DOI: 10.1111/jdv.15314 JEADV

SUPPLEMENT ARTICLE

Sunbeds and carcinogenesis: the need for new regulations and restrictions in Europe from the Euromelanoma perspective

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Abstract Experimental investigations have definitely assessed that ultraviolet A (UVA) as well as ultraviolet B (UVB) radiation induce mutagenic DNA photoproducts and other cell damages with a carcinogenic potential. Artificial tanning increases significantly the lifetime risk for basal cell carcinoma, squamous cell carcinoma and melanoma particularly in subjects with fair skin type, subjects with a history of skin cancer or frequent childhood sunburn or if exposures took place at an age younger than 18 years. In addition, experimental and clinical evidence indicate that UVA exposure promotes skin photoageing. Therefore we are dealing with a recreational activity (for customers) and a profitable business (for the tanning industry) with human costs, i.e. an increase in morbidity and mortality by skin cancer, and health and social costs leading to an increased expenditure by the European national health systems. In a few European countries, legislation has recently prohibited the use of sunbeds for minors, pregnant women, people with skin cancer or a history of skin cancer and individuals who do not tan or who burn easily from sun exposure. However, this legislation seems to be insufficient from a photobiological perspective, and importantly, it is largely disregarded by consumers and tanning industry. Therefore the Euromelanoma group proposes a new, more stringent regulation for the tanning industry and restrictions for customers, particularly for those individuals with constitutional and anamnestic risk factors. Finally, we ask for an enhanced commitment to increase the awareness of the general population on the risk of artificial tanning.
Received: 20 March 2018; Accepted: 20 September 2018

Conflicts of interest

None.

Funding sources

None.

Introduction

Since the early 1980s, tanning beds became more and more popular and the tanning industry accredited them of a 'safe' tan.[1,2] However, it is now well established that ultraviolet A (UVA), as well as ultraviolet B (UVB), have skin carcinogenic and photoageing potentials. Furthermore, the use of sunbeds does not meet other putative claims of positive health effects, e.g. the protection from damage of subsequent sun exposure[3] and a significant and persistent increase in vitamin D levels.[4]

The present paper aims to update the knowledge on the detrimental health effects of artificial tanning in order to improve the general awareness of risks and to emphasize the need for a new, more stringent European Union (EU) regulation.

Sunbeds

The most popular artificial UV sources belong to two distinctly different types. The fluorescent lamps with a low-intensity emission with an emission spectrum that is dependent by the fluorescent phosphors coating the inner walls of the thin glass tube and the high-pressure lamps with high-intensity broadband UV emission that is confined in the wanted spectral interval by cut-off glass filters placed in front of the lamp.

In 1995, the Commission Internationale de l' Eclairage (CIE)[5] classified UV lamps into four types according to the emission spectrum weighted with the efficacy spectrum for erythema (Table 1). Therefore, the CIE- EN 60335-2-27 regulation classifies light sources according to the risk of sunburn of a single exposure and not to the carcinogenic hazard of single or repeated exposures at doses lower or above the erythema threshold.

In both type 1 and type 2 light sources, the percentage of UVA is usually 98.5–99% of the total output.[6] Those sunbeds are commonly used in suntan salons, and the overall UVA irradiance of some tanning beds can be 10–15 times greater than

Table 1 Limits of effective irradiance for UV type classification of the Commission Internationale de l' Eclairage (CIE)

UV type appliance	Effective irradiance (W/m^2)	
	250 nm < λ <320 nm	320 nm < λ <400 nm
1	<0.0005	≥0.15
2	0.0005–0.15	≥0.15
3	<0.15	<0.15
4	≥0.15	<0.15

λ is the wavelength of the radiation.[5]

that provided by outdoor exposure to natural sunlight.[7,8] These lamps usually have mean unweighted UVB irradiances lower than that provided from natural summer sun (at latitudes from 37 °S to 35 °N).[8] However, the UVB content is often greater than 0.8%, and therefore, the contribution of UVB to the overall DNA damage and erythematogenic effect is biologically predominant on that of UVA.[9] In addition, when the fluorescent lamps age through prolonged operation, their emission spectrum shifts towards a higher UVB content. In order to limit the UVB irradiance, the revised standard EN 60335-2-27:2013[10] established that appliances should have a total effective irradiance not exceeding 0.003 W/m^2 for wavelengths between 200 and 280 nm. UV type 3 sources are characterized by a low effective output in the UVA and UVB range, and they are freely accessible in the mass market for home tanning. However, it is clear that they could become threatening if the consumer does not respect the suggested duration and number of exposures.[11] Finally, the use of UV type 4 sources should be limited to medical administrations, e.g. UVB phototherapy, under medical supervision. However, sunbeds with higher (>1.5%) UVB levels have been manufactured to speed up the tanning process, and they belong to the CIE type 4 as far as the effective UVB output is calculated.[8]

Photobiology of UV wavebands

Ultraviolet photons are absorbed by skin chromophores like nucleic acids, lipids and proteins, and all of them have a characteristic absorption spectrum that is the relative plot of the sensitivity to absorb photons at specific wavelengths. UV radiation is considered being a complete carcinogen, and the first step is the mutagenic change in DNA.[12] DNA pyrimidine bases are primarily chromophores for UV radiation.[13,14] Upon DNA photoexcitation a direct anaerobic photochemical change in two adjacent bases takes place leading to the formation of cyclobutane pyrimidine dimers (CPD), mainly thymine dimers and pyrimidine (6-4) pyrimidone photoproducts (6-4 PP), which make up 65% and 35% of the DNA photoproducts, respectively.[15] CPDs are responsible for a considerable fraction of the mutations induced by sunlight in mammalian cells. If the nucleotide excision repair system fails to restore genomic integrity, C (cytosine) → T (thymine) mutations and CC → TT tandem mutations at di- or multipyrimidine sites occur. These canonical mutations are unique to the mutagenic UV activity, and therefore, their detection permits inference backward from mutations to mutagen.[14] Once they were called UVB signatures or fingerprint mutations, but it became clear in the meantime that they can also be generated by UVA, although with approximately 1000 times lower efficiency,[13,14] through additional different mechanisms: directly, after the formation of oxidative DNA damage or after the transfer of energy from oxidized non-DNA endogenous chromophores such as porphyrins, flavins and NADH/ NADPH.[15,16]

Furthermore, UVA enhances the mutagenic impact of DNA photoproducts because it causes oxidative damages of the proteome, including the DNA repair enzymes, thus impairing the protective, anti-mutagenic and reparative responses of the damaged cells.[17] In addition, UVA-induced reactive oxygen species (ROS), e.g. superoxide anion, hydroxyl anion and peroxide, produce 8-hydroxydeoxyguanosine (8-OHdG) that causes G (guanosine)-T transversions[18] and induce other types of DNA damage with a mutagenic potential such as protein-DNA cross-links, thymine glycols and single and double DNA strand breaks leading to the loss of genetic material.[19]

The high *in vivo* biological danger of UVA is related also to its deep skin penetration that increases the probability to damage DNA of keratinocyte stem cells and biologically active melanocytes.[20] Both UVA and UVB, even at suberythematogenic levels, can also favour skin carcinogenesis via local and systemic immune suppression[21,22] through the production and release of immunosuppressive cytokines, such as TNF-α or IL-10,[23] the emigration of Langerhans cells from the skin, the immigration of Cd11b positive dendritic cells, the depletion of natural killer cells[24] and the production of regulatory T cells.[25–27] For a long time, UVB has been thought to be the major immunosuppressive waveband, but, more recently, it has been demonstrated that UVA accounts for approximately 75% of natural sunlight-induced immune suppression.[28]

The molecular mechanisms, by which UV radiation leads to immune suppression are abundant and include DNA damage,[29] cell membrane damage (formation of PAF-like biolipids)[30] and trans-urocanic isomerization.[31]

Health hazard of sunbeds

The main detrimental effects of artificial tanning can be classified schematically into short-term, i.e. sunburn and tanning, and long-term, i.e. solar ageing and skin carcinogenesis.

Sunburn

Sunburns are not rare with artificial tanning because super erythematogenic UVA doses are frequently sought by customers aiming to achieve an immediate 'burned' appearance.[32]

The absorption spectrum of DNA and the action spectra of sunburn and squamous cell carcinoma (SCC) are quite

superimposable for wavelengths above 280 nm[13] suggesting that DNA damage is the main responsible for both.[13] In these action spectra, an UVB photon is approximately 1000 times more efficient than an UVA photon at 330 nm[33] but, in the action spectrum of sunburn, there is evidence for a distinct peak in the UVA range at about 360 nm.[33]

Obviously, this peak becomes very relevant following the exposure to high dosages of artificial UVA.

DNA damage is also responsible for tanning via the p53-induced stimulation of the production of proopiomelanocortin that, in turn, generates the release of melanocyte-stimulating hormone.[34] Therefore tanning is a form of stress response of the skin, as well as erythema, and overall, it is induced more efficiently by UVB than UVA.[35] However, unlike fair skin, the action spectra of erythema and tanning diverge in melano-competent skin in the UVA range, and therefore, even suberythematogenic UVA can tan these subjects.[35]

Squamous cell carcinoma (SCC)

At the molecular level, UVA, like UVB, can cause the same C→T mutations that are the hallmarks of UV-induced SCC.[14] In addition, human SCC samples have a high frequency of UVA-induced DNA lesions, such as oxidative base damage and single-strand breaks.[36]

Mutations affecting genes that encode proteins or enzymes involved in cell cycle control, apoptosis, e.g. p53 and RAS oncogenes, or DNA repair are particularly important for carcinogenesis because they persist with a clonal multiplication of keratinocytes through subsequent cell divisions.[37,38]

Therefore, there is a progressively abnormal gene expression from normal keratinocytes over sun-damaged skin to actinic keratosis (AK), that is considered the biological precursor of SCC and, finally, to invasive SCC.[39] The biological basis of the progression of only a minority of AKs to invasive SCC is still unknown although a possible explanation is that focal UV inactivation of NOTCH pathway in fibroblasts can lead them to acquire a cancer-activated fibroblast (CAF)-like state with a reduced production of elastin and collagen and increased secretion of fibroblast growth factors, extracellular matrix proteins and proteases. This in turn results in increased proliferation of the overlying epidermal keratinocytes.[40]

Subjects who use tanning beds are 1.4–13.4 times more likely to develop SCC after adjustment for confounding factors such as age, sex, eye and hair colour, skin type, ethnicity and sun exposure.[32] A systematic review and meta-analysis[32] has provided the estimation that more than 6200 invasive SCCs per year could be caused by indoor tanning in selected Western and Northern countries.

Basal cell carcinoma (BCC)

In the pathogenesis of BCC, the key events are the mutational inactivation of the PTCH1 gene or the activation of SMO gene that thereby lose their control activity on the hedgehog signal transduction pathway.[41] UV fingerprints predominated in the PTCH mutation spectra of 48% of BCC, and the rate was even higher in early-onset BCC (first lesion at age <35 years) and multiple BCC (>10 lesions) in comparison to regular BCC (first lesion at age >35 years and <10 lesions).[42] Unlike in SCC, mutations at p53 or other pro-apoptotic genes are found only in a smaller portion of BCC and their contribution to the development of the later tumour is at present unclear.[42]

An increased BCC risk by 15% was detected for tanning bed users with an exposure frequency of four times per year or more, and the risk was 73% and 28% higher for sunbed use during high school or college and in the age between 25 to 35 years, respectively.[43]

Furthermore indoor tanning increases the risk for early-onset BCC by 69% in subjects younger than 40 years of age[44] and by 60% in subjects younger than 50 years of age.[41] The hazard moreover rose with the duration and frequency of tanning as well as the use of high-pressure tanning beds.[44] In addition, a strong association for early-onset BCCs occurring on the trunk and extremities, sites less likely to receive high doses of natural UV radiation was reported in the sunbed users.[44]

Cutaneous malignant melanoma (CMM)

Pathogenesis of CMM of chronically exposed skin [lentigo maligna melanoma (LMM)] and CMM of intermittently exposed skin [superficial spreading melanoma (SSM) and nodular melanoma (NM)] appears to have divergent pathways.

Superficial spreading melanoma and NM have a high mutational load with a very high number of mutations with UV signatures.[45] However, it still remains to be clarified why known oncogenic mutations in melanoma, including BRAF, CDKN2A and NRAS have frequent mutations that are unrelated to sun exposure in a large proportion of lesions.[45,46] A possible explanation is that mechanisms other than the CPD mutation-driven inactivation of tumour suppressor genes may be more relevant.[47] It has been suggested that CPDs have the potential to elicit epigenetic responses that result in shifts from transient to permanent changes in melanocyte gene expression patterns.[48]

Ultraviolet A can contribute to overall CPDs formation,[14] and furthermore, it can cause a delayed and reduced repair of this damage thereby amplifying the mutagenic potential.[49] Oxidative DNA damages are particularly dangerous in melanocytes because they have a high susceptibility to develop them via oxidation of both eumelanin and phaeomelanin[50,51] and, at the same time, they have a reduced capacity to repair oxidative DNA lesions.[52] It is of great concern that the oxidative genotoxic effect of chemiexcited melanin lasts for several hours after the end of exposure.[53]

Lentigo maligna melanoma has a lower prevalence of mutant BRAF than SSM and NM with 30–40% showing mutations in KIT or NRAS, and a considerable proportion

likely to have mutations in as yet undiscovered oncogenes. Unlike NM and SSM, LMM primarily affects the chronically sun-exposed skin and it is often associated with solar lentigines, actinic keratoses and non-melanoma skin cancers.[54] Together, these findings suggest that LMM require high cumulative doses of UV radiation to develop, and therefore, subjects with a high cumulative number of sunbed exposures seem particularly at risk. Beside DNA damages, UVA may contribute to promotion of CMM via growth factor release,[55] induction of matrix metalloproteinases, possibly via a Warburg-like effect,[56] the intracellular degradation of collagen by cathepsin K[57] and immunosuppressive effects.[28]

Meta-analyses of several epidemiological and case–control studies have found that the usage of tanning salons leads to a 1.25-fold risk of CMM[58] with a significant correlation with parameters like 'first exposure as a young adult' (risk of 1.69) and 'longest duration or highest frequency of exposure',[58] a 1.34 risk with 10 tanning sessions,[59] a 1.11 risk with at least four sessions per year[43] and a 1.59 risk with exposure before the age of 35 years with an increase in risk by a factor of 1.8 for each additional tanning session a year.[60] Artificial tanning at home seems even more dangerous than indoor tanning exclusively in suntan parlours; the risks were 4.14 vs. 1.82, respectively, in comparison to non-users.[61]

Photoageing

Ultraviolet A, and particularly UVA1 (340–400 nm), plays a substantial role in photoageing because it can penetrate the upper dermis targeting fibroblasts leading to ROS-induced damage of lipids and amino acids, release of arachidonic acid, activation of secondary cytosolic and nuclear messengers (that activate UV response genes) and upregulation of metalloproteinases which directly break down collagen and elastic tissue and inhibit repair.[62]

Ultraviolet A exposure, even at low doses, results also in an accumulation of mutations in mitochondrial (mt) DNA, namely the so-called 4977-bp common deletion and a 3895-bp deletion in dermal fibroblasts.[62,63] These deletions together with the disruption of the mitochondrial electron transport chain decrease the generation of ATP from ADP leading to the distraction of the mitochondrial function (the so-called 'defective powerhouse' model). In a vicious cycle, this leads to an increased production of ROS, thereby initiating retrograde signalling responses that are directed from the mitochondria to the nucleus activating nuclear transcription of genes, such as MMP-1 and COL1A1.[64]

In comparison to natural sunlight, it has been calculated that the photoageing effect of 1 MED from UVA sunbeds is 2–4 times larger than that of the same physical solar dose.[8,9] In addition, UVA1 tanning does not prevent further collagenolytic changes from environmental exposures in lightly pigmented individuals.[65]

Governmental actions and conclusions

Together, the recent experimental, clinical and epidemiological findings have provided stronger and stronger evidence to support more intense warning against use of tanning beds. Beside damage to human health, the deleterious effects of the suntan industry cause an increment of the total expenditure for diagnosis and treatment of skin tumours and photoageing for consumers and national health systems.

Both the National Institutes of Health (NIH), in 2005,[66] and the International Agency for Research on Cancer (IARC), in 2007[67] and 2009[68] have classified UVA tanning devices as carcinogens for humans In 2014, the Food and Drug Administration (FDA) officially reclassified sunlamps from a class I (low risk) to a class II (moderate risk) devices.[68]

The growing awareness of health authorities enacted governments of several countries to promote current restrictions on customers and regulations on the indoor tanning industry.[43,69,70]

Nowadays, legislation bans sunbeds entirely in Brazil and Australia and prohibits the use for minors, pregnant women, people with skin cancer or a history of skin cancer and individuals who do not tan or who burn easily from sun exposure in several European countries, including UK, Italy, Spain, Portugal, Denmark, France and Germany, nine of the 10 provinces of Canada and 41 US states.[71–78] In addition, adequate information for users and technical preparations for workers are recommended.

However, the present regulations show main limitations from a photobiological perspective. Indeed, in spite of the suggestions of the World Health Organization,[9] the use of tanning is discouraged but it is not banned for individuals with many (>25) nevi, freckles or a history of frequent sunburns during childhood and adolescence or individuals under treatment with photosensitive drugs or with clinical signs of photoageing.[72] Furthermore, there is no regulation of the maximal dose of a single exposure and the personal maximal cumulative dose during a year or a longer period of time.

However, we emphasize with great concern that there is not a careful application of the present, albeit insufficient, legislation and the regulations are widely disregarded by consumers and the tanning industry pointing out that controls by health authorities are often poor.[76,79,80]

Two recent surveys from Italy[79] and Germany[80] have found that consumer guidance in tanning studios is not properly given, the labelling of the sunbeds fails to comply in at least 20% of the cases, and the maximum EWI values for sunbeds are frequently violated.[76]

However, we must take into account that even if careful and regular controls are needed, some controls, such as the limitations on the emission spectrum and irradiance of lamps, are impossible to control without expensive equipment that is not usually available for peripheral control facilities.

In 2017, the World Health Organization published a catalogue of interventions that have should be used to reduce risks associated with artificial cosmetic tanning and to guide policy makers that are considering the development or revision of regulations relating to sunbed use.[81,82]

However, it is clear that health surveillance is easier and more efficient in those countries such as Brazil and Australia that have simply completely banned the use of sun beds.

Therefore, on behalf of the Euromelanoma Group, we strongly recommend that better controls and more restrictions are put into action.

Acknowledgement

The authors are very grateful to Dr. H.N. Ananthaswamy, Houston, TX, for critical reading of the manuscript.

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