Products provided an Opinion on the biological effects of ultraviolet radiation (UVR) from sunbeds and stated that the use of UVR devices for cosmetic tanning was likely to increase the risk of malignant melanoma of the skin and possibly ocular melanoma. In 2009 the International Agency for Research on Cancer (IARC) reviewed all the evidence pertaining to the carcinogenic effects of UVR from sunbeds, and classified use of UV-emitting devices for tanning as carcinogenic to humans (Group 1). The European Commission therefore requested the SCENIHR to review recent evidence in order to improve the understanding of risks associated with UVR in general and with sunbeds in particular and provide an updated Opinion.

Legal background

In the EU, placing sunbeds on the market with an input voltage between 50 and 1000 volts for alternating current or between 75 and 1500 volts for direct current is regulated by the Low Voltage Directive (LVD) (Directive 2006/95/EC)[1]. This directive requires that only safe products are placed on the market and covers all risks, not just the electrical safety aspects.

The General Product Safety Directive (Directive 2001/95/EC)[2] (GPSD), which requires that products to provide a reasonably expected level of safety throughout the lifetime of the product and contains specific obligations for producers, distributors and national authorities, is applicable to sunbeds used by consumers, including in the context of a service, in so far as the LVD does not already contain specific provisions governing the same aspects with the same objectives. This is without prejudice of any other EU applicable legislation.

The voluntary harmonised standard EN 60335-2-27:2013 sets out requirements for the safety of sunbeds, including limits for ultraviolet radiation emission. If this standard is applied, it provides a presumption of conformity with the safety objectives of Directive 2006/95/EC with respect to the risks covered by the standard.

In recent years some Member States have adopted national legislation regulating the tanning services (including, for example, a ban below the age limit of 18 years, the need for properly trained staff, etc.). These measures, when properly enforced, should ensure that tanning studios provide a better level of protection to consumers who use these devices.

Exposure

It is currently estimated that UV emission of a modern tanning appliance corresponds to an UV index of 12, i.e. equivalent to midday tropical sun. There are large variations in the UV output of different machines, and the UV spectrum emitted by devices used for tanning has evolved in recent years towards higher UVA irradiance.

[1] Directive 2006/95/EC on the harmonisation of the laws of Member States relating to electrical equipment designed for use within certain voltage limits, OJ L 374, 27.12.2006, p. 10. As of 20 April 2016, it will be replaced by Directive 2014/35/EU (OJ L 96, 29.03.2014, p. 357).

[2] Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on General Product Safety, OJ No L 11 of 15 January 2002.

The prevalence of sunbed use for tanning purpose varies greatly from one country to another and according to sex and age: it is higher in white-skinned populations from Northern Europe, and in young or middle-aged women. A recent meta-analysis of data from 16 Western countries (406,696 participants) showed that the overall summary prevalence of ever exposure to indoor tanning was as high as 35.7% (42% N and W Europe) for adults, 55.0% for university students (US studies only), and 19.3% for adolescents (24% for N and W Europe). The summary prevalence of last year exposure was 14.0%, 43.1% for university students, and 18.3% for adolescents, higher among women. An increase in prevalence of sunbed use over time was noted; the most recent estimates (2007-2012) of use in the last-year exposure to indoor tanning gave last-year prevalence of 18.2% in adults, 45.2% in university students (US studies only), and 22.0% adolescents. These are absolute increases of 3.4% in adults, 2.1% in university students (US studies only), and 1.7% in adolescents from the results of the primary analyses.

Health effects: Non-cancer health effects

UV radiation has both a local (i.e. in the skin) and a systemic immunosuppressive effect. There is evidence that UVB emitted from sunbeds can induce vitamin D production, but excess exposure leads to photodegradation of pre-vitamin D3 in the skin. There is widespread consensus that it is not necessary to use sunbeds to enhance vitamin D levels even in winter. Usual exposure of face and hands to UVR from the sun (even on cloudy days) and common diet are sufficient to achieve a sufficient vitamin D level. If needed, dietary supplements for vitamin D are available.

UVB-induced immunosuppression is well established, but there is now evidence for an immune suppressive effect also by UVA in the wavelength range from 350 – 390 nm.

Exposure to UVA as well as to UVB enhances photoaging of the skin.

Health effects: Melanoma, Non-melanoma skin cancer, other cancers

There is consistent evidence from meta-analyses, case-control studies and cohort studies of a statistically significantly increased risk from cutaneous melanoma associated with sunbed use, with a dose-response proportional to the number of sessions and frequency of use. The three most recent cohort studies showed an increase in melanoma risk associated with sunbed exposure at a younger age. In addition, since all analyses were adjusted for host factors and for sun exposure, they also suggest that sunbed use adds a specific risk of melanoma independently from individual susceptibility and behaviour in the sun. Although based on a smaller number of studies than for melanoma, there is consistent evidence from meta-analyses and individual studies that indicates that sunbed use is also a risk factor for squamous cell carcinoma, especially when exposure takes place at a younger age and to a lesser extent for basal cell carcinoma. There was no evidence from recent studies of an increase in incidence of internal cancers associated with sunbed use. The current evidence does not suggest a decreased risk in all-cause mortality associated with sunbed use; the only available cohort study suggests an increased risk of death from all cancers taken together. There is an increased risk of ocular melanoma associated with sunbed use especially if exposure starts at an early age.

Mechanistic studies

Evidence for carcinogenicity of UV exposure is supported by experimental animal studies and by mechanistic studies. In vivo experimental studies on neonatal transgenic mice

have shown the induction of melanoma by UVB irradiation, and a study has shown also the induction of melanoma with UVA irradiation. The existence of two distinct pathways for melanoma (an UVB-dependent pathway associated with direct UVB-type DNA damage and an UVA pathway associated with indirect oxidative DNA damage in melanocytes) is under investigation. In vitro mechanistic studies on human derived tumour cell lines and skin biopsies, underpin the outstanding importance UVA and UVB-induced molecular and cellular events involved in human skin photocarcinognesis. A UVA and UVB signature mutation pattern could be identified. Importantly, UVA has been shown to be at least as much involved as UVB in DNA damage and mutation induction. UV-signatures could be detected in a wide range of genes involved in photocarcinogenesis. There is increasing evidence that epigenetic changes are also induced via UVA/B, further highlighting the importance of UV on several regulation mechanisms involved in human photocarcinogenesis.

Risk characterisation

The contribution of sunbed exposure to skin cancer incidence is far from being negligible. It was estimated that in Europe, 3,438 (5.4%) of 63,942 new cases of melanoma diagnosed each year may be related to sunbed use, women representing 68% of this burden, and about 498 women and 296 men may die each year from a melanoma as a result of indoor tanning. The increase in melanoma risk associated to sunbed use in the general population amounts to +15%, with most of the risk concentrated in the population that started sunbed use before the age of 35 (+75%); the fraction of risk attributable to sunbed use in patients diagnosed with a melanoma before the age of 30 may be very high: 43 to 76%.

Overall Conclusion

The SCENIHR concludes that UV is a complete carcinogen, both an initiator, and a promoter. There is strong evidence that sunbed exposure causes skin melanoma, squamous cell carcinoma and, to a lesser extent, basal cell carcinoma, more especially when first exposure takes place in younger ages. There is moderate evidence that sunbed exposure may also cause ocular melanoma. Sunbed use is responsible for a noticeable proportion of both melanoma and non-melanoma skin cancers and for a large fraction of melanomas arising before the age of 30.

The small potentially beneficial effects of sunbed use are more than outweighed by the many severe adverse effects. There is no need to use sunbeds to induce Vitamin D. On contrary, UV overexposure may even reduce the vitamin D level.

Because of evidence of the carcinogenic effects of sunbed exposure and of the nature of skin cancer induction (there are no indications for threshold levels of UV-irradiance and UV–dose), there is no safe limit for UV irradiance from sunbeds.

Keywords: Ultraviolet radiation, UV-tanning devices, Sunbeds, Health effects, Risk assessment, SCENIHR

Opinion to be cited as:

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1. EXECUTIVE SUMMARY

1.1 Introduction

In 2006, the Scientific Committee on Consumer Products provided an Opinion on the biological effects of ultraviolet radiation (UVR) from sunbeds and stated that the use of UVR tanning devices to achieve and maintain cosmetic tanning, whether by UVB and/or UVA, was likely to increase the risk of malignant melanoma of the skin and possibly ocular melanoma and that sunbeds should not be used by individuals under the age of 18 years. In 2009 the International Agency for Research on Cancer (IARC) reviewed all the evidence pertaining to the carcinogenic effects of ultraviolet radiation (UVR) from sunbeds, and classified use of UV-emitting tanning devices as *carcinogenic to humans (Group 1).*

The health and safety hazards associated with the use of sunbeds are determined by two key elements: a) the safety of the sunbed itself (and its compliance with existing applicable legislation and device standards), and b) the way in which the product is used (or misused) by the consumer – this depends greatly on the knowledge of the consumer and on the information and advice given to the user by the tanning service operator. At EU level, a legal framework exists that aims at reducing the risks posed by sunbeds themselves, e.g., as regards the emitted UV radiation. In recent years some Member States have adopted national legislation regulating the tanning services. Market surveillance has shown that consumer guidance in tanning studios is not regularly given and labelling of sunbeds often fails to comply with regulations. In addition, there have been growing concerns about the higher risks of developing skin cancer and other skin-related diseases associated with the use of sunbeds. The European Commission therefore requested the SCENIHR to review recent evidence in order to improve the understanding of risks associated with UV radiation in general and with sunbeds in particular and provide an updated Opinion.

In this Opinion, the term "sunbed" refers to all types of UV tanning devices for cosmetic purposes.

1.2 Legal background

In the EU, placing sunbeds on the market with an input voltage between 50 and 1000 volts for alternating current or between 75 and 1500 volts for direct current is regulated by the Low Voltage Directive (Directive 2006/95/EC)[1]. This directive requires that only safe products are placed on the market and covers all risks, not just the electrical safety aspects.

The General Product Safety Directive (Directive 2001/95/EC)[3] (GPSD), which requires that products must provide a reasonably expected level of safety throughout the lifetime of the product and contains specific obligations for producers, distributors and national authorities, is applicable to sunbeds used by consumers, including in the context of a service, in so far as the LVD does not already contain specific provisions governing the same aspects with the same objectives. This is without prejudice of any other EU applicable legislation.

The voluntary harmonised standard EN 60335-2-27:2013 sets out requirements for the safety of sunbeds, including limits for ultraviolet radiation emission. If this standard is

applied, it provides a presumption of conformity with the safety objectives of Directive 2006/95/EC with respect to the risks covered by the standard.

In recent years some Member States have adopted national legislation regulating the tanning services (including, for example, a ban below the age limit of 18 years, the need for proper health and safety information, stricter hygiene conditions, the need for properly trained staff, etc.). These measures, when properly enforced, should ensure that tanning studios provide a better level of protection to consumers who use these devices.

1.3 Exposure

A recent meta-analysis of data from 16 Western countries and including 406,696 participants showed that the overall summary prevalence of ever exposure to indoor tanning was as high as 35.7% for adults (42% for N and W Europe), 55.0% for university students (US studies only), and 19.3% for adolescents (24% for N and W Europe). The summary prevalence for use of sunbeds in the last year was 14.0%, 43.1% for university students (US studies only), and 18.3% for adolescents, and higher among women than men. This meta-analysis further showed an increase in prevalence of sunbed use over time; the most recent estimates (2007-2012) of sunbed use in the last year showed a prevalence of 18.2% in adults, 45.2% in US university students, and 22.0% adolescents. These are absolute increases of 3.4% in adults, 2.1% in university students, and 1.7% in adolescents from the results of the primary analyses.

1.4 Health effects: Non-cancer health effects

There is evidence that the fraction of UV-B emitted from sunbeds can induce vitamin D production. However, excess exposure can even be counter-productive due to photodegradation of pre-vitamin D3 in the skin. Production of vitamin D by exposure just of the face and hands to natural sunlight depending on latitude, season and daytime is a matter of a few minutes to about half an hour. There is widespread consensus from various professional and public organisations in the UK, Germany and France that it is not necessary to use sunbeds to enhance vitamin D levels even in winter. Usual exposure to UVR from the sun (even on cloudy days) and a normal diet are sufficient to achieve a sufficient vitamin D level. In addition, special dietary vitamin D sources are amply available.

The role of UVB in immunosuppression is well established, but there is now evidence for an immune suppressive effect by UVA in the wavelength range from 350 – 390 nm. UV light (UVA as well as UVB) has both a local (i.e. in the skin) and a systemic immunosuppressive effect.

Exposure to UVA as well as to UVB enhances photoaging of the skin, among others, by damaging collagen and elastin.

1.5 Health effects: Melanoma, Non-melanoma skin cancer, other cancers

There is consistent evidence from meta-analyses, case-control studies and cohort studies of a significantly increased risk from cutaneous melanoma associated with sunbed use, with a dose-response with increasing number of sessions and increasing frequency of use. The three most recent cohort studies showed an increase in melanoma risk associated with sunbed exposure at a younger age. In addition, since all analyses were adjusted for factors such as tendency to sunburn, hair colour, individual susceptibility and behaviour regarding sun exposure, they also suggest that sunbed use adds a

specific risk of melanoma. Although based on a smaller number of studies than for melanoma, there is consistent evidence from meta-analyses and individual studies that indicates that sunbed use is also a risk factor for squamous cell carcinoma and to a lesser extent for basal cell carcinoma, especially when exposure takes place at a younger age. It should be noted that the use of sunbeds was generally self-reported and there was no information on the specific sunbed used. With the exception of a negative association for breast cancer in one cohort no association was found between sunbed use in adolescence and/or early adulthood and internal cancer risk. The current evidence does not suggest a decreased risk in all-cause mortality associated with sunbed use and the only available cohort study suggests an increased risk of death from all cancers taken together. There is an increased of ocular melanoma with sunbed use, which increases when exposure starts at a younger age.

1.6 Mechanistic studies

Evidence for the carcinogenicity of UV exposure is supported by experimental animal studies that have shown the induction of melanoma and squamous cell carcinoma, and by mechanistic studies. Several *in vivo* experimental studies conducted on neonatal HGF/SF transgenic mice irradiated with UVB have shown the induction of melanoma, and a study with irradiation with UVA also showed has shown also the induction of melanoma. The existence of two distinct pathways for melanoma: an UVB-dependent pathway associated with direct UVB-type DNA damage and an UVA pathway associated with indirect oxidative DNA damage in melanocytes is under investigation. Many mechanistic studies, mainly *in vitro* with human derived (tumour) cell lines and skin biopsies, underpin the outstanding importance UV-induced (UVA and UVB) molecular and cellular events involved in human photocarcinogenesis (non-melanocytic skin cancer and melanoma). A UVA and UVB signature mutation pattern could be identified. Importantly, UVA has been shown to be at least as much involved as UVB in processes leading to DNA damage and mutation induction. UV-signatures could be detected in a wide range of genes involved in photocarcinogenesis. In the last years, increasing evidence has been collected that epigenetic changes, which play a crucial role in (skin-) cancer induction and development, are also induced via UVA/B. This highlights, furthermore, the importance of the effects of UV on several regulation mechanisms involved in human photocarcinogenesis.

1.7 Risk characterisation

The contribution of exposure to sunbeds to skin cancer incidence is far from being negligible. It was estimated that in Europe, 3,438 (5.4%) of 63,942 new cases of melanoma diagnosed each year may be related to sunbed use, women representing 68% of this burden, and about 498 women and 296 men may die each year from a melanoma as a result of being exposed to indoor tanning. Although the increase in melanoma risk due to sunbed use may appear modest in the general population (+15%), most of the risk concentrates in the population that started sunbed use before the age of 35 (+75%) and the fraction of risk attributable to sunbed use in patients diagnosed with a melanoma before the age of 30 may be very high: 43 to 76%.

1.8 Overall Conclusion

The SCENIHR concludes that UV is a complete carcinogen, acting as both an initiator, through genotoxicity, and a promoter, through immunosuppression. There is strong evidence that sunbed exposure causes skin melanoma, squamous cell carcinoma and, to

a lesser extent, basal cell carcinoma, more especially when first exposure takes place in younger ages. There is moderate evidence that sunbed exposure may also cause ocular melanoma. Sunbed use is responsible for a noticeable proportion of both melanoma and non-melanoma skin cancers and for a large fraction of melanomas arising before the age of 30.There is no need to use sunbeds to induce Vitamin D. Because of evidence of the carcinogenic effects of sunbed exposure and of the nature of skin cancer induction (there are no indications for threshold levels of UV-irradiance and –dose), there is no safe limit for UV irradiance from sunbeds.

2. BACKGROUND

In 2006, the Scientific Committee on Consumer Products provided an Opinion on the biological effects of ultraviolet radiation (UVR) from sunbeds. In 2012 the International Agency for Research on Cancer (IARC) reviewed all the evidence pertaining to the carcinogenic effects of UVR from sunbed use and classified this as a group 1 (definite) human carcinogen. The recently published fourth edition of the European Code against Cancer[3] has recommended that sunbeds should not be used at all based on evidence from epidemiological studies, established causal mechanisms, the increasing skin cancer burden in the mostly fair-skinned European populations, and the modifiability of the risk factor by individual action, acknowledging also the beneficial effects of sunlight such as vitamin D production.

The health and safety hazards associated with the use of sunbeds are determined by two key elements: a) the safety of the sunbed itself (and its compliance with existing applicable legislation and device standards), and b) the way in which the product is used (or misused) by the consumer – this depends greatly on the knowledge of the consumer and on the information and advice given to the user by the tanning service operator[4].

In the EU, the placing on the market of sunbeds with an input voltage between 50 and 1000 volts for alternating current or between 75 and 1500 volts for direct current is regulated by the Low Voltage Directive (Directive 2006/95/EC)[1]. This Directive requires that only safe products are placed on the market and covers all risks, not just the electrical safety aspects.

The General Product Safety Directive (Directive 2001/95/EC)[3] (GPSD), which requires that products must provide a reasonable level of safety throughout the lifetime of the product and contains specific obligations for producers, distributors and national authorities, is applicable to sunbeds used by consumers, including in the context of a service, in so far as the LVD does not already contain specific provisions governing the same aspects with the same objectives. This is without prejudice of any other EU applicable legislation.

The voluntary harmonised standard EN 60335-2-27:2013 sets out requirements for the safety of sunbeds, including limits for ultraviolet radiation emission. If this standard is applied, it provides a presumption of conformity with the safety objectives of Directive 2006/95/EC with respect to the risks covered by the standard.

In recent years some Member States have adopted national legislation regulating the tanning services (including, for example, a ban below the age limit of 18 years, the need for proper health and safety information, stricter hygiene conditions, the need for properly trained staff, etc.). These measures, when properly enforced, should ensure that tanning studios provide a better level of protection to consumers who use these devices.

In 2008-2009, market surveillance, including inspection of tanning salons, was carried out in ten EU Member States[5]. The overall conclusions were that: (i) Consumer guidance

[3] http://cancer-code-europe.iarc.fr/index.php/en/

[4] The requirements for information to be provided to consumers are different, depending on national legislation in each Member State.

[5] http://europa.eu/rapid/press-release_MEMO-10-37_en.htm?locale=en

in tanning studios was not regularly given and, where it was claimed to be given, this was often not verifiable (ii) the labelling of the sunbeds failed to comply with the requirements in at least 20% of the cases, (iii) the percentage of sunbeds not in compliance with the regulations varied between 10 and 90%.

The above described situation and the growing health concerns expressed by various medical and scientific experts about the higher risks of developing skin cancer and other skin-related diseases from the use of sunbeds have led the European Commission to request the SCENIHR to review recent evidence in order to improve the understanding of risks associated with UV radiation in general and with sunbeds in particular and provide an updated Opinion.

3. TERMS OF REFERENCE

In view of new medical evidence and the development of science and technology over the past decade, including the Scientific Justification which underpins The European Code against Cancer and in particular the recommendation on UV radiation, the SCENHIR is asked to reassess the safety risks associated with the use of sunbeds and to provide an answer to the following questions:

1. *Does new scientific and medical evidence (collected over the past decade) have a significant impact on the conclusion of the previous SCCP Opinion of 2006 {sccp_o_031b.pdf} with regard to the general health and safety implications relating to the exposure of people to UV radiation (UVR)? If yes, what are the key elements to be considered and how is the health of users of tanning devices for cosmetic purposes (sunbeds) likely to be affected (both positively e.g., Vitamin D regulation and negatively, e.g., skin and ocular melanoma).*

2. *Does SCENIHR uphold the assessment of the SCCP that the limit value of the Erythemally-weighted irradiance of 0.3 W/m^2 (equivalent to an UV index of 12) ensures sufficient levels of protection for the health and safety of users? If this is not the case, please specify if it is sufficient to give specific information. If it is not sufficient to provide information, please specify the limit values above which adverse health effects can occur.*

3. *What should be the wavelength range for which the total Erythemally-weighted irradiance should be negligible (e.g. under 0.003 W/ m^2) to minimise the risks of developing skin cancer due to the use of sunbeds?*

4. APPROACH TO THE DEVELOPMENT OF THIS OPINION

4.1 Summary of SCCP Opinion 2006

To support revision of legislation, the SCCP was requested by the Commission in 2006 to provide an Opinion on the general health and safety implications (negative and positive) relating to the exposure to UVR and in particular from use of sunbeds. The SCCP was asked to evaluate potential differences in health risks between exposure to UVR from natural and artificial sources and between UVA, UVB and UVC radiation, and to consider the need for and ranges of limit values to reduce these risks, taking into account skin phototype, intensity of exposure, duration of exposure and associated uncertainties. The SCCP was of the Opinion that (i) the use of UVR tanning devices to achieve and maintain cosmetic tanning, whether by UVB and/or UVA, is likely to increase the risk of malignant melanoma of the skin and possibly ocular melanoma (ii) people with known risk factors for skin cancer, especially melanoma (skin phototypes I and II, presence of freckles, atypical and/or multiple moles, family history of melanoma) should not use sunbeds, (iii) eye protection from UVB and UVA should be worn (iv) UVR tanning devices should not be used by individuals under the age of 18 years. They note that UVR tanning devices were not in widespread use before the 1990s and therefore the full health effects of their use will not emerge for several years due to the long latency of these cancers.

4.2 Summary of IARC Monograph 2012

IARC reviewed the literature on UVR from natural and artificial sources as part of the general update and review of radiation (IARC 2012). IARC also carried out a systematic review and meta-analysis of cohort and case-control studies of sunbed use (IARC 2006b). The summary estimates (adjusted for confounding factors, including measures of exposure to sunlight) reported positive associations between ''ever'' versus ''never'' indoor tanning for melanoma (RR, 1.15, 95%; CI, 1.00–1.31) and Squamous Cell Carcinoma (SCC) (RR=2.25 95% CI 1.08, 4.70) but not for Basal Cell carcinoma (BCC), (RR=1.03, 95%CI 0.5-1.90).The risk of melanoma was increased if first exposure took place at a young age (RR=1.75, 95%CI 1.35, 2.26).

IARC concluded that the use of UV-emitting tanning devices is *carcinogenic to humans (Group 1)* and that UV-emitting tanning devices cause cutaneous malignant melanoma and ocular melanoma (observed in the choroid and the ciliary body of the eye). IARC noted that a positive association was also observed between the use of UV-emitting tanning devices and squamous cell carcinoma of the skin.

4.3 Update of the evidence since 2006

The health risks associated with the use of sunbeds have been investigated through different approaches such as epidemiologic studies, experimental studies in humans, experimental studies in animals, and cell culture studies. A health risk assessment evaluates the evidence within several areas of concern (skin, eye, immune system) and then weighs the evidence across the areas to generate a combined assessment. This combined assessment addresses the question of whether or not a hazard exists, i.e. whether there is a causal relationship between exposure and some adverse health effect. The answer to this is not necessarily a definitive "yes" or "no", but may be expressed as the weight of evidence for the existence of a hazard. If such a hazard is judged to be present, the risk assessment should also address the magnitude and shape of the effect

and the dose-response function including characterising the magnitude of the risk for various exposure levels and exposure patterns. Detailed criteria that are used to evaluate the documents which the Opinion is based on and criteria for the weighting process has been described in a the SCENIHR memorandum (SCENIHR 2012).

Information has primarily been obtained from papers and reports published in international peer reviewed scientific journals in the English language in the years 2006-2015 (see Annex 1 for search terms). Additional sources of information have also been considered, including web-based information retrieval and other documents in the public domain, e.g. from governmental bodies and authorities, Non-Governmental Organizations (NGOs).

The weight of evidence for a particular outcome is based on data from human and mechanistic in-vitro studies (the primary evidence) along with exposure. The overall quality of the studies is taken into account, as well as the relevance of the studies for the issue in question. The weighting of evidence also considers whether causality was shown or not in the relevant studies.

In the present Opinion, the following categories are used to assign the relevant weight of evidence for the specific outcomes.

Strong overall weight of evidence: coherent evidence from human in the absence of conflicting evidence from one of the other lines of evidence (no important data gaps).

Moderate overall weight of evidence: good evidence from a primary line of evidence but evidence from several other lines is missing (important data gaps).

Weak overall weight of evidence: weak or conflicting evidence from the primary lines of evidence (severe data gaps).

Throughout the Opinion, consistency and adherence to SI (International System of Units, Système International d'unités) regarding the use of terms and units has been attempted.

5. TECHNICAL BACKGROUND

Although the term sunbed is frequently defined as equipment consisting of rows of lamps that expose a person to ultraviolet radiation for tanning, in this Opinion the term "sunbed" is used for all types of UV tanning devices for cosmetic purposes. The Opinion does not address medical devices for UVR treatment.

5.1 Physical characteristics of UVR

Ultraviolet radiation (UVR) comprises invisible electromagnetic waves at the borderline between non-ionising and ionising radiation with wavelengths from 400nm to 100nm (Figure 1, Table 1).

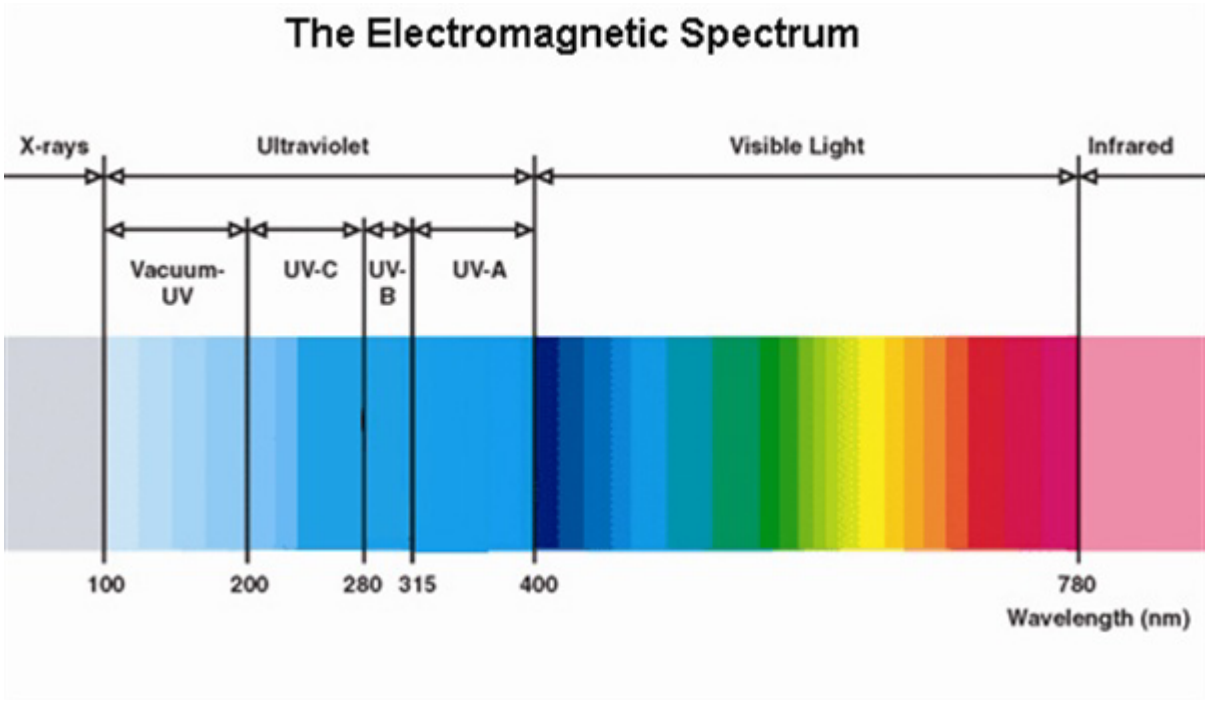


Figure 1: *The electromagnetic spectrum*
(http://www.nailsmag.com/article/93494/the-difference-between-led-and-uv-lamps)

Table 1: *Spectrum of Electromagnetic Radiation*

Region	Wavelength (nm)	Frequency (Hz)
Infrared	10^6- 700	$3x10^{11}$ – $4.3x10^{14}$
Visible	700 - 400	$4.3x10^{14}$-$7.5x10^{14}$
Ultraviolet	400 - 100	$7.5x10^{14}$ – $3x10^{15}$
X-rays	< 100	> $3x10^{15}$

To account for the different physical and biological effects of UVR, its wavelength range is subdivided into three main zones A, B and C. The most common definitions, which are used also in this Opinion are

UVA (400 nm – 315 nm),

UVB (315 nm – 280 nm),

UVC (280 nm – 200 nm)

Vacuum UV (200 nm – 100 nm)

However, it should be noted that some organisations may define these ranges differently such as in the standard EN 60335-2-27.

Long wave UV (400 nm – 320 nm),
Short wave UV (320 nm – 280 nm)

5.2 UVR spectra

To measure UVR, narrow band-pass filters (monochromators) are used for wavelength selection. The detectors consist either of radiometric devices, which make use of the temperature increase induced by the absorbed radiation, or photoelectric devices that respond to electrons released as a result of the photoelectric quantum effect.

Solar radiation

Solar UVR is part of the broad and continuous electromagnetic spectrum which is emitted by a thermal source like the sun which can be considered to emit radiation like a "black body". The wavelength of the maximum spectral power density decreases with increasing surface temperature according to Wiener's law. At solar the maximum spectral power density appears at 550nm (at green light) corresponding to a solar surface temperature of about 6000°K. Depending on daytime and season, the spectrum varies due to different atmospheric pathways and wavelength-dependent atmospheric absorption. Due to the latter solar UVC radiation can be neglected. However, this may not be justified in artificial UVR sources.

Solar UV irradiation is currently measured using multi-frequency imaging detectors on the earth's surface or at higher altitudes with the aid of meteorological satellites. Measurements of UVB and UVA are difficult because of the impact of the needed spectral filters to manage the steep increase of the ambient solar irradiance in the UVB range, which at between 290–320 nm amounts to more than fivefold. Extensive measurements of ambient UVR including this spectral band have been made worldwide. Measurements of terrestrial solar UVA radiation are less critical, because in this range the spectral irradiance curve is flat and the irradiance does not vary so much with solar zenith angle (IARC, 1992).

UVR from sunbeds

Commercial sunbeds came into widespread use in the 1990s. Most modern sunbeds have not changed much from the original devices. The lamp technology and electronics have evolved over the years; however, the lamps are still the fluorescent type, using special phosphors that create a spectrum in the UVA and UVB range. Sunbed lamps emit spectral peaks of mostly UVA radiation, although there has been development over the

years to broaden the emitted light spectrum and make it more "sun-like". There are two different types of lamps which by filtering may emit either virtually only UVA or UVA mixed with UVB, with different bandwidths from narrow until to wide:

- low-pressure mercury fluorescent tubes
- high-pressure mercury fluorescent tubes.

In general, the UVR spectra of artificial sources differ considerably from natural sunlight, in particular with considerable higher irradiance in the UV range. Among sun beds the spectra and intensities of emitted UVR can vary considerably depending on the type of device, manufacturing tolerances, filtering and age of lamps.

Emission spectra of different types of sunbeds are shown in the Figure 2. It can be seen that there are considerable differences, which would require careful consideration to avoid unintended side effects and health risks. In contrast to sunlight, mercury fluorescent lamps generate line spectra with dominating peaks in the UV range and the adjacent range of visible light. The main emission lines are at UVC- wavelengths 185 nm, 254 nm, at UVB- wavelengths 297 nm and 313 nm, at UVA- wavelengths 334 nm and 365 nm and in the visible light at 404 nm, 436 nm and 577 nm.

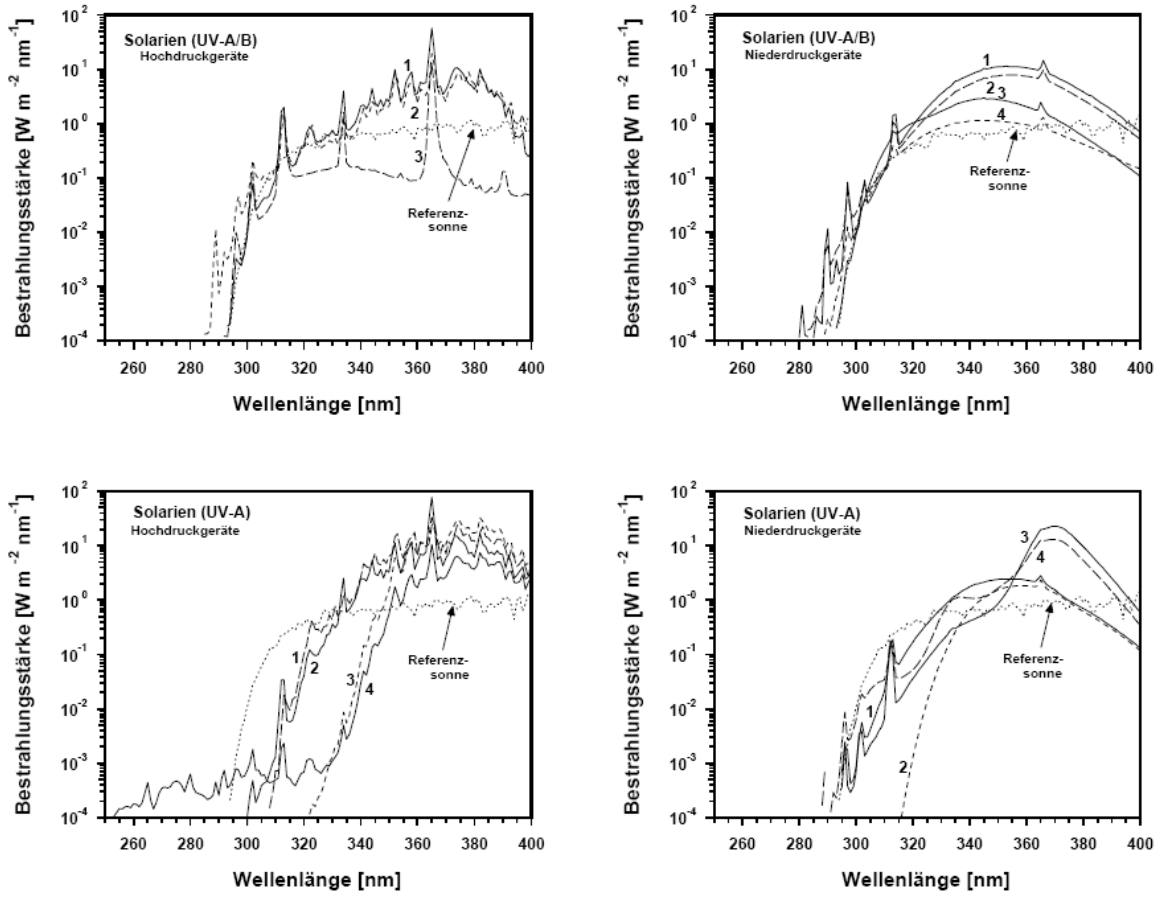


Figure 2: *UVR spectra of high-pressure (left) and low pressure of UVR lamps (right) of devices UV type 1 and UV type 2 (above) and UV type 3 and UV type 4 (below) (SSK 2003)[6] The dotted line indicates the reference spectrum of the sunlight – there is almost*

[6] SSK (2003): Schutz des Menschen vor den Gefahren der UV- Strahlung in Solarien (Protection of humans against hazards of UV radiation in solaria). http://www.ssk.de

no UV radiation below 290 nm since it has been absorbed by the earth's atmosphere. The worst case is shown in the left corner of the Figure – UVC is present.

According to their UVR emission the related European standard EN 60335-2-27[7] classifies tanning devices into four classes, namely UV type 1 to UV type 4 (Table 2).

Table 2: *Classification of UV tanning devices (EN 60335-2-27)*

Class	Wavelength range [nm]	UVR effective irradiance [mW/m²]	Spectral characteristic
UV type 1	320 - 400	≥ 150	high UVA irradiance
	250- 320	≤ 0,5	
UV type 2	320 - 400	≥ 150	high UVA + some UVB
	250-320	0,5 - 150	
UV type 3	320-400	≤ 150	limited UVA+UVB
	250-320	≤ 150	
UV type 4	320 - 400	≤ 150	high UVB irradiance

5.3 Regulations and standards

Technical regulations

The directive 2001/95/EC[8] contains the overarching requirement that all products, placed on the European market shall be safe in terms of complying with the state of the art and technology (as laid down in specific regulations such as directives, technical specifications and standards) and meet reasonable consumer expectations. Compared to the previous standard (EN 60335-2-27:2003 + A1:2008 + A2:2008), the revised standard EN 60335-2-27:2010 introduced a modification in the requirements for sunbeds in particular with regard to the UVB and UVC radiation: now, the total irradiance[9] between 200-280 nm should not exceed 0.003W/m^2, whereas the previous specification from the 2008 version of the standard imposed a limit of 0.03 W/m^2 total irradiance[10], however, just for the range 200-290 nm.

The voluntary harmonised standard EN 60335-2-27:2013 sets out requirements for the safety of sunbeds, including limits for ultraviolet radiation emission. Appliances shall

[7] EN 60335-2-27:2010: Household and similar electrical appliances - safety - part 2-27: particular requirements for appliances for skin exposure to ultraviolet and infrared radiation

[8] EU 2001/95/EC: Directive on general product safety, OJEC L 11/4, 2001

[9] EN 60335-2-27:2010, Page 20: "Appliances shall have a total irradiance not exceeding 0,003 W/m^2 for wavelengths between 200 nm and 280 nm and measured by a spectroradiometer between 250 nm and 280 nm.

[10] EN 60335-2-27:2003 + A1:2008 + A2:2008, Page 21: "Appliances shall have a total irradiance not exceeding 0,03 W/m^2 for wavelengths between 200 nm and 290 nm".

have effective irradiances (weighted with the erythema action spectrum) limited as follows:

- a total effective irradiance not exceeding 300 mW/m²
- the total wavelength-band related effective irradiance not exceeding
  - 150 mW/m² for wavelengths 250-320nm and 320-400nm, respectively if useable in the household or
  - 700 mW/m² for wavelengths 250-400nm if for commercial use

  a total effective short-wave irradiance for wavelengths 200-280nm not exceeding 3 mW/m².

There are 8-hourtime weight averaged (TWA) occupational exposure limits for UVR (180-400nm) to protect both skin and eyes from acute adverse health effects. While sensitive persons are excluded, the guidelines of ICNIRP[11] and the Directive 2004/25/EC specify UVR limits as follows:

eyes ≤ 30J/m^2,(180-400nm, spectrally weighted),
≤ 10^4 J/m^2 (UVA, unweighted)
skin ≤ 30J/m2,(180-400nm, spectrally weighted).

However, the limits do not account for potential long-term effects such as skin cancer. There are no specific regulations either for continuous exposure, such as from air processing appliances, nor shorter exposure durations. The objective of the limits is to protect most sensitive, non-pathologic, skin phototypes (known as "melano-compromised").

There are no regulations for the general population except the fact that ICNIRP states that its recommended exposure levels for workers may also apply to the general population for exposure during any 8-hour period, however, without further regulation for continuous exposure or other exposure durations.

Regulation of sunbed use

Over the last two decades, a growing number of countries and states have introduced regulations to reduce public's exposure such as limitation of UVB output, age restrictions for access to sunbeds, or special taxes.

France, in 1997, was the first country to publish a decree to control the commercial use of tanning devices (Decree n°97-617 of 30 May 1997). The main features of this regulation were the following: only type 1 and 3 sunbeds (according to the standard EN 60-335-2-27) were allowed and the UVB component of the emitted UV limited to 1.5%; unstaffed machines (coin/credit card self-operated) were no longer allowed and specific training of the personnel became mandatory as well as declaration of tanning machines to local authorities and control; mandatory provision of protective eyewear; prohibition of use by minors (<18 years). This decree was reinforced in 2013 (Decree n° 2013-1261 of 27 December 2013).

By January 2014, 14 European countries including Austria, Belgium, Finland, France, Germany, Iceland, Ireland, Italy, Lithuania, Netherlands, Norway, Portugal, Spain, and United Kingdom: England, Northern Ireland, Scotland and Wales had passed legislation

prohibiting the use of commercial sunbeds by minors (Virginia Joint Commission on Health Care, 2014).

However, legislation of sunbed use is not yet harmonised within the EU. Not all Member States follow the Opinion of the European Scientific Committee on Consumer Products recommending a limitation of UVR intensity of sunbeds to 300 mW/m^2; in many countries unstaffed machines are not banned nor do all countries require declaration/registration of the tanning facilities. Importantly, not all Member States restrict sunbed access to those over 18 years of age. Currently, the WHO INTERSUN programme in cooperation with the French Ministry of Health, is conducting a survey of national sunbed regulations, the results of which will be entered into a WHO web-based public database.

In Canada most provinces have passed regulations restricting minors' access to sunbeds: British Columbia, Labrador, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, Quebec (Virginia Joint Commission on Health Care, 2014).

In the USA the situation is more complex (Gosis *et al*., 2014; Pan and Geller, 2015; Bowman *et al*., 2015) since responsibility for regulating indoor tanning facilities falls mainly to the individual states. As of January 2015, all U.S. states, and the District of Columbia, had enacted legislation to regulate tanning facilities. However, these legislations vary substantially, and only 11 states such as California have prohibited indoor tanning by minors, and even local jurisdictions such as Howard County (Ma), have adopted similar bans, while other states have weaker regulations (ban under 14, 16 or 17 year olds, parental accompaniment/consent) and 10 states have no regulation at all (Corbyn, 2014, Indoor Tanning Association, 2014).

Several surveys have shown that even where stringent regulations are in place compliance may be poor, either in terms of UVR emission of devices (APPGS, 2014), or in terms of respecting the under-18 ban (Benmarhnia *et al*., 2013). Moreover, compliance with regulations has been misused by tanning operators as an argument to promote tanning (Autier *et al*., 2011).

Bans of indoor tanning for cosmetic purposes

Following the 2009 IARC classification of UV radiation emitted by sunbeds as a Group 1 carcinogen, two countries introduced legislation banning the use of sunbeds for cosmetic (non-medical) purposes. Brazil became the first country to pass legislation banning the use of indoor tanning for cosmetic purposes (ANVS, 2009). Brazil's ban has been followed by the Australian state of New South Wales, imposing a ban in 2014. Similar bans have been enacted by all but one other Australian states (Victoria, Australian Capital Territory, Queensland, Northern Territory, South Australia); the remaining state (Western Australia) is currently planning its own sunbed ban (Bowman *et al*., 2015).

Efficacy of sunbed regulations

There are some indications that restrictions in sunbed use may succeed in reducing prevalence of use and, eventually, associated risks.

In the USA, prevalence of indoor tanning use by adolescents within the past year changed little from 1998 to 2004 (10% to 11%). In states with policies regarding minors' access to indoor tanning, the prevalence stayed the same or decreased from 1998 to 2004, whereas it increased in states without such policies. However, neither trend was found to be statistically significant (Cokkinides *et al*., 2009).

In the USA, an analysis of data from the 2009 and 2011 national Youth Risk Behaviour Surveys (n = 31 835) showed that female high school students in States with indoor tanning laws were less likely to engage in indoor tanning than those in states without any laws. The association was stronger in states with systems access, parental permission, and age restriction laws than among those in States without any laws. No significant association was found among male students. These data suggest that indoor tanning laws, particularly those including age restrictions, may be effective in reducing indoor tanning among female high school students, for whom rates are the highest (Guy *et al*., 2014).

In Iceland, where the high prevalence of sunbed use probably contributed to the sharp increase in the incidence of melanoma; the decrease in incidence of trunk melanoma observed in women after 2002 is most probably due to campaigns initiated by the Icelandic health services end of the 1990s. A campaign by health authorities in 2004 to discourage sunbed use especially by teenage girls resulted in a 50% reduction in the number of sunbeds by 2008 (Héry *et al*., 2010).

Arguing that tanning devices emit carcinogenic UVR, without any beneficial health effect, and in view of the limited efficiency of control measures, ANSES (the French Agency for Food, Environmental and Occupational Health & Safety) and two non-governmental organisations (Sécurité Solaire, a WHO collaborating centre, and the European Society for Skin Cancer Prevention – EuroSkin) have recently recommended the cessation of the marketing and commercial use of UV-emitting sunbeds (ANSES, 2012; Boniol *et al*.,2015).

6. EXPOSURES FROM SUNBEDS

Sunbeds apply several fluorescent lamps with phosphor blends designed to emit UVR. Smaller home sunbeds usually have 12 to 28 lamps, 100W each, while systems found in tanning salons can consist of 24 to 60 lamps, each of 100 to 200W.

There are also "high pressure" sunbeds that generate primarily UVA with some UVB by using highly specialised quartz lamps, reflector systems and filters. These are much more expensive, thus less commonly used.

Although there are few data on home use of sunbeds there is concern about the uncontrolled use including the duration of use and the age of the user.

6.1 Prevalence of sunbed use

The prevalence of sunbed use varies greatly from one country to another and according to sex and age.

Numerous surveys have been conducted in Europe, USA and Australia to more specifically address the characteristics of sunbed users, their motivation and their perception of the risks of tanning. Twenty-six of these surveys have been summarised in a recent review (Doré and Chignol, 2012). More recently, 8 further studies have been conducted among adult sunbed users, and 17 surveys have explored sunbed use by children and adolescents. These surveys are summarised in Annex 2.

Wehner *et al*. (2014) reviewed publications published between 1966 and 2013, reporting data from 16 Western countries and including 491,492 participants. The 88 included reports contributed 115 individual data points. After exclusion of 12 studies using exposure measures other than ever or past-year exposure, or assessing specific occupational groups, 76 records with 406,696 total participants were included in a meta-analysis. 34 of these records reported prevalence in adults, 15 reported prevalence in university students, and 34 reported prevalence in adolescents.

The overall summary prevalence of ever exposure to indoor tanning was 35.7% (95% CI, 27.5%-44.0%) for adults (42% (95%CI 29%-54%) for N and W Europe), 55.0% (95% CI 33.0%-77.1%) for university students (US studies only), and 19.3% (14.7%-24.0%) for adolescents (24% (95% CI 7%-30%)for N and W Europe). The summary prevalence of past year exposure was 14.0% (95% CI, 11.5%-16.5%) for adults, 43.1% (95% CI 21.7%-64.5%) for university students, and 18.3% (95% CI 12.6%-24.0%) for adolescents. Analyses stratified by sex showed a higher prevalence of indoor tanning among women compared with men (see table in Annex II). Analyses of adults and adolescents stratified by geographic region showed highest summary prevalence in Northern and Western Europe, followed closely by the United States and Canada, with Australia consistently having the lowest.

This meta-analysis further showed an increase in prevalence of sunbed use over time. Estimates of past-year exposure collected in the most recent 5 years of available data were higher than estimates including all time periods. A meta-analysis of the most recent estimates (2007-2012) of past-year exposure to indoor tanning yielded past-year prevalence of 18.2% (95% CI, 12.2%-24.1%) in adults, 45.2% (95% CI 9.4%-81.0%) in university students, and 22.0% (95% CI 17.2%-26.8%) in adolescents. These are absolute increases of 3.4% in adults, 2.1% in university students, and 1.7% in adolescents from the results of the primary analyses.

Generally speaking, it appears that prevalence of sunbed use for tanning purpose is higher in white-skinned populations from Northern Europe, and in young or middle-aged women.

Some surveys in Europe have shown that indoor tanning is frequent among sun-sensitive individuals, e.g. individuals with phototypes I or II (according to the Fitzpatrick scale) (Grange *et al*., 2015), or individuals with fair skin (19% prevalence) or freckles (25%) (Stanganelli *et al*., 2013).

According to a recent review (Schneider and Krâmer, 2010), the typical sunbed user is female, between 17 and 30 years old, and tends to live a comparatively unhealthy lifestyle: users smoke cigarettes and drink alcohol more frequently and eat less healthy food than non-users. Users are characterised by a lack of knowledge about health risks of sun and ultraviolet radiation exposure, and prompted by the frequent use of sunbeds by friends or family members and the experience of positive emotions and relaxation by indoor tanning. There is still a lack of information among users, particularly among young people regarding the safety of solariums.

Surveys addressing the prevalence of sunbed use by children and adolescents in Northern Europe and in the USA showed that the highest figures were observed among girls in Scandinavia (Krarup *et al*., 2011), but also among non-Hispanic female high school US students (Guy *et al*., 2013). In Denmark, not only the prevalence of sunbed use in children is noticeable (Krarup *et al*., 2011), but also the age at first use may be very young: up to 13% of ever sunbed users having started sunbed exposure before the age of 13, and up to 75% between the ages of 13 to 15 (Koster *et al*., 2011).

Motivation for indoor tanning among adolescents is the desire to be more attractive but also the belief that sunbeds are not as harmful as sun exposure (e.g. Fabbrocini *et al*., (2012) noted that 83% of 191 students fully understood the risk of developing cancer through sun exposure, but only 65% of students believed that sunbeds could be dangerous).

Finally, it should be noted that under-18 ban may be rather effective, as shown by the 1.4% past year exposure in a recent French survey (Tella *et al*., 2013). Similarly, in Denmark a Danish Cancer Society campaign launched in March 2007 led to a significant reduction of indoor tanning: the odds ratio (OR) for being a sunbed user in 2009 when compared with 2007 was 0.61 (95% CI 0.54–0.69); in the age group of 15–19 years, the OR was 0.42 (95% CI 0.30–0.69) (Koster *et al*., 2011).

6.2 UV exposure from sunbeds - Trends in UV irradiance

It is currently estimated that UV emission of a modern tanning appliance corresponds to an UV index of 12, i.e. equivalent to midday tropical sun, and that the median annual exposure dose from artificial tanning is probably 20-30 times the MED (minimal erythemal dose, corresponding to 200 J/m² for a sun-sensitive individual). By comparison, the annual exposure dose of solar UV to the face for indoor workers in European mid-latitudes is of about 40-160 MED (IARC, 2012). However, there are large variations in UV output of different machines and the UV spectrum emitted by tanning machines has evolved in recent years.

In Europe, UV emission by sunbeds is regulated by European legislation and voluntary harmonised standards. However, although controls are prescribed by some of these regulations, there are only few publications that report on systematically measured UV-irradiances in sunbed studios (solaria), in order to check whether exposure is in

agreement with national or international recommendations (or laws) compared to natural (sunlight) exposures.

It should be noted that it is not the dose rate (irradiance = 0.3W/m² = 0.3 J/m² sec) which is prominently introducing a possible harmful effect, but the dose received, i.e. irradiance x duration of exposure.

In 2008-2009, ten market surveillance authorities from ten European Union Member States participated in a cross border action to enforce the safety requirements for sunbeds and sunbed services[12]. During the action, tanning salons and similar facilities were inspected, as well as the sunbeds offered there for use to the general public. The overall conclusions from the results of the inspections in this action on sunbeds is that consumer guidance in tanning studios is not regularly given and, where it is claimed to be given this is often not verifiable. Moreover, the labelling of the sunbeds fails to comply in at least 20% of the cases. In addition, how often the maximum values for sunbeds are violated varies between the Member States. In several Member States the percentage may be above 90%, while in others the percentage of sunbeds not complying is estimated to be between 10% - 20%. A new Joint Market Surveillance Action, termed "Sunbeds and Solarium Services 2", involving market surveillance authorities from 11 Members States and Norway, was conducted in 2010-2011, and showed little improvement13.

In Norway about 90% of machines are unstaffed, and tanning facilities must inform the National Radiation Protection Authority (NRPA) about their operation and all indoor sunbedneed an approval from the NRPA before being sold or used. The NRPA conducted several inspections to measure UV irradiance from a large number of solariums (sunbeds and stand-up cabinets) currently in use (Nilsen *et al*., 2008, 2011).

In 2008 Nilsen *et al.* investigated trends in UV irradiance of tanning devices in Norway (1983-2005) and concluded that UVC- and UVB-rich mercury arc sunlamps were replaced by UVA-dominated sunbeds in the early 1980s in Norway. The mean CIE-weighted short wave irradiance (280-320 nm) of approved sunbed devices (n = 446) increased from 1983 to 2005 from half of summer sunlight in Oslo which corresponds to an UV index of about 6 to the same level as the summer sun with less variation. CIE-weighted UVA irradiance (320 – 400 nm) of approved devices has been about 3-3.5 times higher than summer sunlight in Oslo in the whole period (1983-2005) (Nilsen *et al.*, 2008). Mean CIE-weighted short wave irradiance of approved devices increased from 50 mW/m² in the years 1983-1992 to 101 mW/m² in 1993-2005, and mean UVA increased from 91 mW/m² (1983-1992) to 112 mW/m² (1993-2005). UV indices have been recorded in the range 8.5 -12.2 (Nilsen *et al.*, 2008).

In a second inspection, irradiance from a large number of Norwegian solaria (sunbeds and stand-up cabinets) currently in use was analysed. Excessive ultraviolet (UV) irradiance and a lack of compliance with regulations were reported. Compliance (solaria and facilities) with national regulations and the effect of inspections delegated to local

[12] http://europa.eu/rapid/press-release_MEMO-10-37_en.htm?locale=en

[13]http://www.prosafe.org/images/Documents/JA2009/SunBeds2_Final_report_20130304-published.pdf

authorities (since 2004) were also studied. In 2008, 78 tanning facilities were selected from six regions throughout Norway that contained municipalities with and without local inspections. 410 solaria were inspected and UV irradiance of 194 solaria was measured with a CCD spectroradiometer in 194 out of 410 inspected solaria. In total, 89.9% of the tanning facilities were unattended.

Mean erythema weighted short (280–320 nm) and long (320–400 nm) wave UV irradiances were 0.194 (95% confidence interval (CI) 0.184–0.205) and 0.156 (95% CI 0.148–0.164) W/m², respectively. Only 23% of the solariums were below the UV type 3 limit (<0.15 W/m², short and long wave). Almost all inspected solaria models were approved by NRPA but only 74.4% of the devices had lamps that met approval.

Irradiances varied between solaria: spectral UVB (280–315 nm) and UVA (315–400 nm) irradiances were 0.5–3.7 and 3–26 times, respectively, higher than from the Oslo summer sun, which indicates that the limit of the standard is considerably exceeded. By comparison, mean short and long wave irradiances of the inspected tanning devices in 2003 were 1.5 and 3.5 times, respectively, higher than the irradiance of natural summer sun in Oslo.

Overall compliance increased since the first study in 1998-1999, but total UV irradiance did not decrease, mainly because of higher UVA irradiance in 2008. Thus, in Norway, in recent years, solaria UVR have become even less similar to natural sun due to higher UVA irradiance. Local inspections gave better compliance with regulations, but irradiances were significantly higher in municipalities with inspections ($p \leq 0.001$, compared to missing inspections). Unpredictable UV irradiance combined with insufficient customer guidance may give a high risk of negative health effects from solarium use (Nilsen *et al.,* 2011).

In Greece analysis of the measurements from sunbeds revealed that effective irradiance in approximately 60 % of the measured sunbeds exceeded the 300 mW/m^2 limit as set by EN 60335-2-27:2010, and only 20 % of the devices could be categorised as UV-type 3 (Petri *et al.,* 2014).

In England, between October 2010 and February 2011, Tierney *et al*. (2013) measured UV emission levels from a total of 402 artificial tanning units, and compared these levels with both current standards and natural sunlight. While according to the European standard, erythemal-effective irradiance should not exceed 0.3 W/m^2. The values measured ranged between 0.10 and 1.32 W/m^2 with a mean of 0.56 ± 0.21 W/m^2. Only 10% of sunbeds surveyed were within the recommended limit. Application of a skin cancer weighting factor, to compare the carcinogenic potential of sunbeds with that of sunlight, produced values that varied from 0.17 to 2.52 W/m^2 with a mean of 0.99 ± 0.41 W/m^2. By comparison, the value for Mediterranean midday sun is 0.43 W/m^2. Thus, 9 out of 10 sunbeds surveyed throughout England emitted levels of UV radiation that exceed the maximum levels prescribed by the European standard. In addition, the skin cancer risk for comparable times of exposure was up to six times higher than that for Mediterranean sunlight.

In 2008 the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) measured UVR irradiances and spectral distributions in 20 solaria in Australia. Irradiance of solaria of different manufactures were determined in the range of 250nm-400nm in W/m², weighted with the spectra erythemal response function of CIE, and subsequently converted to a corresponding UV-Index (UVI) for comparison to natural conditions (Gies,

et al., 2011) (a UVI=1 corresponds to an erythemically weighted irradiance of E=25 mW/m^2).

The study indicated that solaria in Australia emitted very large amounts of UVA and very intense levels of UVB in comparison to midday summer sunlight. Only one of the solaria was found with an UVI < 12 (300 mW/m²) which is the maximum allowed by European legislation. Three of 20 solaria showed an UVI >36 (limit value in Australia, AS/NZS). At all other solaria irradiances were found in the range of 10 – 30 W/m².

All sunbeds measured showed irradiances above 70 W/m² with 9 – 438 W/m² in the UVA range, a value which can be found in sunlight at noon in mid-latitudes. In 14 of 20 solaria the 3.6 W/m² of sunlight was exceeded although the percentage of UVB to UVA content in solaria's UVR was less than in sunlight.

Summary

The prevalence of sunbed use varies greatly from one country to another and according to sex and age. Prevalence of sunbed use for tanning purpose is higher in white-skinned populations from Northern Europe, and in young or middle-aged women. A recent meta-analysis of data from 16 Western countries including 406,696 participants showed that the overall summary prevalence of ever exposure to indoor tanning was as high as 35.7% for adults, 55.0% for university students US studies only), and 19.3% for adolescents. The summary prevalence of past year exposure was 14.0%, 43.1% for university students, and 18.3% for adolescents, and higher among women compared with men. This meta-analysis further showed an increase in prevalence of sunbed use over time.

Sunbed UV emitters have varied in the mix and intensity of UVA and UVB generated. Data from countries where restrictions in sunbed use have been introduced indicated a reduction of the prevalence of use which may eventually lead to reduced risks. It is currently estimated that UV emission of a modern tanning appliance corresponds to an UV index of 12, i.e. equivalent to midday tropical sun. However there are large variations in the UV output of different machines and inspections showed violations of the maximum values. The UV spectrum emitted by tanning machines has evolved in recent years towards higher UVA irradiance. There are few data on home use of sunbeds and there is concern about uncontrolled use.

1 **Table 3:** *International prevalence of indoor tanning (Wehner et al., 2014)*

Overall			Female Participants		Male Participants	
Exposure by Group	**Summary Prevalence (95% CI)**	**No. of Records**	**Summary Prevalence (95% CI)**	**No. of Records**	**Summary Prevalence (95% CI)**	**No. of Records**
Adults						
Ever exposure	35.7 (27.5-44.0)	22	39.8 (30.0-49.7)	9	20.4 (12.4-28.3)a	7
Past-year exposure	14.0 (11.5-16.5)	21	19.0 (14.7-23.4)	15	9.0 (6.6-11.5)	13
US University students						
Ever exposure	55.0 (33.0-77.1)	11	69.3 (45.4-93.2)	5	40.0 (14.1-66.0)	3
Past-year exposure	43.1 (21.7-64.5)	7	64.9 (41.2-88.5)	4	26.8 (15.6-37.9)	4
Adolescents						
Ever exposure	19.3 (14.7-24.0)	23	31.5 (22.3-40.8)	16	14.1 (10.5-17.7)	17
Past-year exposure	18.3 (12.6-24.0)	23	21.3 (8.5-34.1)	14	7.5 (4.1-11.0)	14

7. HEALTH EFFECTS

Introduction

UVR from whatever source can induce cell and tissue damage. Excessive exposure results in signs of premature skin aging and the development of wrinkles. Long-term eye damage including the formation of cataracts can also occur, as can eye irritation, photo-keratitis and conjunctivitis. UVR exposure is also causally related to skin cancer. The three main types are malignant melanoma and two non-malignant skin cancers (NMSC), namely basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Melanoma is fast growing, proliferates readily and is lethal unless detected early. BCC is the most common non-melanoma skin cancer (NMSC) and is a slow growing, locally invasive skin cancer, common in fair-skinned populations. BCC metastases are exceptional. SCC is often found in older people for which photoaging is an accepted predisposing factor. Like melanoma, SCC is capable of metastatic spread. Section 7.1 reviews recent literature on non-malignant effects from the use of sunbeds and also evaluates vitamin D production from this source of UVR. Sections 7.2 and 7.3 review the evidence from humans and animal studies for melanoma and NMSC respectively and include an evaluation of the mechanistic evidence for the development of these cancers. Section 7.4 reviews the evidence on other cancers including internal cancers, all causes of death, all cancers taken together and ocular melanoma. The final section (7.5) considers risk characterisation and dose-response of skin cancer and exposure to sunbeds and quantifies the burden associated with sunbed use.

7.1 Non-cancer health effects

7.1.1 Vitamin D

Vitamin D (a steroid hormone) is essential for human health. It is essential for bone growth and for maintaining bone strength. In addition, vitamin D plays a role in cell growth and in reducing inflammation; the function of many genes is modulated by vitamin D, and many cells have vitamin D receptors (Holick 2007, Fleet 2012).

Vitamin D in the skin has a protective effect against UV induced damage (Song 2013). The association between low vitamin D status and various diseases, including cancer, is the subject of numerous publications, (Holick 2008, IARC 2008, IOM 2011, NIH 2014) and a consensus statement (BAD 2010). Recent reviews have re-examined the association of low vitamin D status with cancer and with mortality (Yin 2013, Autier 2014, Schöttker 2014). These analyses confirm the association with colon cancer, whereas the association with other types of cancer is as yet unclear. A systematic review supports the notion that low vitamin D status is often a consequence of (chronic) inflammatory disease (Autier 2014).

A good indicator of vitamin D in the human body is the presence of 25-hydroxyvitamin D in the blood. Its optimal level in the blood is not known, but levels below 10ng/ml are considered to indicate deficiency.

Pre-Vitamin D is rapidly produced in the skin from a conversion of 7 dehydrocholesterol by UV light in the UVB range. Further conversion into the physiologically active 25-hydroxy- and 25-dihydroxy-vitamin D occurs in the liver and kidney. Studies in Lille, France (Lat 50.28 N) have shown that in June, for phototype II skin 20-30 minutes of exposure of the face and hands to sunlight are sufficient to produce 1,000 international

units vitamin D (*Colette Brogniez, personal communication*). In Manchester, UK, 13 minutes exposure of 35% body surface to midday sun in June is sufficient to achieve satisfactory vitamin D status (Rhodes 2010).

A major source of vitamin D can be dietary intake: fish and fish liver oils contain ample amounts of it and to a lesser extent vitamin D is present in beef liver, cheese and egg yolk (NIH 2014).

Although the UV exposure from sunbeds is mainly in the UVA range, the small amount of UVB that is present in the radiation from many sunbed lamps can raise the levels of 25-hydroxyvitamin D in the blood (Rhodes 2010, Sallander 2013). However, the increase of UV-induced vitamin D production is limited. After reaching a plateau it will not increase; on the contrary: high UV doses can lead to degradation of vitamin D and reduce the vitamin D level (Holick 1981, Webb 1989).

In several countries at tanning salons in each session users receive a much higher amount of UVB radiation and a much larger area of their skin is exposed than is needed for vitamin D production which may compromise the vitamin D level. Extensive sunbed exposure may therefore undermine vitamin D production (Levine 2005). It must be noted that other sources of adequate vitamin D supply to the human body are available. A few minutes outdoors around the middle of the day is sufficient. When this is impractical, or impossible, then dietary sources (especially fish) or vitamin D supplements (10 microgram/day) are suitable and affordable alternatives. Chronic low vitamin D status is a medical issue for which treatment by means of diet, supplements or (in rare cases) medication is the best possible approach (Diffey 2011). There is wide-spread concern about the promotion of rising vitamin D levels by artificial UV: professional and public organisations in the UK, Germany and France have evaluated this issue and do not recommend sunbed use to enhance vitamin D levels (BAD 2010, BfR 2014, INCa 2011).

7.1.2 Immunosuppression

The immunosuppressive effect of UV is a well-known phenomenon in dermatology: various inflammatory skin diseases can effectively be treated by UV and the induction of contact allergy of the skin as well as the elicitation by patch-testing is reduced. Nowadays it is clear that UV- (UVA and UVB) induced suppression of skin immunity plays a role in skin cancer outgrowth (Schwarz 2010). Clinical dermatologists have known for many years that skin cancers in patients taking immunosuppressive medication are almost entirely originating in the currently or previously UV exposed skin areas.

One of the mechanisms is via the immunologically important T lymphocytic cells: besides the reduced activation of effector and memory T cells, UV irradiation also activates the regulatory T and B cells (Schwarz 2008, Halliday 2012). Exposure to UV upregulates several other factors involved in immunosuppression, e.g.. TNF and the cytokines IL-10 and IL-33; this may explain that the suppressive effects of UV on skin immune status occur in the UVB as well as in the UVA range whereby the mechanisms may be different for UVA and UVB (Halliday 2012).

The Langerhans cells in the skin (cells that take up antigens, and process them towards activation of immunity) are also a target of UV irradiation. These cells can be damaged by UV and upon UV exposure they migrate away from the skin.

The role of UVB in immunosuppression is well established in mice and humans, but in the years preceding the SCCP report the role of UVA was much less clear (SCCP 2006).

Using a contact allergy model, it has been shown that there is evidence of a positive interaction of UVB and UVA in human immunosuppression (Poon 2005). Based on a human contact allergy model the optimal wavelengths of the immunosuppressive action by UV-B appear to be around 300 nm and for UV-A around 370 nm. The latter is important in view of the predominant emission of UVA from sunbed lamps. The effects are dose dependent. The immunosuppressive effect of UVA was apparent at doses in the range 300 to 1000 J/m^2; this effect of UVA disappeared at higher doses (Matthews 2010, Damian 2011). In a reconstructed human skin model exposure to longwave UVA (340-400 nm) strongly down regulated genes that are involved in antibacterial and antiviral defence (Marionnet 2014).

Besides its effects on the skin, UV irradiation can influence immune reactivity in different internal organs that play an important role in immunity. This is linked by some to the protective effect of UV to autoimmunity, while others explain this by the complex interaction between (UV-induced) vitamin D production and altered immunoregulation by UV radiation (Hart, 2011). In mice neonatal exposure to solar-simulated UV alters the development of the immune system into adult life (McGee, 2011)

The immunologic environment in the regional lymph nodes draining the skin is altered by the reception of the UV-influenced T lymphocytes, Langerhans cells and mast cells. In addition, notably in the spleen and bone marrow, there is evidence of UV-induced immune suppression, although this seems to be based on different, incompletely understood mechanisms (Halliday, 2012).

7.1.3 Skin aging

Photoaging of the skin can frequently be observed in the sun-exposed skin of individuals who have spent much time outdoors, often because of their occupation. Several studies provide evidence that both UVB and UVA contribute to photoaging and wrinkling. It is based on loss of collagen and on deposits of fragments from elastin, caused by a chronic inflammatory response to UV light (Runger, 2012). In addition to cumulative collagen damage (Fisher, 2002) and UVA-induced alterations in fibroblasts are assumed to play a role (Marionnet 2014). It is a gradual process, which is irreversible, even if the low-level inflammation is reversed. Photoaging results from changes in several molecular mechanisms; in an overview of these mechanisms the role of telomers, mitochondrial DNA mutations, matrix proteinases, collagen synthesis, modulation of vascularisation, inflammation and protein oxidation are reported (Fisher, 2002, Krutmann, 2006).

UVA-induced deletions of mitochondrial DNA (Common Deletion) are relevant for photoaging of the skin (Berneburg 2004). This phenomenon has been reproduced in skin samples taken from volunteers who started to use sunbeds (Reimann 2008). The UV-induced mitochondrial DNA deletions are central in the proposed defective powerhouse model of premature skin aging (Krutmann 2009).

Freckling (lentigines) is also a consequence of UV exposure. The appearance of typical lentigines induced by artificial UV exposure ('sunbed lentigines') has been documented for decades (Kadunce, 1990)

7.1.4 Mood and behaviour

In many cultures the exposure to sunlight is experienced as pleasant, and in countries at higher latitudes bright visible light is used in the therapy of seasonal depression. The inclusion of UV into this 'light therapy' has no additional benefit (Lam 1992). Feelings like being comfortable and the perceived cosmetic attractiveness of a tanned skin are

reported by sunbed users (Brandberg 1998, Bloodstock 1992), although having a tan is not an issue in several cultures. In a blinded experiment the majority of 13 indoor tanners chose the UV exposure over the non-UV (mock) exposure (Feldman 2004). Their main reason for tanning was relaxation. It is as yet unclear whether the UV exposure-seeking behaviour is a psychological/behavioural phenomenon or whether this has a biological basis.

Phenomena such as UV addiction and even withdrawal-like symptoms (by administering the opioid receptor antagonist naltrexone) have been reported in frequent tanners (Harrington 2011, Kaur 2006a). However, the criteria to assess the prevalence of tanning dependency have been challenged (Schneider 2015). From an animal model, there is evidence supporting a role of enhanced synthesis of beta-endorphin by low dose UV (Fell 2014). The human studies on plasma beta-endorphin have thus far not demonstrated clear evidence of raised blood levels (Kaur 2006b).

Summary

Production of vitamin D by exposing only of the face and hands to natural sunlight takes just a few minutes to about half an hour, depending on latitude, season and daytime. There is widespread consensus that sunbeds should not be used to enhance vitamin D levels even in winter. Usual exposure to UVR from the sun (even on cloudy days) and a normal diet are sufficient to achieve a sufficient vitamin D level. In addition, special dietary vitamin D sources are amply available.

UV light (UVA as well as UVB) has an immunosuppressive effect on the skin and also a systemic immunosuppressive effect.

Exposure to UVA as well as to UVB enhances aging of the skin, among others, by damaging collagen and elastin.

A number of individuals have a UV exposure-seeking behaviour (sometimes addictive) because of a perceived positive influence on mood.

7.2 Melanoma

7.2.1 Human health effects

7.2.1.1 Meta-analyses and systematic reviews

The SCCP report (2006) reviewed a single meta-analysis of 9 case-control studies and one cohort study of melanoma risk associated with exposure to sunbeds, which came to the conclusion that sunbed use significantly increased the risk of melanoma with an OR of 1.25 (1.1-1.5) for "ever" versus "never" use, increasing to 1.69 (1.3-2.2) for "first exposure as young adult" (Gallagher *et al*., 2005). Four new meta-analyses published since 2006 are reviewed below.

Studies published since 2006

An International Agency for Research on Cancer (IARC) Working group conducted a meta-analysis of skin cancer in relation with sunbed use (IARC 2006, 2007). Based on 19 informative published studies (18 case-controls, of which 9 were population based, and one cohort) that included 7 355 melanoma cases and 11,275 controls from case-control studies and 106,378 cohort members. The summary RR risk ever versus never use of indoor tanning facilities from the 19 informative studies was 1.15 (1.00–1.31).

When the analysis was restricted to the nine population based case–control studies and the cohort study, the summary RR was 1.17 (0.96–1.42). IARC did not attempt to carry out a meta-analysis of the dose-response results because of heterogeneity among the categories used for duration and frequency of exposure used in the various studies. All studies that examined age at first exposure found an increased risk for melanoma when exposure started before approximately 30 years of age, with a summary RR of 1.75 (1.35–2.26).

Hirst *et al.* (2009) conducted a similar meta-analysis, based on the same studies used by the IARC meta-analysis, but including an additional nested case-control study of melanoma (Han *et al*., 2006), bringing the total number of melanoma cases to 7,855 and the total number of controls in analysis to 24,209. A significant excess risk of approximately 20% was estimated for melanoma in relation to *ever* versus *never use* of sunbeds (Meta-RR= 1.22; 95% CI 1.07-1.39).

Grant (2009) criticised IARC's meta-analysis, arguing that it did not consider confounding factors such as phototype and latitude, and was no longer significant when studies in UK, where the population is in majority of sensitive skin type, were omitted. In fact Grant is mistaken in that 8 of the 19 studies included in the meta-analysis were adjusted for multiple confounders. It should be noted that Grant was supported by the tanning industry.

To update and extend IARC's 2006 meta-analysis, Boniol *et al.* (2012) conducted a meta-analysis of melanoma risk associated with sunbed use based on 27 studies: 2 cohort studies, 15 population-based case control studies and 10 other case-control studies, from Europe, USA and Australia. Risks adjusted for confounders were used when available. Ever use of sunbeds was associated with a similar 20% excess risk, meta-=1.20 (95% CI 1.08-1.34). Publication bias was not evident. Restricting the analysis to cohorts and population-based studies, the summary RR was 1.25 (95% CI 1.09-1.43). Calculations for dose-response showed a 1.8% (95% CI 0, 3.8) increase in risk of melanoma for each additional session of sunbed use per year. Based on 13 informative studies, first use of sunbeds before age 35 years was associated with a summary RR of 1.59 (95% CI 1.36-1.85), with no indication of heterogeneity between studies.

The most recent meta-analysis (Colantonio *et al.,* 2014) of melanoma risk associated with sunbed use was based on 31 studies, from Europe, North-America and Oceania, including 14,956 melanoma cases and 233,106 controls. Where available risk estimates adjusted for confounders were used. Compared with never using sunbeds, the OR for melanoma associated with ever using indoor sunbeds was 1.16 (95% CI 1.05-1.28). Similar findings were identified in recent studies with enrolment occurring in the year 2000 onward (OR 1.22, 95% CI 1.03-1.45). The authors suggest that this result implies that newer tanning technology is not safer than the older one. A dose-dependent relationship was suggested from the effect of duration of exposure: based on 3 studies, exposure less than or equal to 1 year was associated with a 37% increased risk (OR 1.37, 95% CI 1.06-1.77), whereas exposure for more than 1 year was associated with a 61% increased risk (OR 1.61, 95% CI 0.98-2.67). Similarly, based on 10 studies, lifetime exposure to more than 10 tanning sessions was associated with a 34% increased risk (OR 1.34, 95% CI 1.05-1.71).

Summary

In summary, all four recent meta-analyses show a consistent increased risk of approximately 20% for melanoma with ever use of artificial tanning. The two meta-

analyses (IARC 2006, 2007, Boniol *et al*., 2012) that examined risk by age at first use both show a more pronounced risk when exposure began at a younger age. In addition, the two meta-analyses (Boniol *et al*., 2012, Colantonio *et al*., 2014) that investigated dose-response both indicate an increasing risk with increasing sunbed use.

7.2.1.2 Case-control studies

The SCCP report (2006) briefly reviewed a number of case-control studies published up to 2005. Most of these studies were included in meta-analyses by IARC (2006) and Hirst *et al.* (2009) – see section 8.2.2.1. Key case-control studies published since 2006 are reviewed below.

Studies published since 2006

In a population case-control study (the Skin Health Study) people diagnosed with invasive cutaneous melanoma in Minnesota between 2004 and 2007 at ages 25 to 59 years (case patients) were identified from the state cancer registry Controls were frequency matched to case patients on age and sex and were randomly selected from the state drivers' license register (Lazovich *et al*., 2010). Among potential participants, 1167 case patients and 1101 control subjects (84.6% and 69.2% of eligible, respectively) provided written consent and completed a self-administered questionnaire and telephone interview. Participants who reported indoor-tanning-related burns were excluded. Adjustment was made for potential confounders including age, gender, eye and skin colour, freckles and moles, annual income, education, family history of melanoma, lifetime sun exposure (routine, leisure activities outdoors, during work) and sunscreen use. Indoor tanning use was reported by 62.9% of cases and 51.1% of controls. The adjusted risk of melanoma associated with ever sunbed use was 1.74 (95% CI 1.42-2.14). There was a significant increasing dose-response relationship with increasing number of sessions per year: ≤10 OR= 1.34(95%CI 1.00-1.81); 11-24 OR=1.80 (95%CI 1.30-2.49); 25-100 OR=1.68 (95%CI 1.25-2.26); >100 OR=2.72 (95%CI 2.04-3.63) (p-trend 0.0002). Risk also increased with years of sunbed use: 1 OR=1.47 (95%CI 1.06-2.02); 2-5 OR=1.64 (95%CI 1.26-2.15); 6-9 OR=1.85 (95%CI 1.31-2.61); 10+ OR=2.45 (95%CI 1.83-3.28) (p-trend 0.006). Cases were also more likely than controls to report having experienced painful burns from indoor tanning (adjusted OR, 2.28; 95% CI, 1.71-3.04), a greater number of indoor tanning-related burns (P trend = 0.01), or painful sunburns at a time when they thought they were protected from the sun by indoor tanning (adjusted OR, 2.00; 95% CI, 1.48-2.70).

Melanoma risk was pronounced among users of UVB-enhanced (adjusted OR, 2.86; 95% CI, 2.03-4.03) and primarily UVA-emitting devices (adjusted OR, 4.44; 95% CI, 2.45-8.02). The likelihood of melanoma was significantly increased 2.86 and 4.44 times for users of high-speed/high-intensity devices and high pressure devices, respectively; and 1.76 and 1.85 times for users of conventional devices and sunlamps, respectively, relative to never users.

A letter by Grant *et al.* (2010) suggested that having fair or red hair and many moles might explain the increased risk found by Lazovich *et al*. (2010) and that there was overlap between those reporting indoor tanning and a history of sunburns. These factors were adjusted for in multivariate analyses by Lazovich *et al*; Grant *et al* suggest additional analyses stratified by these factors would be informative. It should be noted that two of the authors of this letter acknowledge conflicts of interest with Grant receiving funding from the UV Foundation (McLean, VA), the Sunlight Research Forum (Veldhoven), Bio-Tech-Pharmacal (Fayetteville, AR), the Vitamin D Council (San Luis

Obispo, CA), and the Danish Sunbed Federation and his co-author, Pope, acknowledging tanning salons among his clients for computer and electrical work.

Another analysis of the same data set from Lazovich *et al.* (2010), excluding those who had reported burns from indoor tanning use, investigated the interaction between sunbed use and sunburns from outdoor solar radiation and the risk of melanoma (Vogel *et al*. 2014). Significantly increased risks were found for melanoma across all sunburn categories for participants who had tanned indoors without burning compared with those who never tanned indoors, with the highest risk being for those who reported zero lifetime sunburns (OR = 3.87; 95% CI 1.68, 8.91).

In a letter about this study, Boniol *et al*. (2015) discuss the potential for misinterpretation of the decline in risk associated with sunbed with increasing sunburns, found by Vogel *et al*. (2014), as being a protective effect. They suggest that sunbeds have an effect on melanoma independently from the effect of sunburns and that the additive effect could have been masked by using models that assume a multiplicative effect.

A further paper reporting results from the same study found that persons who used indoor tanning exclusively in businesses as opposed to in their homes were at increased risk of melanoma (OR=1.82, 95% CI 1.47-2.26) compared with non-users (Ferruci *et al* 2014). Melanoma risk was also increased in the small number who reported tanning indoors only at home relative to non-users (OR= 4.14, 95% CI 1.75-9.78); 67.6% used sun lamps.

From the Australian Melanoma Family Study, a multicentre, population-based, case-control-family study, data on 604 cases of melanoma diagnosed between ages 18 and 39 years and 479 controls were collected by interview (Cust *et al*., 2011). Compared with having never used a sunbed, the OR for melanoma associated with ever-use was 1.41 (95%CI 1.01-1.96), and 2.01 (95% CI 1.22-3.31) for more than 10 lifetime sessions (p-trend=0.01 with cumulative use), adjusting for age, sex, city, education, family history, skin colour, usual skin response to sunlight and sun exposure. The association was stronger for those aged <25 year first use (OR= 1.64 (1.07–2.51) and for melanoma diagnosed when aged 18-29 years (OR for more than 10 lifetime sessions = 6.57, 95% CI 1.41-30.49) than for melanoma diagnosed when 30-39 years (OR 1.60, 95% CI 0.92-2.77; p (interaction) 0.01). Among those who had ever used a sunbed and were diagnosed between 18 and 29 years of age, three quarters (76%) of melanomas were attributable to sunbed use.

A UK study used the same questionnaire and method of analysis as the Australian study by Cust *et al.* (2011) for a study of 959 incident cases of melanoma and 513 population-ascertained controls and 174 sibling controls (Elliott *et al.,* 2012). The locations where sunbeds were used were private home (54%), tanning salons (34%), gyms/spas (32%), hairdressers/beauty salons (13%) and hospital/medical facilities (9%). Ever-use of sunbeds was not a significant risk factor for melanoma (OR 1.06, 95% CI 0.83–1.36, adjusted for age, gender, education, sun sensitivity phenotype, family history and cumulative lifetime total sun exposure. Age at first use of sunbeds showed a small non-significant increased risk for use <25 years compared with never use (OR 1.16, 95%CI 0.84–1.62), as did age at last use <25 years (OR 1.49, 95% CI 0.95–2.34). Number of sessions and years since first use did not show an increasing trend effect on melanoma risk.

A letter by Autier *et al.* (2013) about this paper questions whether the design of the study was adequate. They point out that having 44% fewer controls than cases is an unusual feature of a case-control study, and that the family doctors who selected controls did not appear to have successfully selected controls who were within 5 years of age of the cases as a large imbalance in age of cases and controls resulted; controls were also of a higher socioeconomic status than the cases. They also suggest that the use of sibling controls may be problematical in that siblings may share identical behaviours such as visiting indoor tanning parlours. Elliott *et al.* (2013) responding to this letter point out that other studies have not found a clear relationship between socio-economic status or educational level on sunbed use.

The US Nurses' Health Study was established in 1976, when 121 700 female registered nurses between the ages of 30 and 55 completed a self-administered questionnaire on their medical histories and baseline health-related exposures. Updated information has been obtained by questionnaires every 2 years. A nested case-control study of 200 melanoma cases found that sunlamp usage or tanning salon attendance was a risk factor for melanoma after adjusting for age, skin and hair colour, tendency to burn and presence of moles (OR for ever vs never usage, 2.06, 95% CI 1.30–3.26) and similar results for both <10 years and >10 years of use (Han *et al* 2006). Melanoma risk was associated with both family history of melanoma (OR, 1.81; 95% CI 0.99–3.29) and that of non-melanoma skin cancer (OR, 1.49; 95% CI 0.99–2.25).

An analysis of a large case-control study carried out in 1991-92 of melanoma cases investigated the characteristics of and risk for subjects who used sunbeds or sunlamps (Fears *et al.* 2011). Risk was estimated for ever/never use of a sunbed /sunlamp, the total number of sessions (reported in categories of zero, <10 times, 10–50 times or >50 times) and typical session times reported in minutes. Females were more likely than males to have used sunbeds (OR = 1.5, 95% CI 1.2, 1.8), especially at younger ages. Adjustment was carried out for average residential UVR flux, hours outdoors, tan type, and presence of nevi. For females, the individual risk for melanoma increased with typical session time and frequency of sessions. Use before age 20, current use and years of use were not significant. The use patterns of occasional and frequent users were very different. Typical 5-min sessions were estimated to increase the risk for melanoma by 19% (95% CI -14%, 23%) for frequent users (total 10+ sessions) and by 3% (95% CI 2%, 38%) for occasional users (total 1–9 sessions). Body sites that are not generally exposed to sunlight were more common sites of primary melanomas for frequent sunbed / sunlamp users. For males, measures of sunbed / sunlamp use were not significantly associated with melanoma risk.

A population-based case–control study of 423 cases of melanoma identified from the State cancer registry and 678 controls selected from driving licence registries was carried out in the state of New Hampshire (Clough-Gorr *et al*., 2008). Exposure data, including sunlamp and sunbeduse, were collected by telephone interview. About 17% of participants had used a sunlamp at least once and most use (89%) occurred before 1980. The OR was 1.39 (95% CI 1.00–1.96) for ever using a sunlamp, 1.23 (95% CI 0.81–1.88) for those starting sunlamp use at <20 years, and 1.71 (95% CI 1.00–2.92) for those starting ≥20 years. There was an increasing risk with number of sunlamp uses 1.29 (95% CI 0.84–1.99) for use less than 6 times, and 1.54 (95% CI 0.93– 2.57) for use 6 or more times. The overall prevalence of sunbed use was 22% (86 cases and 102 controls) and most use (83%) occurred after 1980. The OR was 1.14 (95% CI 0.80–1.61) for ever using a sunbed(adjusted for age, gender, family history of melanoma, hair

colour, freckles, sun sensitivity, total sun exposure hours). The OR for age at first use <20 was 1.78 (95% CI 0.76-4.15) and for more than 10 times use was 1.25 (95%CI 0.79-1.98). The OR was 1.96 (95% CI 1.06–3.61) for having used both devices. The authors suggest that there a sufficient lag time may not have elapsed to assess a true effect.

Summary of case-control studies

The majority of these more recent case-control studies show significantly increased risks of melanoma associated with sunbed use and add weight to the literature reviewed by IARC. Most have a large sample size and collect and adjust for relevant confounders such as sunlight exposure, hair colour, presence of moles/freckles etc. It should be noted that the use of sunbeds was generally self-reported and there was generally no information on the specific sunbed type used.

The excess risk of melanoma associated with ever using a sunbed varied from 40% to double the risk. Only one study, in the UK, found no risk. However, this study was unusual in design in that there were fewer controls than cases, there was an imbalance of age between cases and controls and some of the controls were case siblings for whom there may have been similar behaviours.

There is also evidence from a few of the reviewed studies that the risk of melanoma increases with increasing number of sessions and increasing frequency of use (number of sessions per year).

7.2.1.3 Cohort studies

Cohort studies are known to be less susceptible to biases than case-control studies and bring a higher level of evidence. The SCCP report (2006) reviewed a cohort that followed more than 100,000 Norwegian and Swedish women for an average of 8 years and identified use of sunbeds as a risk factor for melanoma, more especially when exposure took place at a younger age (Veierod *et al*., 2003). A new analysis of the Norwegian-Swedish cohort and two new cohorts are described below.

Studies published since 2006

The first cohort on sunbed use and melanoma was published in 2003 by Veierød *et al.* and updated in 2010 (Veierod *et al*. 2003, 2010). This study was conducted in Norway and Sweden and included 106,379 women aged 30 to 50 years at recruitment in 1991-1992. The authors reported risk adjusted for host factors (age, hair colour and sunburns), and sun exposure (annual summer vacations). In the first report published in 2003, 187 melanoma cases had been diagnosed during a follow-up of 8.1 years on average. For women exposed 1 time per month to sunbeds or more between 10 to 39 years of age, the risk of melanoma was increased by 55% (RR=1.55 95%CI 1.04-2.32). In the updated analysis published in 2010 with an average follow-up of 14 years, a total of 412 melanoma cases have been diagnosed. In this update, the increased risk of melanoma was confirmed with a RR of 2.37 (95% CI 1.37-4.08) for exposure 1 time per month or more in two or three decades between 10 to 39 years. A significant test for this trend was also reported with a p-value of 0.003, and a clear incremental risk with use: as compared to never use, the risk was of 1.24 for rare exposure, 1.38 for exposure 1 time or more in one decade between 10-39 years, 2.37 for exposure 1 time or more in two or three decades between 10-39 years. Hence, this cohort study showed both an increased risk of melanoma, and a dose-response association.

The Nurses' Health Study II (NHSII) cohort study included 73,494 female nurses residing in the United States. Women were aged 25 to 42 years of age in 1989 at inclusion in the cohort and were followed on average 18.5 years. Participants self-reported frequency of sunbeduse during high school/college or between ages 25 and 35 years. The authors reported risks adjusted for host factors (age, hair colour, moles, tendency to sunburn), and sun exposure during different period of life (outdoor exposure at high school/college and UV index). During the follow-up period 5,506 nurses were diagnosed with a BCC, 403 with a SCC and finally 349 with melanoma. This study found some significant increase risk of BCC and SCC associated with past history of sunbed use. For melanoma, there was no significant increase in risk with relative risk above 1 such as the risk of melanoma with 4 times use of solarium per year associated with RR of 1.11 (95% CI 0.97-1.27). However, there was no clear dose-response relationship when the frequency was analysed as a categorical variable with 4 categories. There was a stronger effect for those with low skin pigmentation. Reported RR were slightly higher when restricted to exposure during high school and college (Zhang *et al*., 2012).

Nielsen *et al*. (2012) published results from the analysis of another Swedish cohort of 40,000 women aged 25-64 at enrolment in 1990. After an average follow-up of 11.5 years, 215 melanoma have been observed (155 invasive and 60 in situ melanoma). The authors reported relative risks adjusted for host factors (nevi, hair colour, freckles), UV exposure (sun vacation in winter, sunbathing) and sunscreen use. Overall, no significant risk of melanoma was observed for sunbed exposure 1-10 times/year (HR=1.0 95% CI 0.6 – 1.6) and a insignificantly increased risk was observed for sunbed use more than 10 times per year (HR=1.5 95% CI 0.8-2.8). But for younger women (25-39 years at inclusion), there was a significant risk of melanoma associated with sunbed exposure more than 10 times/year (HR=2.5; 95% CI, 1.0–6.2). The authors also report (data not shown) that when adjusting also for frequent sunbathing events, the risk associated with highest degree of sunbed use was reduced, but still doubled compared to baseline risk.

Summary of cohort studies

In summary, the three most recent cohort studies show an increase in melanoma risk (up to double in one study) associated with sunbed exposure at a younger age. In addition, since all analyses were adjusted for host factors such as tendency to sunburn, hair colour, and for sun exposure, they also suggest that sunbed use adds a specific risk of melanoma independently from individual susceptibility and behaviour in the sun.

7.2.1.4 Other designs

Although ecological and cross sectional studies are usually considered as of limited weight in evidence building, some may, in specific circumstances, be of interest. This is the case for the analysis of a melanoma epidemic in Iceland (Héry *et al*., 2010).

Iceland is a Nordic country situated at 64–66° North latitude where bright, sunny days are rare. In a collaborative work with the Iceland Cancer Registry and Icelandic dermatologists, an epidemic of melanoma starting in 1995 was described. Before 1995, the melanoma incidence in Iceland was lower than in Denmark and Sweden. In 1990s, it started to rise steeply and after 2000 it surpassed the incidence in other Nordic countries. This phenomenon was mainly noticeable among women. In women, the slow increase in trunk melanoma incidence before 1995 was followed by a significantly sharper increase in incidence, mainly among women aged less than 50 years, resembling an epidemic incidence curve (estimated annual percent change 1995–2002: 20.4%, 95%

confidence interval: 9.3, 32.8). In 2002, the melanoma incidence on the trunk had surpassed the incidence on the lower limbs for women; this latter aspect was in sharp contrast with the usual observations prior to 1995 whereby the greatest increase in melanoma incidence in women occurred on lower limbs. The investigation concluded that the only plausible explanation for this epidemic was the massive exposure of Icelandic youths to artificial tanning devices after 1985. In 1979, there were only 3 salons in Reykjavik, and by 1988, 56 salons with 207 sunbeds were operating. Sunbed use in Iceland expanded rapidly after 1985, mainly among young women, and in 2000 it was approximately 2 and 3 times the levels recorded in Sweden and in the United Kingdom, respectively. In 2002, 70% of women and 35% of men had used sunbeds at least once for tanning purposes in Iceland. Travelling abroad to more southern areas represents an important source of sun exposure for Icelanders. However, travelling abroad was more prevalent among older Icelanders: in 2001–2002, 6% of women and 5% of men aged 20–39 years had travelled abroad 10 times or more during their lifetime, in contrast, these proportions were 17% among women and men aged 50 years or more. (Rafnsson *et al.,* 2004).

The high prevalence of sunbed use probably contributed to the sharp increase in the incidence of melanoma in Iceland. The decrease in incidence of trunk melanoma incidence observed in women after 2002 is most probably due to campaigns initiated by the Icelandic health services at the end of the 1990s. A campaign by health authorities in 2004 to discourage sunbed use especially by teenage girls resulted in a 50% reduction in the number of sunbeds by 2008.

In an invited commentary accompanying Héry's *et al.* publication, Berwick (2010) noted that this ecologic study was consistent with biologic evidence and case-control and cohort analyses of sunbed use associated with melanoma, and added to the evidence that sunbeds are health hazards and that UV-A has a biologically plausible role in the development of melanoma.

In a letter, Alberg (2011) noted that, despite its reliance on population-level data, the study by Héry *et al*. provided a stronger level of evidence than might first be apparent and was important in complementing the evidence provided by observational epidemiologic studies.

In Germany, individuals over the age of 35 years are eligible for the national skin cancer screening program. A study evaluated the effectiveness of this screening and assessed the risk factors associated with them. (Schmitt *et al*., 2011). A total of 12 187 individuals age 14 to 34 years were screened in Saxony for skin cancer by a dermatologist in the screening program of a large German health insurance company. Demographic, clinical and histopathological data and UV-exposure data were collected from each participant. In 1072 individuals (8.8 %) the screening included at least one excision of a skin lesion leading to the diagnosis of melanoma in two participants, melanoma *in situ* in four persons, and atypical nevus in 641 persons. 13% of those screened regularly used sunbeds with a third of these using them all the year round. Higher age, number of nevi, and previous cutaneous excision were independent risk factors for the detection of a melanoma or atypical nevus. In addition, a histological diagnosis of dysplastic nevus or melanoma was associated with sunbed use both all the year round (OR=1.73, 95% CI 1.17-2.56) and also just in the winter (OR=1.35, 95% CI 1.17-2.56) (adjusted for confounding factors).

A survey of 1518 dermatology clinic patients collected information on the extent of sunbedexposure and history of skin cancer (Ting *et al.,* 2007). Of these, 551 (36.3%) completed all components of the survey. The available medical records, including pathology reports (n = 501; 33%), were reviewed to confirm cases of skin cancer. Data on potential confounding factors, including indoor/outdoor occupation and leisure activities, Fitzpatrick skin type, history of blistering sunburn, use of sunscreen and sun protective clothing, history of phototherapy and level of education, were assessed and compared. Of the patients surveyed, 487 (32.1%) reported sunbedexposure, with 60% being women aged 45 years or younger. Seventy-nine cases of malignant melanoma were reported, 22 in women aged 45 years or younger. Overall "ever use" of sunbeds was significantly associated with melanoma (OR=1.64, 95% CI 1.01–2.67). Risk was greater in women aged 45 years or younger (OR = 3.22, 95% CI 1.01–11.46). Patients with a history of melanoma were significantly more likely to report sunbedsessions exceeding 20 min (OR = 3.18, 95% C, 1.48–6.82); this association was even stronger for women aged 45 years or younger (OR, 4.12; 95% CI, 1.41–12.02).

Summary of other designs

The association of sunbed use and increased risk of melanoma was supported in an ecological study in Iceland, from skin cancer screening data in Germany and from a US survey of patients attending a dermatology clinic.

Overall Summary of the epidemiological literature on melanoma risk and sunbed use

New papers reporting epidemiological studies since 2006 have been reviewed. It should be noted that the meta-analyses also include studies published before that date. There is consistent evidence from meta-analyses and individual studies of an increased risk of melanoma with ever use of sunbeds. In addition those papers where risk by age and frequency of use were examined show a more pronounced risk when first exposure begins at a younger age and an increasing risk with increasing use of sunbeds (number and frequency of sessions per year). These analyses are adjusted for host factors such as tendency to sunburn, hair colour, and for sun exposure; this suggests that sunbed use adds a specific risk of melanoma independently from individual susceptibility and behaviour in the sun.

7.2.2 Mechanistic studies

7.2.2.1 Experimental animal studies

According to the previous SCCP report (2006), sunburn, an important risk factor for melanoma, has implicated UVB in its pathogenesis (Wang *et al.*, 2001). The incidence of melanoma, as well as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is very high in xeroderma pigmentosum (XP) with defective excision repair of UVB-type DNA damage, e.g cyclobutane pyrimidine dimers (CPD). The wavelength dependency for melanoma however is not yet established because of the lack of a good animal model (Noonan *et al*., 2003).

As murine melanocytic tumours are dermal in origin and lack the epidermal component that characterizes human melanoma, melanomas have proven extremely difficult to induce by UVR alone in mice (SCCP report, 2006). Wavelength dependency has been determined in a fish model (Xiphophorus) (Schartl *et al.*, 1997) the value of which is limited because its melanoma-like lesions arise from the dermis instead of the epidermis

and fish are phylogenetically very different from humans. Studies in these fish however showed that visible and UVA radiation, as well as UVB (Setlow *et al.*, 1993) induced lesions that raised concern that UVA might be causal for human melanoma as well or instead of UVB. A mammalian opossum model also developed melanoma-like lesions after broad-band UVA exposure but with low potency compared to broad-band UVB (Robinson *et al.*, 2000).

A mouse model was described in 2000 (the hepatocyte growth factors/scatter factor (HGF/SF) transgenic mouse) which has melanocytes in the dermis, epidermis and dermal–epidermal junction. This mouse model is thus more suitable for an extrapolation to human skin (Noonan *et al.,* 2000).

Adult chronic sub-erythemal UV radiation did not significantly accelerate melanoma genesis in this mouse model (Noonan *et al.,* 2000). In this study, mice of 4 to 6 weeks of age started to be exposed with a bank of six FS40 sunlamps (60% UVB, 290–320 nm; 40% UVA, 320–400 nm; and 1% UVC, 250–290 nm) leading to an incrementally graded UV protocol: three times weekly a UV dose was delivered of 2.25 kJ/m^2 (7.5 min) for 12 treatments (weeks 1–4), 4.05 kJ/m^2 (13.5 min) for 24 treatments (weeks 5–12), 5.1 kJ/m^2 (17 min) for 12 treatments (weeks 13–16), and 6 kJ/m^2 (20 min; week 17 to the end of the experiment). This treatment was able to increase the number of lesions (squamous cell carcinoma, papilloma, sarcoma) but without significant increase in melanoma.

For neonatal mice (3.5 days of age) an erythemal dose of UV radiation was necessary and sufficient to induce melanoma (Recio *et al*., 2002). Neonatal mice were irradiated with a bank of six Phillips F40 UV lamps. The exposure time was 15 min for a total dose of 6.24 kJ/m^2 UVB (280–320 nm), 3.31 kJ/m^2 UVA (320–400 nm), 0.03 kJ/m^2 UVC (<280 nm), and 5.04 kJ/m^2 of visible radiation (400–800 nm). The effectiveness of neonatal UV irradiation in melanoma development in HGF transgenic mice was also confirmed in an mouse models (Hacker *et al*., 2005 and 2006; Kannan *et al*., 2003).

In 2004, the team of Noonan (De Fabo *et al*., 2004) using the same experimental species (neonatal HGF/SF-transgenic mice) irradiated the animals with specialised optical sources emitting isolated or combined UVB or UVA wavebands and showed that UVB (280-320 nm) corresponding to 13.5 kJ/m^2 is responsible for the induction of melanoma whereas UVA (320-400 nm) 150 kJ/m^2 is ineffective at doses considered physiologically relevant, providing perhaps more persuasive evidence that UVB exposure is causal rather than UVA14.

The role of UVA, which can initiate different molecular events, in melanoma has, however, also been questioned. The same group (Noonan *et al.,* 2012) exposed neonatal C57BL/6-HGF and C57BL/6-c-HGF transgenic mice (3 days of age) to an absolute UVB dose of 14 kJ/ m^2 (unweighted) or to a UVA dose of 150 kJ/m^2. They reported the existence of two distinct pathways for melanoma: an UVB-dependent pathway independent of pigmentation associated with direct UVB-type DNA damage and an UVA pathway that requires eumelanin which is associated with indirect oxidative DNA damage

[14] Note: For comparative purposes, the number of SEDs given to neonatal mice in these experiments was calculated as 23. De Fabo *et al*., 2004 determined previously that 23 SEDs could have been received in 2 h and 40 min of sunlight exposure at northern mid-latitudes.

in melanocytes.[15]

The relative contributions of phaeomelanin pigment and of pigment-independent MC1R signaling effects to melanoma risk were investigated by the same team (Wolnicka-Glubisz *et al.,* 2015). Neonatal mice (C57BL/6-Mc1r$^{+/+}$-HGF, C57BL/6-Mc1r$^{e/e}$-HGF, C57BL/6-Mc1r$^{e/+}$-HGF) were irradiated at 3.5 days of age with 9.5 kJ/m^2 of UV radiation which consisted of 6.2 kJ/m^2 of UVB (280–320 nm) and 3.3 kJ/m^2 of UVA (320–400 nm). However, their relative contributions to melanoma risk remains unclear.

Viros *et al.* identified TP53/Trp53 as a UVR target gene that cooperates with BRAF(V600E) to induce melanoma, providing molecular insight into how UVR accelerates melanomagenesis. *Viros et al*., 2014 exposed BRAF(V600E) mice (pretreated with tamoxifen at approximately 2 months old), to 160 mJ/cm^2 UVA/UVB at 3 months of age using a broad-spectrum UVA/UVB lamp, performing weekly re-exposures for up to 6 months.

So far evidence so far for the presence of UVB-generated signature mutations in melanoma that could be ascertained as the driver mutations has been considered less than compelling (Hocker and Tsao, 2007). UVB exposure is undoubtedly mutagenic and signature mutations are starting to be uncovered. Support is strong for the notion that UV is a complete carcinogen, acting with respect to melanoma as both an initiator, through genotoxicity, and a promoter, through immunosuppression. Zaidi *et al.* 2011 and 2012 showed that IFN-gamma is the driver of novel cellular and/or molecular inflammatory mechanisms that may underlie the initiation, immunoevasion and/or survival, and outgrowth of UVB induced melanoma. Knowing that melanocytes are built for enhanced survival to withstand both UV exposure, ensuring the continued synthesis of melanin, and the chemical stresses associated with the synthesis of melanin itself.

Summary

In summary, several in vivo experimental studies conducted on neonatal HGF/SF transgenic mice irradiated with UVB have shown the induction of melanoma. A study with irradiation with UVA has shown also the induction of melanoma. The existence of two distinct pathways for melanoma: an UVB-dependent pathway independent of pigmentation associated with direct UVB-type DNA damage and an UVA pathway that requires eumelanin which is associated with indirect oxidative DNA damage in melanocytes is under investigation. Overall, UVB exposure is undoubtedly mutagenic, and signature mutations are starting to be uncovered. Support is strong for the notion that UV is a complete carcinogen, acting with respect to melanoma as both an initiator, through genotoxicity, and a promoter, through immunosuppression.

[15] Noonan *et al.,* 2012 investigated the effect of Mc1r deficiency in a mouse model of UV-induced melanoma The MC1R controls the balance between black eumelanin and red/yellow phaeomelanin, and polymorphisms in the MC1R are one of the best described risk factors for melanoma and confer melanoma risk independent of pigment.

7.3 Non–melanoma skin cancer

7.3.1 Human health effects

7.3.1.1 Meta-analysis and systematic reviews

No meta-analysis of non-melanoma skin cancer risk associated with sunbed use were available for SCCP at the time of the previous Opinion (2006). Four meta-analyses published since 2006 are reviewed below.

Studies published since 2006

Regarding basal cell carcinoma and squamous cell carcinoma, the meta-analysis conducted by the IARC working group of 3 studies on ever use of indoor tanning versus never use found an increased risk of double for squamous cell carcinoma meta-RR=2.25 (95% CI 1.08-4.70) after adjustment for sun exposure and sun sensitivity, especially when age at first use was below 20 years. Based on one study that reported information on age at first exposure to indoor tanning, it was suggested that the risk increased by 20% (OR = 1.2: 0.9-1.6) with each decade younger at first use (IARC 2006, 2007). The four studies on BCC did not support an association with exposure to indoor tanning.

In a meta-analysis of non-melanoma skin cancer risk associated with sunbed use, based on 6 studies that included 1,812 cases and 2,493 controls, Hirst *et al*. (2009) reported a summary relative risk of 1.34 (95% CI 1.05-1.70). However, this study made no distinction between BCC and SCC.

In their update of the IARC's 2006 meta-analysis (IARC, 2006, 2007), Boniol *et al*. (2012) added two new studies published since 2005 and looked at the risk of non-melanoma skin cancer associated with sunbed use. Adding data from these studies to the 2006 meta-analysis gave a similar results to those of IARC i.e. an excess risk of double ever versus never sunbed use Meta-RR= 2.23 (95% CI 1.39 - 3.57) for SCC (1242 cases in five studies); the evidence for BCC was weaker at 9% excess risk, meta-RR=1.09 (95% CI 1.01 - 1.18) (6995 cases in six studies).

Wehner *et at al.* (2012) conducted a meta-analysis of non-melanoma skin cancer risk associated with sunbed use, based on 12 studies that collected data in 6 different countries and including included 80,661 total participants and 9,328 non-melanoma skin cancer cases. Effect estimates for ever exposure to indoor tanning compared with never exposure were available for 10 out of 12 studies. A meta-analysis of these studies yielded summary relative risks of 1.29 (95% CI 1.08 to 1.53) for BCC and 1.67 (1.29 to 2.17) for SCC. No significant heterogeneity existed between studies. Two additional studies reported only higher dose exposure, and considered only BCC; with these two studies included, the summary relative risk for BCC was 1.25 (95% CI 1.01 to 1.55). In a sub-analysis of 4 studies to assess a dose-response effect, high dose exposure (frequent use) was associated with a relative risk of 1.50 (95% CI 0.81 to 2.77) for BCC. In a sub-analysis of 3 studies that included effect estimates for early life exposure, indoor tanning exposure before age 25 was associated with a relative risk of 1.40 (95%CI 1.29 to 1.52) for BCC and 2.02 (0.70 to 5.86) for SCC.

Summary of meta-analyses

There were no meta-analyses on sunbed use and non-melanoma skin cancer available at the time of the SCCP Opinion. Although based on a smaller number of studies than for melanoma, the four meta-analyses published since 2006, including one as part of the IARC review, consistently indicate that sunbed use is a risk factor for squamous cell carcinoma and to a lesser extent for basal cell carcinoma, especially when exposure takes place at a younger age. Ever use of sunbeds approximately doubles the risk of SCC; the evidence of an increase of BCC is weaker being between 10% and 30%.

7.3.1.2 Case control studies

Some of the case-control studies reviewed in section 7.2.1 also investigate the relationship between sunbed use and NMSC.

The paper by Han et al (2006) also includes case-control studies of 275 SCC and 283 BCC cases nested within the US Nurses' Health Study. Sunlamp usage or tanning salon attendance was non-significantly associated with risk for both SCC and BCC after adjusting for age, skin and hair colour, tendency to burn and presence of moles (OR for ever vs never usage: SCC 1.44, 95% CI 0.93–2.24; BCC 1.32, 95%CI 0.87, 2.03). NMSC risk was not associated with family history of melanoma but was strongly associated with both family history of SCC (OR, 1.86; 95% CI 1.29–2.68) and BCC (OR, 2.65, 95% CI 1.86–3.76).

The paper by Ferrucci *et al.* (2014) also included 375 cases of early-onset BCC (382 controls, age 40 years) and found that persons who used indoor tanning exclusively in businesses were at increased risk of BCC (OR=1.69, 95% CI 1.15-2.48) compared with non-users. The association between business only indoor tanning and BCC was unchanged (OR 1.74, 95% CI 1.17-2.58) among 28 individuals (19 reported business-only indoor tanning) who reported any UV light therapy for medical conditions (eg, acne, psoriasis were removed).

An earlier paper by Ferrucci *et al*. (2012) evaluated the association between indoor tanning and early-onset BCC. Patients with BCC (n = 376) and control subjects with minor benign skin conditions (n = 390) who were younger than 40 years of age were identified through Yale Dermatopathology. Participants provided information on ever indoor tanning, age of initiation, frequency, duration, burns while tanning, and type of tanning device during an in-person interview. Patients with BCC were more likely to have fairer pigment-related characteristics, a family history of skin cancer, regularly used sunscreen on the body site of their skin biopsy, spent more time outdoors during warm months, and sunburned more frequently than control subjects. Ever indoor tanning was associated with a 69% increased risk of early-onset BCC (95% CI 1.15-2.48). This association was stronger among females (OR 2.14, 95% CI 1.31-3.47), for multiple BCCs (OR 2.16, 95% CI 1.26-3.70), and for BCCs on the trunk and extremities (OR 2.81, 95% CI 1.57-5.02). Having been burned while indoor tanning (OR 1.87, 95% CI 1.17-2.97), particularly burning at the site of the skin biopsy (OR 2.72, 95% CI 1.57-4.69), was strongly associated with early-onset BCC. There were significant increases in risk for regular use (OR=1.68, 95%CI 1.14, 2.46), high-speed/high-intensity use (OR=2.26, 95%CI 1.33, 3.83) and for high pressure use (OR=2.89, 95%CI 1.34, 6.24). Risk increased dose dependently with years using regular indoor tanning devices (P trend = .003).

In a population-based case-control study from New Hampshire, US data on indoor tanning was obtained on 657 cases of 'early onset' BCC (aged <50 years) and 452 controls (randomly selected from resident lists) (Karagas *et al.*, 2014). BCCs were located on head and neck sites in 57% of the cases, and about 50% had histologic evidence of severe solar elastosis. Early-onset BCC was related to indoor tanning, with an adjusted odds ratio (OR) of 1.6 (95% CI, 1.3-2.1). Associations were present for each type of device examined (i.e. sunlamps, sunbeds, and tanning booths). Elevated ORs were found for both early (<1975) and late (>1986) calendar periods of first exposure. ORs were elevated among those whose first exposure was before age 20 (OR = 2.0; 95% CI, 1.4–3.0) and those who began later in life but to a lesser extent (OR for first use at 20–35 years = 1.4; 95% CI, 1.0–2.0; and OR for first use at >36 years = 1.6; 95% CI, 1.0–2.6). There was a 10% increase in the OR with each age younger at first exposure (OR per year of age ≤23 = 1.1; 95% confidence interval, 1.0-1.2). Positive associations were found between tanning lamp use and early-onset BCC in all categories of skin types, sunburn history, and hours of outdoor exposure
(see table in Annex II). In subgroup analyses, ORs were higher for tumours on the trunk (OR = 2.1; 95% CI, 1.5–3.1) and upper limbs (OR = 2.0; 95% CI, 1.0–4.3) than on the head and neck (OR = 1.4; 95% CI, 1.1–1.9).

A hospital-based case-control study investigated the association between pigmentary characteristics, patterns of solar exposure, habits and lifestyle, and risk for BCC among patients attending a dermatology centre in a region in southern Brazil (Gon *et al.,* 2011). The study included 127 cases with histologically confirmed BCC and 280 cancer-free control subjects with other dermatologic conditions. The study was conducted using a questionnaire and physical examination by a dermatologist. Risk for BCC was associated with family history of skin cancer, Fitzpatrick skin type I, and the presence of actinic keratosis, solar lentigines, leukoderma, and elastosis romboidalis nuchae. No effect was found for different patterns of solar exposure, eye, hair or skin colour, lifestyle-related habits such as sunscreen use and cigarette smoking or exposure to non-solar ultraviolet radiation (UVR). However, it should be noted that only 3 cases and 25 controls had used artificial tanning.

Summary of case-control studies

The IARC systematic review and meta-analysis which included 5 case-controls studies of SCC and/or BCC concluded that there is some evidence of an excess risk for SCC; the more recent study by Han found a 40% excess risk for SCC (statistically non-significant). IARC found no evidence for an increase in BCC. In contrast several new studies of BCC have found positive associations with sunbed use with the excess risk ranging from 30% to over 60%. One study showed an increase with first use in early life and regular use and showed an increased dose with increasing years of use.

7.3.1.3 Cohort studies

The analysis of the US nurses' cohort data that investigated the influence of sunbeduse during high school/college and at ages 25 to 35 years with risk of melanoma also gave results for the risk of BCC and SCC (Zhang *et al.,* 2012). The multivariable-adjusted HR for an incremental increase of use of sunbeds 4 times per year during high school/college and between ages 25 and 35 years was 1.15 (95% CI, 1.11-1.19) for BCC, 1.15 (95% CI, 1.01-1.31) for SCC. Multivariable adjusted ORs for BCC were associated with significant trends in increasing use (times/year) during high school/college (1-2 OR=1.25 95%CI 1.10,1.41; 3-5 OR=1.20 95%CI 1.00,1.43; >6

OR=1.73, 95%CI 1.52, 1.98; (p-trend<0.001)) and at ages 25-35 (1-2 OR=1.19 95%CI 1.08,1.31; 3-5 OR=1.21 95%CI 1.06,1.38; >6 OR=1.28, 95%CI 1.16, 1.41; (p-trend<0.001)). For SCC multivariable adjusted ORs were associated with significant trends in increasing use at ages 25-35 (1-2 OR=1.60 95%CI 1.15, 2.22; 3-5 OR=1.51 95%CI 0.95,2.42; >6 OR=1.61, 95%CI 1.13, 2.31; (p-trend<0.001)).

An investigation of the association between SCC risk and host characteristics, **sun** exposure, and indoor tanning was carried out in the population-based Norwegian-Swedish Lifestyle and Health women's cohort study together with SCC incidence data from national cancer registries (Veierod *et al*., 2014). Host characteristics and exposure to sun and indoor tanning devices before 50-years old were recorded by questionnaire at inclusion (30-50 years) in 1991/92. Before 1982/83, tanning devices mainly used UVB-rich mercury arc lamps and after that UVA-rich fluorescent lamps. The age group 20-29 at cohort inception represents women exposed to the more recent lamps. During follow-up of 106,548 women through December 2009, SCC was diagnosed in 141 women. Very few women (2%) had used an indoor tanning device before the age of 20. There was a significantly increased risk of SCC following indoor tanning at age 40-49 years (RR = 2.17, 95% CI 1.29-3.67, for ≥ 1 time/month versus never), adjusted for age, region, hair colour, colour after heavy sun exposure, age-specific sunburns and weeks' vacation. However, the risk for the younger age groups was non-significantly raised. Over all ages there was a statistically significant trend with increasing frequency of use with the ORs being consistently significant for all categories of use.

Summary

The large well-conducted US nurses' study showed increasing risks with increasing frequency of use of sun beds (times/year) at ages 25-35 for both BCC and SCC. In contrast the other cohort study showed only a weak increased risk at younger ages.

Overall Summary of the Epidemiological Literature on the association of NMSC and sunbed use.

New papers reporting epidemiological studies since 2006 have been reviewed. It should be noted that the meta-analyses also include studies published before that date. There is consistent evidence from meta-analyses and individual studies of an increased risk of squamous cell carcinoma and to a lesser extent for basal cell carcinoma, especially when exposure takes place at a younger age. Ever use of sunbeds approximately doubles the risk of SCC; the evidence of an increase of BCC is weaker being between 10% and 30%. Rregular use and increasing years of use shows an increased risk of NMSC.

7.3.2 Experimental animal studies

The wavelength dependencies for skin cancer (SCC - squamous cell carcinoma) have been determined in hairless mouse models (de Gruijl, 1995; Kligman and Sayre, 1991) and these studies have shown action spectra similar to that for human erythema (CIE, 1998; Young *et al.*, 1998). Figure 2 shows the action spectra for human erythema and non-melanoma skin cancer (SCC) (CIE 1998, 2000) and it can be seen that these are very similar, especially in the solar UVB and UVA-II (315-340nm) ranges. Thus, one might conclude that erythema, primarily caused by UVB, can be regarded as a surrogate risk factor for SCC and photo-aging. There is no animal model for UVR-induced BCC.

As highlighted by IARC in its last evaluation of the radiation including UVR (IARC, 2010), most of the recent animal studies were not designed to test whether or not the radiation used was carcinogenic *per se* but to investigate the process of UV carcinogenesis, or to

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

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

Further study from Sand *et al.,* 2010 indicates that transgenic SKH-1 hairless mice overexpressing PKCε may also provide a useful model to investigate UVR carcinogenesis. Furthermore, their results indicate that the PKCε level dictates susceptibility, irrespective of genetic background, to UVR carcinogenesis.[16]

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

Summary

In summary, several in vivo experimental animal studies have demonstrated UV carcinogenesis and namely, squamous cell carcinoma (SCC). It remains that most of the recent animal studies were not designed to test whether or not the radiation used was

[16] CBL note: PKCε overexpression sensitizes skin to UVR-induced carcinogenesis, suppresses UVR induced apoptotic cell formation, and enhances both UVR-induced levels of TNFalpha and hyperplasia.

carcinogenic *per se* but to investigate the process of UV carcinogenesis, or to test enhancement or inhibition of photo-carcinogenicity by drugs and chemical agents.

7.3.3 Mechanistic studies

The clinical effects of UVR exposure, whether acute or long-term, are underpinned by many molecular and cellular events (Matsumura and Ananthaswamy, 2002). Mechanistic studies mainly focus on the molecular events associated with different wave lengths (UVA/UVB) in relation to tumour formation. The mechanistic studies are mainly *in vitro* studies with human-derived cell lines or skin biopsies. Additional information is obtained from molecular screening of melanoma and non-melanoma derived skin tumours.

UVB radiation directly damages the DNA molecule. It covalently links pyrimidines. This typically includes the formation of cyclobutane pyrimidine (CPD) dimers and 6-4 photoproducts (6-4P) which are premutagenic lesions (Daya-Grosjean L *et al.,* 2005). The CPDs are the most abundant and block transcription and replication. They can be demonstrated in human skin immediately after exposure to erythemal and sub-erythemal UVR (Young *et al*., 1998). CPDs and 6-4Ps in double stranded DNA are normally repaired by nucelotide excision repair (NER) using the undamaged DNA strand as a template. If the lesions are not repaired, they can lead to misreading of the genetic code and cause mutations and cell death. Mutations induced by UVB are conversions such as C → T and CC → TT, commonly named the "UVB fingerprint" or "UVB signature". Unlike UVB, UVA is not absorbed by DNA and so has no direct effect. Instead, UVA indirectly induces damage to DNA through the absorption of photons by other cell structures (chromophores) and the subsequent formation of oxygen reactive species. These principally react with guanine that may lead to G→T conversions, known as "UVA fingerprint" or "UVA signature" mutations (Drobetsky *et al*., 1995; Pfeifer *et al*., 2005). This is challenged, however, in recent findings. The signatures partially overlap. It is now concluded that back-extrapolation from a mutation to an exposure to a single wavelength region of the UVR spectrum is not possible (Mitchell *et al.*, 2012). A typical solar UV signature is: ≥60% of mutations are C→T at a dipyrimidine site, with ≥5% CC→TT (Brash *et al.,* 2015).

The UV exposure fingerprint was recently confirmed in a malignant melanoma cell line with significantly higher frequencies than expected on the basis of chance alone for C>T mutations and CC>TT at the 3'base of a pyrimidine dinucleotide, and a high-frequency frequency of C>T and CC>TT mutations at CpG dinucleotides (Pleasance, Nature, 2010).

Both of these mutation signatures have been described in melanomas and non-melanoma skin cancers (Pfeifer *et al.,* 2012; Griewank *et al.* 2013, Roberts *et al.,* 2014).

Sequencing of skin tumour genomes revealed UV signature mutations in key cell cycle regulatory genes such as in the p53 tumour suppressor gene and Hedgehog signalling pathway related Patched (PTCH) gene in basal cell carcinomas (Kim et al., 2002) and squamous cell carcinomas (SCC) (Brash et al., 1991). UV-signature mutations were also detected in the p53 gene of UVA irradiated skin cells long before squamous cell carcinoma becomes visible (de Gruijl and Rebel, 2008; Runger and Kappes, 2008). Mutation of p53 can be an important step in the development of UV-induced skin carcinogenesis since the p53-dependent apoptosis of UV-damaged normal cells is prevented due to p53 mutation. Thus, these mutated cells can clonally expand to form skin carcinogenesis following subsequent UVR exposures. The patched/hedgehog intracellular signaling pathway plays a central role and are specifically mutated in BCCs (Seghal *et al.,* 2014).

More recently in SCC, UV-induced signature mutations could be detected in another important tumour suppressor PTEN (phosphatase and tensin homologue deleted on chromosome 10) that affects the nucleotide excision repair capacity (Ming *et al.*, 2011; Wang *et al.*, 2009). Melanoma and nevi from Xeroderma pigmentosum (XP) patients also contain UV signature mutations in PTEN. It is well known that these DNA repair deficient XP patients are particularly UV sensitive and have a high risk of developing skin cancers in childhood (Masaki *et al.,* 2014).

Although the role of UV in melanoma was controversial for many years, next-generation sequencing of melanomas from sun-exposed body sites has now revealed UV signatures in many genes such as RAC1 and the apparent tumour suppressor PPP6C (Brash, 2015). New highly mutated target genes have been identified in melanomas and include BRAF, NRAS (Hodis *et al.*, Cell 2012, Krauthammer *et al.*, 2012). However the BRAF and NRAS genes that are mutated in melanoma do not show the typical UVB induced signature. In contrast mutations in BRAF resemble more the UVA induced DNA lesions (Garibyan and Fisher 2010). In addition it has been recently shown that TP53, that contains mutations that display the typical UV radiation signature, may cooperate with BRAF(V600E) to induce melanoma, providing molecular insight into how UVR accelerates melanomagenesis (Viros *et al.*, 2014).

Recently, three driver mutations in the promotor of the telomerase reverse transcriptase (TERT), needed for telomere maintenance in cancer cells, close to the transcriptional start site, have been described for sporadic (Huang *et al.*, 2013) and familiar (Horn *et al.*, 2013) forms of human malignant melanoma. The mutations have also been found, though less frequently, in other tumours and tumour-derived cell lines. The mutations found were of UV-signature type and therefore consistent with UV-induced DNA damage. The results support evidence that UV-induced mutations can be detected in driver genes (TERT) which play important roles in skin cancer (melanoma) etiology.

In 2009 in was furthermore reported that UVA (and to some extent also UVB) have an indirect adverse effect on the micro-environment in the dermis and dermo-epidermal junction by inducing growth factor release which may have a proliferative effect on melanocytes (Brenner *et al*. 2005). More recently, bystander effects of UVA in human keratinocytes and fibroblasts were reported (Whiteside and McMillan, 2009). Bystander effects, mediated both by gap-junction and extracellular signalling, induce genomic instability in non-irradiated cells (surrounding cells which were not themselves exposed) or the progeny of cells that have survived irradiation. Such persistent genomic instability defined as persistent induction of DNA and cellular damage in irradiated cells and their progeny can lead to a hypermutator phenotype where genetic alterations increase generation upon generation in a large proportion of the progeny of irradiated cells, thus increasing the risk of malignant transformation (Ridley *et al.*, 2009). UVA has also been reported to be involved in telomere shortening (Ridley *et al.*, 2009). UVA can induce DNA damage indirectly via photosensitisation of endogenous molecules such as melanins or proteins containing porphyrin, haeme or flavin groups or by photosensitisation of exogenous molecules. UVA, in addition to inducing a variety of DNA damage, also penetrates the dermis where it interacts with proteins and lipids resulting in skin ageing (for a review, see Ridley *et al.,* 2009).

A recent publication reported the important finding that a UVA-triggered chemiexcitation of melanin derivatives induces DNA photoproducts (CPDs) long after UVA exposure (> 3 hours). These "dark CPD" constitute the majority of CPDs that initiate UV-signature mutations in melanocytes derived from mice and in mice skin. Dark CPDs could also be

detected in human melanocytes after UVA or UVB, although there was inter-individual variation in response, particularly after UVA, most likely reflecting genetic differences between donors. Dark CPDs arise when UV-induced reactive oxygen and nitrogen species combine to excite an electron in fragments of pigment melanin. This creates a quantum triplet state that has the energy of a UV photon but that induces CPD by energy transfer in a radiation-independent manner (Premi *et al*., 2015). Although melanin possesses some protection potential against skin cancer induction, these results further explain the carcinogenic potential of melanin after UV-exposure.

A full genome transcriptomic analysis furthermore shows a clear UVA1 signature with the modulation of expression of 461 and 480 genes in epidermal keratinocytes and dermal fibroblasts. Functional gene ontology (GO) analysis then revealed a stress response with up-regulation of genes encoding heat shock proteins or genes involved in oxidative stress response. UVA1 also affected a wide panel of pathways and functions including cancer, proliferation, apoptosis, development, extracellular matrix and metabolism of lipids and glucose. A quarter of the genes were related to innate immunity: genes involved in inflammation were strongly up-regulated while those involved in antiviral defence were severely down-regulated. The transcriptomic data support the contribution of UVA1 to long-term harmful consequences of UV-exposure such as photo-aging and photo-carcinogenesis (Marionnet *et al.,* 2014).

The importance of UVA in mutation induction has been summarised excellently e.g. by Sage *et al*. (Sage *et al.*, 2012) together with other topics in a themed issue "The biology of UVA" in Photochemical and Photobiological Sciences (vol. 11, 1-228 (2012).

Further evidence for an important role of UVA to introduce harmful DNA lesions, beside that of mutation, comes from a study showing that *in-vitro*-irradiation of human keratinocytes with UVA induces DNA double strand breaks (DNA-dsb) (Greinert *et al.*, 2012). DNA-dsb represents the most severe DNA-lesion leading to chromosomal aberrations, which play important roles in cancer development, including skin cancer.

Interestingly, it has been shown that UVA induces C→T mutations at ^{me}CpG sites more frequently than UVB and that these sites of damage correlate with mutation hotspots in tumour suppressor genes (Ikehata *et al.*, 2011) suggesting that UVA may play an important role in tumour progression (Mitchell *et al.*, 2012). It has long been known that methylation of cytosines at CpG islands (^{me}CpG) significantly increases CPD formation of these sites after *in-vitro* UVB irradiation (Tommasi *et al.*, 1997; Mitchel *et al*., 2000) and, consequently, the formation of C→T mutations. Indeed, cytosine deamination within a T-^{me}C CPD located in a CpG island is greatly enhanced by the 3'G and explains the targeting of these mutations to hotspots in tumour suppressor genes as p53 (Cannistraro *et al.*, 2010).

The above results already show a close link between epigenetic modifications (e.g. methylation of cytosine to yield ^{me}C) and UV-radiation. This was not recognised very much in the last decades. Recent years, however, have shown that UV, itself, is able to induce epigenetic changes, which influence processes deeply involved in skin cancer development.

Epigenetic changes are those changes in DNA, which do not touch DNA sequence but modify bases via chemical modification in order to regulate gene expression, including CpG island promoter methylation, chromatin modification and remodelling, and the diverse activities of non- coding RNAs (e.g. microRNAs (miRNA)).

It has been reported that in chronically UVA-irradiated human epidermal keratinocytes UVA induces an epigenetic regulation of p16INK4a, which leads to repression of the tumour promotor, both, via promotor CpG island hypermethylation and epigenetic histone modifications (Chen *et al*., 2012). These results have not been confirmed in another publication that uses a genome-wide analysis assay to detect DNA-methylation in normal human keratinocytes, however, after chronic UVB-irradiation (Lahtz *et al.*, 2013). On the other hand, *in-vivo* UVB-irradiation of mice leads to remarkable promotor CpG island hypermethylation, both for the $p16^{INK4a}$ as well as the RASSF1A tumour suppressor (Nandakumar *et al.*, 2011).The results might indicate severe differences between the two radiation qualities (UVA vs UVB) used.

New, interesting data have been presented in the last decade concerning the role of UV-radiation in regulating miRNA-expression, clearly demonstrating that UV-radiation is also acting on this level of epigenetic regulation.

miRNAs a small (18-23 bases), non-coding, RNAs that regulates gene expression postranscriptionally by binding to complementary sequences in the 3' untranslated region (UTR) of target mRNAs. The binding subsequently leads to the degradation of the target mRNAs and inhibition of protein synthesis (Syed *et al*., 2013).

In 2009 Guo *et al*. reported differential expression profiles of miRNAs in NIH3T3 cells in response to UVB irradiation (Guo *et al*., 2009). In the same year, Pothof *et al*. using HeLa cells and human primary fibroblasts, reported that microRNA-mediated gene silencing modulates the UV-induced DNA-damage response (Pothof *et al*., 2009). However, in this case, UVC was used as radiation quality.

The first data to compare UV-induced miRNA-expression and miRNA-expression in squamous cell carcinoma SCC) were presented in the year 2010. Dziunycz *et al*. reported that UVA-irradiation of normal human keratinocytes significantly increased the expression of miR-21, -203, and -205, whereas UVB-irradiation only increases the expression of miR-203 and decreases the expression of miR-205. Interestingly, miR-21 and miR-203 were shown also to be differentially expressed in SCC-tissue compared to normal tissue. These data have been interpreted as indicating that UV-induced miRNA-expression might be found again, later, after (UV-dependent) SCC development in the tumour tissue (Dziunycz *et al*., 2010).

After a UVC-irradiation, it became clear later on that miRNA are also involved in a DNA-damage response, e.g., in the case where UVC-induced miR-22 expression, enhanced survival of human embryonic kidney cells (HEK292T) and mouse embryonic fibroblasts via the repression of its target gene PTEN (Tan *et al*., 2012).

In 2013 Kraemer *et al*. reported that UVA and UVB irradiation differentially regulate microRNA expression in human primary keratinocyte. Using array technologies, it could be shown that out of 378 miRNAs tested, 45 where differentially expressed after UVA/B. Interestingly, some miRNAs only reacted on UVA, others only on UVB and a third group on both radiation qualities. Looking for target genes of the miRNAs expressed and performing network-analysis, the authors were able to show that the UV-dependent differentially expressed miRNA built networks of target genes, which are of important role in cancer and other diseases, as well as inflammatory response. Certain miRNAs could be directly linked to processes involved in UV-damage response and skin cancer (Kraemer *et al.*, 2013).

In 2013 Guo *et al*. were furthermore able to show that UVB-induced up regulation of a single miRNA, miR-23a (which is part of a mir-23a ~27a~24-2 cluster, which has been

reported to play a role in anti-tumourigenic pathways, DNA repair, and apoptosis) is able to regulate DNA damage repair and apoptosis in UVB-irradiated human keratinocytes (Guo *et al.*, 2013).

Collectively the (selected, in-vitro-) data demonstrate the important role of UV-radiation in miRNA regulation. Because miRNAs are known to be essential regulators in the development and progression of photo-carcinogenesis (recently reviewed in (Syed *et al.*, 2015), these further underscores how deeply UV-radiation is connected to skin cancer ethology.

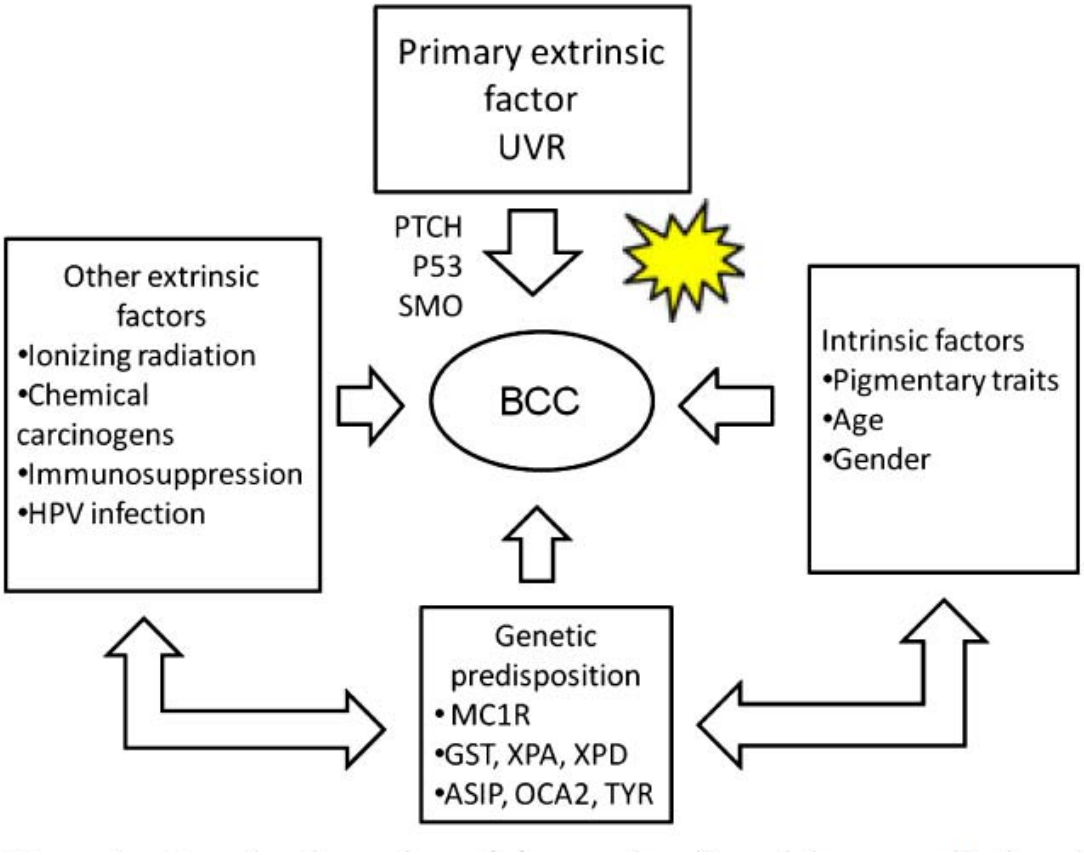
7.3.3.1 Susceptibility

It is hypothesised that polymorphisms in genes implicated in the responses to DNA damage and oxidative stress following exposure to UV constitute genetic susceptibility factors for skin cancers. Genome wide association studies have associated melanoma with SNPs in NER (nucleotide excision repair) genes (Povey *et al*., 2007). Also SNPs in other genes such as the interleukin-6-receptor gene, were associated with an increased risk for melanoma (Gu *et al*., 2008). Polymorphisms in the vitamin D receptor gene were associated with melanoma and non-melanoma skin cancer (Povey *et al*., 2007; Gandini *et al.,* 2009).

Individuals with lower DNA repair capacity may be more vulnerable. Lower DNA repair capacity was measured in a UV-based host-cell reactivation assay in individuals with basal cell carcinoma and cutaneous melanoma (Li *et al*., 2009). Several studies have reported an age-associated decline in NER (Moriwaki & Takahashi, 2008), which could result in an accumulation of damage.

The etiology of BCC (Basal Cell Carcinoma) is still unclear but appears to be of multifactorial origin, resulting from a complex interaction of both intrinsic and extrinsic factors. UV radiation (UVR), and especially UVB, is responsible for the majority of cutaneous damage and is believed to be the primary established risk factor in the development of BCC (Gallagher and Lee, 2006; Oberyszyn, 2008)) Constitutional factors include gender, age, immunosuppression and genetic predisposition (family history of BCC, genetically inherited nucleotide excision repair [NER] defects such as xeroderma pigmentosum [XP]). Also, pigmentary traits, such as fair skin, blond or red hair, light eye colour, tendency to sunburn and poor tanning ability (skin Type I), have all been associated with a higher risk of BCC (Green *et al.,* 1996).
These predisposing factors of BCC were reviewed by Dessinioti *et al*., 2010.

Figure 3: *Complex interplay of factors implicated in sporadic basal cell carcinoma (BCC) in pathogenesis (cited from Dessinioti et al., 2010)*



People with pale skin, red hair, freckles and an inability to tan—the 'red hair/fair skin' phenotype—are at highest risk of developing melanoma, compared to all other pigmentation types (Rhodes *et al.,* 1987). Genetically, this phenotype is frequently the product of inactivating polymorphisms in the melanocortin 1 receptor (MC1R) gene. MC1R encodes a cyclic AMP-stimulating G-protein-coupled receptor that controls pigment production. Minimal receptor activity, as in red hair/fair skin polymorphisms, produces the red/yellow pheomelanin pigment, whereas increasing MC1R activity stimulates the production of black/brown eumelanin (Valverde *et al.,* 1995). Pheomelanin has weak shielding capacity UVR relative to eumelanin, and has been shown to amplify UVA-induced ROS reactive oxygen species) (Rouzaud *et al.,* 2005, Wenczl *et al.,* 1998; Hill and Hill, 2000). Unlike non-melanoma skin cancers, melanoma is not restricted to sun-exposed skin and ultraviolet radiation signature mutations are infrequently oncogenic drivers (Curtin *et al.,* 2005). Although linkage of melanoma risk to UVR exposure is beyond doubt, UVR-independent events are likely to have a significant role (Rhodes *et al.,* 1987) (Elwood and Jopson, 1997). Mitra *et al.,* 2012 experiment suggest that the pheomelanin pigment pathway produces UVR-independent carcinogenic contributions to melanoma-genesis by a mechanism of oxidative damage. Further, Morgan *et al*. 2013 envisaged two possible mechanistic pathways. First, pheomelanin might generate reactive oxygen species that directly or indirectly cause oxidative DNA damage. Second,

pheomelanin synthesis might consume cellular antioxidant stores and make the cell more vulnerable to other endogenous reactive oxygen species.

Summary mechanistic studies

Many mechanistic studies, mainly *in vitro* with human derived (tumour) cell lines and skin biopsies, underpin the outstanding importance UV-induced (UVA and UVB) molecular and cellular events which are involved in human photocarcinognesis (non-melanocytic skin cancer and malignant melanoma).

A UVA/B signature mutation pattern could be identified. Importantly, from a mechanistic point of view, UVA has been shown to be at least as much involved as UVB in processes leading to DNA damage and mutation induction. UV-signatures could be detected in a wide range of genes involved in photocarcinogenesis. New findings, using sophisticated methods in genome sequencing, support this view.

In the last years, increasing evidence has been collected that epigenetic changes, which play a crucial role in (skin-) cancer induction and development, are also induced via UVA/B. This highlights, furthermore, the importance of the effects of UV on several regulation mechanisms involved in human photocarcinogenesis.

7.4 Other cancers

7.4.1 Internal cancers

It has been hypothesised that vitamin D levels may have a favourable impact on incidence of internal cancers and on all-cause or cancer mortality; some groups even advocate increasing vitamin D status through exposure to sunbeds (IARC, 2008).

The IARC monograph (2012) reviewed five studies of use of indoor tanning devices with internal cancers, specifically breast cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, and multiple myeloma. They report that most studies found little evidence of an association. Two studies observed inverse associations between the use of tanning devices and non-Hodgkin lymphoma, and one study with Hodgkin lymphoma. The IARC suggest that possible confounding with exposure to natural sunlight cannot be ruled out in any of these studies.

Two more recent cohort studies have investigated cancer incidence in relation with exposure to sunbeds.

The Swedish Women's Lifestyle and Health cohort followed prospectively 49,261 women aged 30 to 49 years at enrolment in 1991 to 1992 for 15 years (Veierod *et al*., 2003, 2010). During follow-up 2,303 incident cases of cancer were diagnosed within the cohort (breast: 1,053, ovary: 126, lung: 116, colon-rectum: 133, and brain: 116). No associations were found between any cumulative measure of UV exposure (sunbathing vacations and/or sunbed use) at ages 10 to 39 years and overall cancer risk, except for the category of sunbathing vacations between ages 10 and 29 years in which an inverse association was found (HR: 0.70, 95% CI: 0.53–0.93) when compared with women who never went on such vacations. Reduced breast cancer risk consistently appeared among women who spent one week or more per year on sunbathing vacations between ages 10 and 29 years (HR: 0.56, 95% CI: 0.36–0.89), or who used sunbed between ages 10 and 39 years (HR: 0.87, 95% CI: 0.73–1.05 for sunbed use in one decade, and HR: 0.63, 95% CI : 0.41–0.96 for sunbed use in two or three decades), after controlling for the

other risk factors. No other associations were found between sunbed use at ages 10 to 39 years and cancer risk (Yang, Veirod *et al*., 2011).

The Nurses' Health Study II (NHS II) cohort study established in 1989 and enrolled 116,678 female registered nurses aged 25–42, and residing in the United States. In the 2005 questionnaire, participants self-reported frequency of sunbeduse during high school/college and between ages 25 and 35 years (none, 1–2 times/year, 3–5 times/year, 6–11 times/year, 12–23 times/year, and 24+ times/year). Eligible cancer cases consisted of women with incident cancers diagnosed any time after the baseline up to the 2009 follow-up cycle. Only pathologically confirmed invasive cancer cases were included, except for breast cancer, which included both invasive and *in situ* cases. During 20-year follow-up of 73,358 female nurses from 1989 to 2009, a total of 4,271 cancer cases (excluding skin cancers) were diagnosed. The first primary cancers for which at least 100 cases were diagnosed were breast cancer (n=2,779), thyroid cancer (n=306), colorectal cancer (n=186), non-Hodgkin lymphoma (n=185), and endometrial cancer (n=100). No association was found between sunbeduse and risk of total cancers (multivariable-adjusted HR, 0.99; 95% CI, 0.95–1.04 for every 4 times/year use on average during high school/college and at ages 25–35). In addition, no association was found for the risk of any individual major cancers, such as breast cancer, thyroid cancer, colorectal cancer, non-Hodgkin lymphoma, or endometrial cancer (Zhang *et al*., 2013).

With the exception of a negative association for breast cancer in the Swedish cohort (and not in the NHS II cohort), no association was found between sunbed use in adolescence and/or early adulthood and cancer risk.

7.4.2 All-cause mortality

Only one study evaluated whether sunbed use could reduce the risk of death from any cause (Yang *et al*., 2011). This study was an analysis of the Swedish part of the Norwegian-Swedish Lifestyle and Health women's cohort study (Veierod *et al*., 2003, 2010, 2014). Among the 38,472 women followed for 15 years a total of 754 deaths occurred: 457 due to cancer and 100 to cardiovascular disease. The risk of death was not reduced for women using sunbeds; in fact it was even the reverse as solarium use one time or more per month during two or three decades of life between 10 and 39 years of age was associated with an increased all-cause mortality (HR= 1.9, 95% CI 1.3-2.7) for solarium use during two or three decades compared to women with no solarium use. Such increased risk was also reported for cancer (HR 1.4 (1.1–1.8) for solarium use during one decade, and 1.6 (1.0–2.8) for solarium use during two or three decades) and a non-significant increased risk of death from cardiovascular disease.

The analysis could adjust only for a limited number of factors: education, smoking, physical activity, alcohol drinking and body mass index. It cannot be ruled out that other confounding factors could have played on the risk of death from any cause (access to care, behaviour, comorbidities...).

7.4.3 Ocular melanoma

The SCCP report (2006) reviewed four studies published up to 2005 assessing the relationship between sunbed use and ocular melanoma and found varying degrees of association, providing "some evidence" that sunbed use is associated with ocular melanoma, more especially for first use under 21 years, with a significant trend for duration of use. A new case-control study published since 2006 is reviewed below.

In an hospital-based case-control study from Germany, data on sunlamp/sunbed use was obtained from 459 cases of incident primary uveal melanoma diagnosed at one single clinic in Germany (age: 20–74 yrs.), 827 population controls (selected from list of residence, matched 2:1 on age (5-yr age groups), sex and region) and 187 sibling controls (matched 1:1 by age (+/− 10 yr) and sex when possible) (Schmidt-Pokrzywniak et al. 2009). Exposure was assessed by self-administered postal questionnaire and computer-assisted telephone interview. Regular sunlamp/sunbed use was positively associated with ocular melanoma (OR = 1.3; 95% CI 0.9–1.8), the odds ratio being greater when exposure started at a younger age: OR> 20 yr = 1.3 (95% CI 0.9–1.9), OR< 20 yr = 1.7 (95% CI 0.8–3.6). OR calculated with sibling controls were somewhat higher (2.1), but with wider confidence intervals and non-significant. (It should be noted that this study found little evidence of association between personal sun exposure and ocular melanoma.)

Summary

With the exception of a negative association for breast cancer in one cohort no association was found between sunbed use in adolescence and/or early adulthood and internal cancer risk. The current evidence on all-cause mortality does not suggest a decreased risk with sunbed use and the only available cohort study suggests an increase of risk of death from all cancers taken together. A new paper confirms the SCCP Opinion of an association of sunbed use with ocular melanoma, with the risk increased when exposure started at a younger age.

7.5 Risk characterization (dose response in humans and animals by age and other factors)

Risk of skin cancers (melanoma and non-melanoma) attributable to sunbed exposure

The contribution of exposure to sunbeds to skin cancer incidence is far from being negligible.

Based on 88 records reporting a prevalence of indoor tanning, Wehner *et al*. (2014) calculated the population proportional attributable risk and estimated that more than 450 000 non-melanoma skin cancer cases and more than 10,000 melanoma cases each year are attributable to indoor tanning in the US, Europe, and Australia.

Using published emission spectra from sunbeds to quantify the increased risk of SCC induction according to pattern of use and background sunlight exposure, Tierney *et al*. (2015) estimated that by age 55 years, the risk of squamous cell carcinoma induction from exposure to median UV levels [176 standard erythemal dose (SED) per year] in addition to median baseline sun exposure level (166 SED year + 85.5 SED per year holiday) between the ages of 20 and 35 years from a sunbed is increased by 90% (RR 1.9). A higher sunbed exposure (302 SED per year; 20–35 years of age) produced an RR value of 2.8 (180% increase) at 55 years of age.

In France, Boniol, Coignard *et al*. (2012) estimated the attributable fraction (AF) from prevalence data reported in the 'Baromètre cancer 2010' (Léon *et al*., 2012), and from the relative risk of an update of the IARC meta-analysis. The authors estimated that of 7532 new cases of cutaneous melanoma diagnosed each year, 347 (4.6%), of which 76% are women, could be attributed to sunbed use. Under the assumption that cases

attributed to sunbed have the same prognosis as other cases, between 19 and 76 deaths from melanoma annually could be attributed to sunbed use.

By using prevalence data from surveys and data from GLOBOCAN 2008, in 2008 in the 15 original member countries of the European Community plus three countries that were members of the European Free Trade Association, it was estimated that in Europe, of 63,942 new cases of melanoma diagnosed each year, an estimated 3,438 (5.4%) may be related to sunbed use, women representing most of this burden with 2,341 cases (6.9% of all melanomas in women). And about 498 women and 296 men may die each year from a melanoma as a result of being exposed to indoor tanning (Boniol *et al*., 2012).

Although the increase in melanoma risk due to sunbed use may appear modest in the general population (+15%, according to the 2006 IARC report), most of the risk concentrates in the population that started sunbed use before the age of 35 (+75%, according to the 2006 IARC report, and up to more than +200% for frequent use in the 10–39 years period – Veierod *et al*., 2010). Thus, the fraction of risk attributable to sunbed use in patients diagnosed with a melanoma before the age of 30 may be very high: 76% in Australia (Cust *et al*., 2011), and 43% in France (Boniol *et al*., 2010).

8. OPINION

ANSWERS TO TERMS OF REFERENCE

In this Opinion, the term "sunbed" refers to all types of UV tanning devices for cosmetic purposes.

1. *Does new scientific and medical evidence (collected over the past decade) have a significant impact on the conclusion of the previous SCCP Opinion of 2006 {sccp_o_031b.pdf} with regard to the general health and safety implications relating to the exposure of people to UV radiation (UVR)? If yes, what are the key elements to be considered and how is the health of users of tanning devices for cosmetic purposes (sunbeds) likely to be affected (both positively e.g. vitamin D regulation and negatively, e.g. skin and ocular melanoma).*

There is no difference in the biological (and general health) effects induced by UV-radiation in respect to their origin, the natural solar UV or artificial UV from e.g. tanning devices. UV-radiation (UVA, UVB, UVC) from the sun or from tanning devices has been classified by IARC (2009) as carcinogenic to humans (class 1, IARC). During the last decade there is, furthermore, increasing evidence that UVA (the main spectral component in usual tanning devices) is at least as mutagenic as UVB. It has been shown that UV radiation introduces specific mutations in human genes which drive ("driver genes") the induction and development of skin cancer. UV-radiation does not only introduce genetic mutations but also epigenetic alterations, which act in concert with genetic lesions to lead to skin cancer. There is evidence that UV-radiation is a main risk factor for ocular melanoma:

Although there is evidence that the fraction of UV-B emitted from sunbeds can induce vitamin D production. There is widespread consensus that it is not necessary to use sunbeds to enhance vitamin D levels even in winter. Short (minutes to half of an hour) daily exposures to solar UV of unprotected (e.g., no sunscreens applied) face and hands have been shown to build up and restore sufficient levels of vitamin D.

In addition to the knowledge about the immune-suppressing effects of UV-B, there is now evidence for an immune suppressive effect by UV-A in the wavelength range from 350 – 390 nm exposure to UV-A and UV-B contribute to photoaging.

There is consistent evidence from meta-analyses, case-control studies and cohort studies of a significantly increased risk from cutaneous melanoma associated with sunbed use, with a dose-response with increasing number of sessions and increasing frequency of use. The three most recent cohort studies showed an increase in melanoma risk associated with sunbed exposure at a younger age. In addition, since all analyses have been adjusted for host factors such as tendency to sunburn, hair colour, and for sun exposure, they also suggest that sunbed use adds a specific risk of melanoma independently from individual susceptibility and behaviour in the sun. Moreover, it was estimated that in Europe 5.4% of incident melanoma cases may be related to sunbed use, this fraction being much higher in melanomas arising before the age of 30 (43% in France, 76% in Australia). Although based on a smaller number of studies than for melanoma, there is consistent evidence from meta-analyses and individual studies that

indicates that sunbed use is also a risk factor for squamous cell carcinoma and to a lesser extent for basal cell carcinoma, especially when exposure takes place at a younger age.

2. *Does SCENIHR uphold the assessment of the SCCP that the limit value of the Erythemally-weighted irradiance of 0.3 W/m^2 (equivalent to an UV index of 12) ensures sufficient levels of protection for the health and safety of users? If this is not the case, please specify if it is sufficient to give specific information. If it is not sufficient to provide information, please specify the limit values above which adverse health effects can occur.*

Because of the evidence on the carcinogenic effects of sunbed (tanning devices) UV and the nature of skin cancer induction (no threshold levels of UV-irradiance and UV–dose are known), no limit value of either irradiance or dose (irradiance x time of exposure) can be given to ensure protection for the health and safety of the users of tanning devices.

3. *What should be the wavelength range for which the total Erythemally-weighted irradiance should be negligible (e.g., under 0.003 W/ m^2) to minimise the risks of developing skin cancer due to the use of sunbeds?*

There is international agreement that any contribution of UVC (200-280 nm) or UVC including vacuum UV (100-200nm) should not exceed effective irradiance levels higher than 0.003 W/m² in a tanning device. Evidence shows that the DNA molecule in cells absorbs UV-radiation with maximal efficacy at a wavelength of 254 nm. Absorption at this wavelength leads to high rates of mutagenicity and cell death. Reducing the UVC irradiance level below 0.003 W/m² (which corresponds to 1% of maximal irradiance in a tanning device; 0.3 W/m²) does not mean, however, that this limitation leads to "safe" irradiation from a sunbed because, even in the almost complete absence of UVC, there still remain the carcinogenic effect of UVB and UVA.

Since there is no threshold for adverse long-term health effects, there is therefore also no safe limit for any irradiance over the entire spectral range of UV radiation.

9. RECOMMENDATIONS FOR FURTHER WORK

There is a large body of consistent evidence which has established the adverse health effects and the absence of beneficial effects associated with the use of sunbeds. New studies would therefore not be a priority for future work.

10. MINORITY OPINION

none.

ABBREVIATIONS AND GLOSSARY OF TERMS

AF	Attributable fraction
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
BCC	Basal cell carcinoma
CPD	Cyclobutane pyrimidine dimers
CPD	cyclobutane pyrimidine dimer
CPDs	DNA photoproducts
DMBA	7,12-dimethylbenz(a)anthracene
HGF/SF	the hepatocyte growth factors/scatter factor
IARC	International Agency for Research on Cancer
IR	infrared radiation
NER	Nucleotide Excision repair
NER	Nucleotide excision repair
NMSC	Non melanoma skin cancer
NRPA	National Radiation Protection Authority
PTCH	Patched gene
SCC	Non-melanoma skin cancer
SCCs	squamous cell carcinomas
SCTs	spindle cell tumours
SED	Standard erythemal dose
SHH	Sonic hedgehog
SMO	Growth-promoting smoothened
TERT	Telomerase reverse transcriptase
TPA	12-o-tetradecanoylphorbol-13-acetate
XP	xeroderma pigmentosum

Definition of terms used in the report:

Action spectrum - efficiency of inducing an effect by UVR in dependence of its wavelength

Dose - cumulated amount of absorbed UVR power

Effective irradiance – irradiance of electromagnetic radiation weighted according to a specific action spectrum

Irradiance – UVR intensity (power density) incident on a reference area

ANNEX 1

Literature review on biological effects of ultraviolet radiation relevant to health with particular reference to sunbeds for cosmetic purposes

The purpose of the literature review was to provide the SCENHIR with scientific literature papers to help them perform the assessment of the scientific evidence concerning the biological effects of ultraviolet radiation relevant to health with particular reference to sunbeds for cosmetic purposes.

Method

The terms used in the searches are included in the table below. The searches covered the period from 2006 to the present.

Term	Number of hits
Sunbeds	95
sunlamps	36
tanning booths	7
maximum ultraviolet radiation (UVR)*	21
standard erythema doses	67
malignant melanoma*	21
basal cell carcinoma*	45
eyes irritation	27
eyes conjunctivitis	23
Cataracts*	3
actinic keratosis	159
contact hypersensitivity	98
immediate pigment darkening	10
infrared radiation	62
minimal erythema dose	179
matrix metalloproteinases*	2
psoralen plus UVA*	5
reactive oxygen species*	8
squamous cell carcinoma*	46
sun protection factor, based on UVB absorbance	209
solar simulating radiation	25
urocanic acid	64

xeroderma pigmentosum*	3
risk assessment*	24
Attributable risk fraction	1
Prevalence*	197
UVR AND neoplasms	206
UVR AND Immune function	37
UVR AND mood	46
UVA AND neoplasms*	20
UVA AND immune function	41
UVA AND mood	78
UVB And neoplasms*	23
UVB AND immune function	99
UVB AND mood	109
UVC AND neoplasms	50
UVC AND immune function	7
UVC AND mood	16

An initial search was carried out for (ultraviolet) AND (UV), with a date limited of 1/1/2006. The combination was used as the initial number of hits with this was only slightly smaller than the sum of separate searches with ultraviolet or UV. This was used as the basis for the searches with the terms in the table.

Where the number of hits for the specific term combined with the basic search was around 200 or less then the results were retained for screening (the numbers for these are included in the table). For a number of the terms, those marked as "*" in the table, the numbers were much higher. Following discussion with the secretariat, it was agreed that the results for these terms would be combined with three additional terms – sunbeds, sunlamps and indoor tanning. The numbers for the terms marked "*" in the table are the result of applying these additional terms.

The types of documents required are peer reviewed articles, journal entries, book chapters, government funded publications etc. Bibliographic information and abstracts has been obtained for the search results as above. The abstracts were reviewed to identify documents relevant to the Opinion. If there was any uncertainty about the relevance, the document was included in the results.

The results were presented as tables of bibliographic information divided into three sections:

- The first containing papers where artificial sources of UV exposure appear to be the main or a major part of the content.
- The second containing papers which relate to the effects of UV in more general terms.
- The third section containing papers dealing with exposure to UV.

ANNEX II

Prevalence of sunbed use among adults in Europe, USA and Australia

Country	Period	Age (years)	Sample size	Sample source	% sunbed use	Reference
Europe						
France	September 28 - October 20, 2011	≥ 18	1,502 (787 female, 715 male)	Nationwide telephone survey (quota method). 9209 contacted, participation 16,3%	10 (current or past users) 14,5 (female) 5.0 (male) (mean age at 1st use: 27.6 y) 18.9 (female <50 yrs) 5.1 (male <50 yrs) 15.6 (skin phototype 1 and 2)	Grange *et al*. 2015
Germany	2012	14-45	4,851	National telephone survey	39.2 (ever users) 24.7 (past users)	Schneider *et al*. 2015

					14.6 (current users)	
Italy (Romagna)	June-August 2011	Not specified	4,703	Questionnaires distributed and collected at information points in 22 bathing locations and 3 public spaces. (91% response rate)	20 (overall prevalence) 22 (women) 16 (men) 22 (<35 y.o.) 17 (older)	Stanganelli *et al*. 2013
France	April 3 – August 7, 2010	15-75	3,359	National telephone survey (fixed line and mobile) "Baromètre cancer 2010" (acceptation rate 60%)	13.4 (ever use) 19.4 (women) 7.1 (men) 3.5 (use in the last 12 months) 5.0 (women) 2.0 (men) 13.7 (women 20-25 y.o.) 6.1 (men 20-25 y.o.)	Benmarhnia *et al*. 2013
Denmark	2007 - 2009	15-59	13,229 6,049 M	Population based annual web and telephone surveys (following a campaign in March	*Recent users* (past 12 mo.): March 2007: 29.9 (21.8 (M), 35.9 (F))	Køster *et al*. 2011

			7,180 F 15-19: 1,359 20-29: 1,958 30-39: 3,049 40-49: 3,552 50-59: 3,301	2007)	Aug. 2007 : 27.8 (17.2, 35.3) Aug. 2008 : 26.7 (17.5, 35.4) Aug. 2009 : 23.3 (16.7, 30.1) *Age* (Ma 2007; Aug 2007; 2008; 2009) 15-19: 50.3; 47.4; 44.2; 32.9 20-29: 46.7; 45.4; 37.6; 31.5 30-39: 30.6; 30.8; 27.9; 22.0 40-49: 25.7; 22.3; 22.6; 22.5 50-59: 17.8; 15.8; 14.6; 13.8	
USA						
USA (Chicago)	June-August 2010	Not specified	301	Parents with a child 9-16 y.o. attending 3 pediatrics practices (87% participation: 93% mothers, 7%	49.5 (use in the last 12 months)	Cohen *et al*. 2013

				fathers)		
USA	2011 2010	≥ 18 18-34	315 1,857	Data from 2011 national Youth Risk Behaviour Survey (YRBS) of high school students Data from 2010 National Health Interview Survey (NHIS) for adults aged 18 to 34 years.	*non-Hispanic white female high school students:* 43.8% [95%CI: 36.0-52.0] (use in the previous 12 months) 29.97% [95%CI: 23.0-37.8] (frequent use ≥ 10 times in the previous 12 months). *non-Hispanic white women:* 24.9% (use in the previous 12 months) 15.1% (frequent use ≥ 10 times in the previous 12 months). Highest use among 18-21 y (31.8%), lowest among 30-34 y (17.4%).	Guy *et al*. 2013
USA	2008	≥ 18	NHIS : Approx. 20,000- 40,000 adults	Data from National Health Interview Surveys (NHIS) and Health Information National Trends	Use in the past 12 mo.: NHIS: 15.2 HINTS: 9.0	Buller *et al*. 2011

			HINTS : Approx. 7,000 adults	Survey (HINTS)		
Australia						
Australia, Brisbane			2,867	Cross-sectional survey among office workers	2.5 (over 12 months)	Gordon *et al*. 2012

ANNEX III

Prevalence of sunbed use among teenagers in Europe, USA and Australia

Country	Period	Age of interviewed people (years)	Sample size	Sample source	% sunbed use	Reference
Europe						
Denmark	September 2010	14-18	6,059	Adolescents attending 56 continuation schools randomly chosen among schools where smoking was either prohibited (employees and pupils) (n=26) or allowed (n=30).	38 (used at least once the last 12 months)	Bentzen *et al*., 2012
Denmark	2007 - 2009	15-19	1,359	Population based annual web and telephone surveys (following a campaign in March 2007)	*Recent users* (past 12 mo.): (Ma 2007; Aug 2007; 2008; 2009) 50.3; 47.4; 44.2; 32.9 *Age at first use*	Køster *et al*., 2011

					(% ever sunbed users): (Ma 2007; Aug 2007; 2008; 2009) <13 y.o. : 13; 17; 13; 8 13-15 y.o. : 75; 70; 65; 65 16-18 y.o. : 13; 13; 22; 27	
Denmark	August – October 2008	8-18 8-11 12-14 15-18	1871 (864 M, 1007 F) 725 693 453	'Sun survey' (random digit dialing, followed by mailed questionnaire)	Recent sunbed use (past 12 months): 16.5 8-11 y.o.: 2 12-14 y.o.: 13 15-18 y.o. : 43 (Note : more frequent among girls than boys)	Krarup *et al*., 2011
France	April 3 – August 7, 2010	15-75	3,359	National telephone survey (fixed line and mobile) "Baromètre cancer 2010" (acceptation rate 60%)	<18 y.o.: 3.5 (ever)	Benmarhnia *et al*., 2013

France	December 2011	11-17 (mean age: 13.5)	713 (male / female: 1.1)	Students of two middle and high schools from a typical city of the middle class French population, Paris suburbs.	4.5 (ever) 1.4 (past year)	Tella *et al*., 2012
Great-Britain	February 2008-April 2009	11-17	3,509 3,101 (England)	National prevalence study and six cities. Children were interviewed as part of the Youth Omnibus Survey after the weekly Adult BMRB	*National Prevalence Study*: 6.8 : Great Britain (ever) 13.6 (95% CI 9.7-17.5) Scotland 10.6 (6.0-15.2) Wales 5.9 (5.0-6.7) England *England* 6.0% (95% CI 5.1-6.8) ever 8.6 (7.2-10) girls 3.5 (2.6-4.4) boys	Thomson *et al*., 2010

					11.2 (9.5-12.9) 15-17 years 1.8 (1.2-2.4) 11-14 years Note: Sunbed use higher in lower social grade (7.6) and in the North (11) *Six Cities* 20.0 (17.5-22.4) Liverpool 18.0 (15.6-20.3) Sunderland	
Italy	January 2011	16 – 19	191 (74 M, 117 F)	Students "selected" from a high school in Naples	40 (ever)	Fabbrocini *et al*., 2012
United Kingdom **(Sandwell)**	2012	15-17	407	Survey in 5/22 schools	1.7 (95% CI = 0.7-3.9, n = 5)	Lee *et al*., 2013
USA						
USA	2009-2011	Not reported	Not reported	Representative sample of high	*2009*	Basch *et al.,*

				school students Data from the CDC's Youth Risk Behaviour Surveillance System	25.4 (Female) 6.7 (Male) 37.4 (White female) 7.0 (White male) *2011* 20.9 (F) 6.2 (M) 29.3 (White female) 6.2 (White male)	2014
USA	2009-2011	≤14 ≥18	25,861	2009 and 2011 high school students national Youth Risk Behaviour Surveys (YRBS)	2009: 25.4 (22.4-28.6) Female 6.7 (5.6-8.0) Male 2011: 20.9 (17.6-24.7)) Female 6.2 (4.8-7.8) Male	Guy *et al*., 2014
USA	2011	14-18	2,527	Data from 2011 national Youth Risk Behaviour Survey (YRBS) of high school students	*Non-Hispanic white female* *Students, 14-18*	Guy *et al*., 2013

					y.o.: 29.3 (95% CI 25.1-33.9) (use in the previous 12 months) 16.7 (13.4-20.7) (frequent use ≥ 10 times in the previous 12 months).	
USA	n.d.	18-24 (mean age: 19.98)	551	Survey among college students from a large university in north-eastern US	39.6 (ever users) 87.6% women	Banerjee *et al*., 2012
USA (North Carolina)	2010	Not reported	487	Self-administered study in 5 eastern North Carolina community colleges	12.7 current users 24.5 past users (79% women)	Neenan *et al*., 2012
USA	Not	Not reported	153	On-line survey. Undergraduate	60 (recent indoor	Basch *et al*.,

(Western New York)	reported		(response rate 90.8 %, n= 139)	students	tanning)	2012
USA (East Tennessee)	October 2008 - May 2009	21.8 (mean age)	360 (participation rate 90%, n=325; follow-up n = 296)	Randomly selected college students contacted by e-mail, from East Tennessee State University.	26.01 (event tanners) 14.2 (regular tanners)	Hillhouse *et al*., 2012
USA	February – May 2009	≤14 - ≥18 ≤14 15 16 17 ≥18	14,590 (7,314 F ; 7,219 M) 1,471 3,827 3,705 3,755 2,305	Data from 2009 national Youth Risk Behaviour Survey (YRBS) of high school students	Past 12 months : % (95% CI) Overall: 15.6 (13.7 – 17.6) F: 25.4 (22.4 – 28.6) M: 6.7 (5.6 – 8.0) *By age:* ≤14: 9.7 (7.7 – 12.2) 15 : 12.0 (10.1 – 14.1) 16 : 14.9 (12.7 – 17.4) 17 : 19.1 (16.8 – 21.7) ≥18: 22.0 (19.0 – 25.4)	Guy *et al*., 2011

					Frequent use (>10 times/y) among tanners: 49.1 (45.6 – 52.6) F: 51.7 (47.6 – 55.7) M: 40.1 (32.7 – 48.0)	
Australia						
Australia	2003-2004 2006-2007	12-17 12-14 15-17 12-17 12-14 15-17	699 (358 M; 340 F) 351 348 652 (334 M; 319 F) 329 324	National skin cancer prevention survey (summer 2003/04 and 2006/07). Randomly selected households with a landline telephone.	*2003-2004* Ever use : 3.4 (M:2.8; F:3.8) Past 12 months: 1.2 (M: 0.3; F: 2.3) *2006-2007* Ever use: 2.5 (M: 1.5; F: 3.4) Past 12 months: 0.6 (M: 0; F: 1.3)	Francis *et al*., 2010

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