Effects of artificial UV radiation not relevant to skin carcinogenesis

Cutaneous diseases

Skin ageing

Skin ageing is a phenomenon comprising intrinsic processes that are largely genetically determined and extrinsic ageing (or photo-ageing) that is largely related to sun exposure (Jenkins, 2002). Both UVB (Del Bino *et al.,* 2004) and UVA (Marrot *et al.,* 2004) are held to be mediators of these effects. Intrinsic ageing is characterized by thinning of the skin accompanied by reduction in collagen levels. These changes are thought to result at least in part from diminished cellular proliferative activity in the skin (inevitable cellular senescence) and from increased expression of enzymes that degrade the collagen, such as the metallo-proteinases (Jenkins, 2002). The process is undoubtedly complex, and one of the drives to cellular senescence may be chronic exposure to oxidative stress.

The changes resulting from sun exposure that are perceived as ageing are loss of elasticity, pigmentary change and deep wrinkling (Leyden, 1990). Most of these changes result from damage to the dermis, which is visible histologically as elastotic material. This material is comprised of degenerate elastic fibres and newly synthesized dysfunctional elastotic material. Similarly there appears to be a reduced amount of collagen I in the dermis and increased amounts of degenerate collagen. The metallo-proteinases mediate this degradation, at least in part, and their activity appears to be increased both by age and by sun exposure. Increased age is associated with a diminished ability to repair damage induced by exposure to UV radiation (Takahashi *et al.,* 2005).

Comparatively few epidemiological studies have addressed photo-ageing of the skin, not least because of the difficulties of measuring it accurately. Some authors have suggested that ultrasound measurement is of value (Gniadecka & Jemec, 1998); others have used silicone (Green, 1991; Fritschi *et al.,* 1995) to create moulds to allow an estimate of the topography of the skin, a method which appears to be better evaluated. A large study performed in Queensland, Australia demonstrated premature ageing of the skin in a population excessively exposed to the sun (Green, 1991). This was more marked in men who reported outdoor work or leisure, and especially those with fair skin. The presence of photo-ageing was correlated with skin cancer. The relationship between non-melanoma skin cancer and solar keratoses is held to be clear and straightforward (Green *et al.,* 1999). Experimental studies on UV exposure and photo-ageing have been reviewed (IARC, 1992).

Very few studies have investigated the relationship of artificial UV exposure to ageing in humans. Lentigos similar to PUVA freckles have been reported to be induced by exposure to tanning appliances (Roth *et al.,* 1989; Kadunce *et al.,* 1990), which is of concern given the evidence that the risk for skin cancer is increased in PUVA patients. A number of case reports have described an extreme form of cutaneous ageing which resulted from very frequent exposure to tanning appliances in fair-skinned people (Poh-Fitzpatrick & Ellis, 1989). There have been no informative epidemiological studies of the role of indoor tanning facilities in the induction of photo-ageing.

There is some evidence that cigarette smoke exacerbates photo-ageing of the skin (IARC, 2004; Placzek *et al.,* 2004).

Other skin diseases caused or exacerbated by exposure to UV radiation

A wide variety of dermatoses are exacerbated by sun exposure, such as atopic eczema or psoriasis if sunburn occurs. Some skin diseases are directly provoked by sun exposure, the most common of which is polymorphic light eruption, which is common in women. It has been reported in around 20% of healthy women (Millard *et al.,* 2000). Variants occur, such as a blistering eruption seen on the ears in childhood or actinic prurigo, where itchy papules and nodules develop after sun exposure. Such photodermatoses are a nuisance but otherwise relatively trivial problem. Exposure to tanning appliances may precipitate such dermatoses (O'Toole & Barnes, 1995). Medical use of artificial UV radiation may be used to control polymorphic light eruption if used carefully as a means of desensitization.

Photosensitivity is usual in patients with lupus even in the absence of a history of a sun-evoked eruption (Sanders *et al.,* 2003), and light testing reveals that the majority of patients react to both UVA and UVB (Sanders *et al.,* 2003). The cutaneous manifestations of lupus are also commonly precipitated by exposure to the sun. Phototesting with artificial UV radiation sources has been reported to provoke cutaneous lupus (Marguery *et al.,* 2005), and therefore it seems likely that it may also be provoked by other sources of artificial radiation such as tanning appliances.

More significant photodermatoses occur more rarely, such as chronic actinic dermatosis, in which persistent sun-induced eczema occurs. It is a rare condition, usually seen in elderly men. It may develop from an allergic dermatitis for example to pollen or fragrances.

Much more significant are the porphyrias in which sun exposure may trigger photosensitivity. The varieties that induce photosensitivity are variegate porphyria (Mustajoki, 1980) (most common in South Africans of Dutch descent), erythropoietic porphyria (Goerz, 1979) and porphyria cutanea tarda (PCT). PCT is the most common and in 80% of cases occurs because of exposure to estrogens or alcohol. Use of indoor tanning facilities or other artificial UV sources — even fluorescent lights — by patients with latent porphyria is potentially very serious as a result of the possible induction of sunburn.

The overall dose of UVB and UVA incurred by most people using bright light therapy is likely to be considerably less than that received by psoriasis patients treated with PUVA. Exposure is also likely to be limited to the face. It seems likely therefore that the theoretical risk will relate to non-melanoma skin cancer rather than melanoma, but there are no relevant data from epidemiological studies at present to inform. It would seem very reasonable however to conclude that lamps emitting low levels of UVA would be preferred to those emitting higher levels.

Case reports also suggest that use of indoor tanning facilities is associated with development of drug-induced photodermatoses and exacerbation of lupus erythematosus (Spencer & Amonette, 1995).

Drug-induced photosensitivity

A variety of commonly used drugs increase cutaneous sensitivity to the sun and to artificial UV sources, and are predicted therefore to increase the risk for skin cancer. Most drugs have a phototoxic effect rather than a photo-allergenic one (Moore, 2002). Oral photosensitisers include tetracyclines, amioderone, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs) and chlorpromazine (Moore, 2002). Diuretics, antibiotics and NSAIDs are very widely used drugs, and their phototoxic effects therefore have the potential to affect a significant proportion of the population. Topical agents include plant-derived photosensitisers (psoralens) such as bergamot, widely used in perfumed products. Use of perfumes has the potential to increase the photo-damaging effects of indoor tanning appliances.

Effects on the eyes

Cataract

Conditions linked to sub-chronic and chronic exposure to solar UV include pterygium and SCC affecting the cornea; cataract, affecting the ocular lens; and acute macular degeneration affecting the retina (Tomany *et al.,* 2004). Of these, cataracts of the nuclear and cortical types are the most widespread and serious UV-related eye conditions. There is an inverse association between latitude of residence and cataract surgery in Medicare program data from the USA (Javitt & Taylor, 1994), and epidemiological studies conducted in Australia, China, and the USA (see Taylor, 1994, for review) support a role of UV exposure in cataract development. Risk for cortical cataract (opacity of the outer lens) is related to increasing cumulative UVB exposure, while risk for nuclear cataract (opacity of the central lens) has been shown to be significantly increased with increasing UV exposure in young adulthood, consistent with the successive laying down with age of outer lens fibres on the cortical layer exposed in earlier life (Neale *et al.,* 2003). With regard to artificial UVB, there is sufficient experimental evidence that exposure causes cortical lens opacity in the eyes of laboratory animals (IPCS, 1994).

Intraocular melanoma

Early-life exposure to sunlight may be important in the development of intraocular melanoma (Tucker *et al.,* 1985; Seddon *et al.,* 1990), more specifically of choroidal melanoma (Moy, 2001). This is consistent with the observation that after childhood most UV radiation is screened by the lens (Zigman, 1983; Lerman, 1984).

Welding equipment and tanning appliances are sources of intense UV radiation. Five out of eight epidemiologic studies found a significantly increased risk for ocular melanoma with welding exposure, with relative risks ranging from 1.9 to 10.9 (Tucker *et al.,* 1985; Holly *et al.,* 1990; Seddon *et al.,* 1990; Siemiatycki, 1991; Ajani *et al.,* 1992; Holly *et al.,* 1996; Guenel *et al.,* 2001); in contrast, one study conducted in nine European countries found an increased risk only in one country (Lutz *et al.,* 2005).

Four case–control studies have examined the risk for intraocular melanoma in relation to exposure to UV radiation from sunlamps (Table 19). While the earliest study only found a non-significant trend in risk according to frequency of sunlamp use (Tucker *et al.,* 1985), the three more recent studies consistently found an increased relative risk, ranging from 1.7 to 3.6 (Holly *et al.,* 1990; Seddon *et al.,* 1990; Vajdic *et al.,* 2004).

UV exposure and vitamin D

Vitamin D is an essential nutrient, generally quantified by measuring circulating levels of 25-hydroxyvitamin D. There are three major sources of vitamin D: photosynthesis in the skin, ingestion in the diet and oral supplementation. Worldwide, photosynthesis from sunlight is the most common source of vitamin D.

Vitamin D formation by photosynthesis

Previtamin D3 is produced from 7-dehydroxycholesterol (provitamin D_3) by the direct photolytic action of UVB. The precursor, 7-dehydroxycholesterol, is abundant in human skin although levels decrease with age (Holick *et al.,* 1989). On exposure of the skin to sunlight, 7-dehydroxycholesterol in epidermal and dermal cells absorbs UVB radiation to form previtamin D_3. Previtamin D_3 is thermodynamically unstable and is rapidly transformed by rearrangement of its double bonds to form vitamin D_3 (here called vitamin D) before entering the circulation. Vitamin D is a prohormone that is converted by 25-hydroxylation in the liver to the intermediate metabolite 25-hydroxyvitamin D, which is the main circulating and storage form. With physiological demands for calcium and phosphorus, 25-hydroxyvitamin D undergoes 1α-hydroxylation in the kidney to form the active hormone, 1,25-dihyroxyvitamin D. Blood levels of 25-hydroxyvitamin D reflect the availability of vitamin D (Osborne & Hutchinson, 2002).

Main target organs for 1,25-dihydroxyvitamin D include the intestine, kidney and bone, but nuclear receptors have been found in over 30 different tissues, reflecting its many other actions besides parathyroid activity and serum calcium homeostasis, analogous to those of classical steroid hormones. 1,25-dihydroxyvitamin D is also an antiproliferative, prodifferentiation and proapoptotic agent (Osborne & Hutchinson, 2002).

Dietary sources of vitamin D

There are only a few foods (cod liver oil, oily fish such as salmon, mackerel and sardines) that are naturally rich in vitamin D, so in many countries where oily fish are not widely consumed, food fortification or vitamin supplements may be needed. In a global review of vitamin D intake, wide variations were found in food fortification practices and contributions from supplement use

Table 19. Case–control studies of exposure to artificial UV radiation and risk for intraocular melanoma

Reference	Location, Period of Recruitment	Cases and Controls	Age (years)	Adjusted Relative Risk	Characteristics Assessed	Comments
Tucker *et al*. (1985)	Philadelphia, PA, USA, January 1974–June 1979	444 intraocular melanoma (1 hospital) 424 hospital controls with detached retina, matched on age, sex and period of diagnosis	NR	1.4 (0.9–2.2); with cataract: 2.3 (0.9–5.9) without cataract: 1.2 (0.7–2.0)	Eye colour, complexion and hair colour, corrective lenses, sun exposure during leisure time, sun protection, years lived in the South	Telephone interview (45 min.); estimates adjusted for history of cataract; sunlight exposure is an important risk factor for intraocular melanoma (persons born in the South: RR 2.7 (1.3–5.9). Trend in RR according to frequency of sunlamp use rising to twofold for frequent use (P=0.10)
Holly *et al*. (1990)	11 Western States, USA, January 1978–February 1987	407 cases (Ocular Oncology Unit, UCSF); 870 controls (random digit dialling in the same geographic area as the patients), 2 age/sex matched controls per patient	20–74	Exposure to UV or blacklight: 3.59 (1.57–8.70) Welding burn, sunburn to eye, snow blindness: 7.17 (2.5–20.57)	Eye and hair colour, naevi, freckles, tendency to sunburn, other eye conditions, tobacco, coffee, tea, alcohol	Telephone interview; adjustment on eye colour, coffee, effect of 0.5 h exposure to midday summer sun, other UV exposure.
Seddon *et al*. (1990)	New England, USA	197 cases 385 matched population controls (random digit dialling)	17–88	Use of sunlamps: 3.4 (1.1–10.3); with random digit dialled controls 2.3 (1.2–4.3) with sibling controls	Ancestry from Northern or Southern latitudes, latitude of residence, skin colour, naevi	Only choroid and ciliary body melanomas. 2 independent comparisons. Occasional or frequent versus never use.
	all USA	337 cases; 800 sibling controls				
Vajdic *et al*. (2004)	Australia, 1996 –1998	290 cases (246 with melanoma of choroid or ciliary body); 893 population controls (electoral rolls)	19–79	Use of sunlamps: 1.7 (1.0–2.8) Welding: 1.2 (0.8–1.7)	Eye colour, host characteristics, lifetime residence, work calendar, sun exposure, sun protective wear	Population-based prospective recruitment of cases (all ophthalmologists and cancer registries). Telephone interview. Risk increases with increasing duration of use and is greater for exposures begun before the age of 21 years and after 1980. Sunlamp use or welding not associated with iris or conjunctival melanoma.

NR, not reported.

(Calvo *et al.,* 2005). In Canada and the USA, where fortification is mandatory for staple foods such as milk and margarine and optional for other classes of food, vitamin D intake was generally 2–3 μg higher than in either Australia, Ireland, Scotland or the United Kingdom where fortification of staples like margarine and breakfast cereals is optional, or European and other countries where food fortification is restricted. Mean daily vitamin D intakes were reported to be highest in young adult Caucasian men and women in North America (8.1 and 7.3 μg/d) due to milk fortification and in Japanese women (7.1 μg/d) due to high fish consumption. Norwegian men and women, who also have high fish consumption, had higher levels (6.8 and 5.9 mg/d) than their British counterparts (4.2 and 3.7 μg/d). Contributions by dietary supplements to mean daily vitamin D intakes ranged from 49% in Norwegian women to 12% in British men, and on average contributions from supplements increased with age and were more common in women (Calvo *et al.,* 2005).

Vitamin D and exposure to artificial UV radiation for tanning purposes

Available data are inadequate to assess the effect of exposure to UV in indoor tanning facilities on vitamin D status. Our current understanding of the photosynthesis of vitamin D in the skin would suggest that this type of artificial UV exposure would be effective in induction of vitamin D photosynthesis only to the extent that it contains UVB, as opposed to UVA radiation. Practically speaking, the usefulness of these facilities for correcting vitamin D insufficiency is limited by the inability of consumers to ascertain the UVB flux to which they are being exposed in a tanning session, the expense and inconvenience of these sessions compared with oral vitamin D supplementation, and the other health consequences of using these facilities, as outlined in the other chapters of this document.

The nature of the network of photo- and thermoreactions that are involved in vitamin D synthesis in vitro is well established. As measured in vitro the greatest sensitivity of the conversion of 7-dehydroxycholesterol to previtamin D lies in the UVB part of the solar spectrum, 280–320 nm. It is therefore similar to the erythema action spectrum, except for a sharper downturn in provitamin D absorptivity in the UVA spectral region from a maximum at 282 nm (Galkin & Terenetskaya, 1999).

Seasonal and latitude variations in UVB intensity markedly affect vitamin D synthesis, with lowest relative production occurring at high latitudes during winter months. Also, ageing decreases the capacity of skin to produce vitamin D (Holick *et al.,* 1989). Finally, compared with fair-skinned people, those with darkly pigmented skin are less efficient at producing vitamin D and require 10–50 times the level of sun exposure to produce the same amount (Clemens *et al.,* 1982). In addition to season, latitude, ageing, and skin pigmentation, vitamin D photosynthesis may be influenced by factors that affect the intensity of skin exposure to UVB.

For light-skinned adults, a few minutes per day with the face and hands in bright sunshine is sufficient to cover daily needs in vitamin D. Intense UVB exposure may generate little vitamin D beyond that achieved by more modest exposure because previtamin D and vitamin D can readily convert to other photoproducts that have little or no vitamin D action.

Vitamin D and xeroderma pigmentosum patients

A further indication that necessary amounts of vitamin D may be provided through dietary sources comes from a study of patients suffering from xeroderma pigmentosum, a rare disease associated with a deficiency in UV-induced DNA lesion repair (Setlow *et al.,* 1969), and characterized by extreme sensitivity to sunlight (Kraemer *et al.,* 1994). To prevent the development of skin cancers at an early age, these patients wear protective clothing and use sunscreens when outdoors. A six-year follow-up study of eight children with xeroderma pigmentosum showed a normal vitamin D intake and that normal vitamin D levels can be maintained in ambulatory patients despite rigorous sun protection (Sollitto *et al.,* 1997).