The Independent Medical Expert Group (IMEG)

Report and recommendations on medical and scientific aspects of the Armed Forces Compensation Scheme

December 2017

Topic 7 - Recognised Diseases: Ultraviolet Light and Skin cancers

Key Points

1. For a disorder to be a Recognised Disease in the AFCS, we look for evidence that service is consistently associated with an increase in its frequency and whether there are circumstances where the frequency is more than doubled, making it more likely than not in the individual case that the disease was attributable to a cause in service.

2. Skin cancers, the most common cancers in white skinned populations are usually divided into non-melanoma skin cancers (NMSC) and cutaneous malignant melanoma (CMM). The most important types of NMSC are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

   NMSC Basal cell carcinoma (BCC) is commonly called rodent ulcer. The mortality rate is low and they rarely metastasize but they may invade surrounding tissues including cartilage and bone causing significant destruction. Squamous cell carcinomas (SCC) may arise in scar tissue but the majority arise on sun damaged exposed skin, and most commonly in actinic keratosis (AK).

   Cutaneous malignant melanoma. Cutaneous malignant melanoma (CMM) accounts for less than 5% total skin cancers, although the incidence is rising in all parts of the world for which data are available and it leads to 75% of all deaths from skin cancers.

3. By April 2005 public health education on the dangers of sun exposure were well developed including in the UK amongst the military medical services, the chain of command and Service personnel. The avoidance of direct UVR exposure and sunburn, use of suitable protective clothing, sunglasses, and sunscreens, were standard practice.

4. While total cumulative lifetime sun exposure is casually associated with AK and SCC, the evidence is that BCCs are more related to short intermittent burning episodes. Sun exposure plays a primary role and supporting role in most cases of CMM with the pattern of exposure in the sub-types varying. The risk for CMM in older people, developing over many years and of generally lower mortality is as for SCC, i.e. chronic long term excess UV exposure. Superficial spreading melanomas, the most common type in working age adults are related to short sharp episodes of burning exposure especially in youth and adolescence.

5. We conclude that in general none of these circumstances is likely to be met at this date due to AFCS service and so most cases of NMSC and CMM claimed under AFCS will be for rejection. However each case should be considered on its facts.

Introduction

Ahead of the detailed discussion on ultraviolet light and skin cancers we have reproduced the introduction to Recognised Diseases included in the May 2013 IMEG report.

1. Lord Boyce in his review of the AFCS raised the issue that while under the War Pensions Scheme the majority of medical discharge cases suffering from physical disorders receive entitlement to a war pension, this is not the case under the AFCS. This is a reflection of the different standards of proof required in the two schemes. The standard of proof in AFCS is "on the balance of probabilities" (or "more likely than not"), which is the standard of proof in both civil compensation and the statutory compensation scheme for civilian occupational injury and disease, the Industrial Injuries Scheme.

2. At its inception in 1917, the standard of proof used in the War Pensions Scheme was "on the balance of probabilities". This was changed in 1943, at the height of the Second World War, when for injuries and disorders arising in service, the burden of proof transferred to the MOD to demonstrate that a service cause was "beyond reasonable doubt" not the cause of the disease or injury. The change was introduced at this time because inadequate record-keeping was leading to large numbers of claimants unfairly not receiving compensation.

3. In his report, Lord Boyce proposed that the IMEG should develop a list of Recognised Diseases for the AFCS. By this he meant that IMEG should review the medical literature and receive evidence from experts to provide guidance about the circumstances when "on the balance of probabilities", a disease having onset in or around service was more likely than not to be attributable to service in the Armed Forces.

4. The normal burden of proof in civil compensation and other statutory compensation schemes such as the Industrial Injuries Disablement Benefit (IIDB) Scheme is "on the balance of probabilities". For claims under AFCS, this implies demonstrating that military service is more likely than not (more than 50:50) the predominant cause of the injury or disease in the individual case. In the Industrial Injuries Disablement Benefit Scheme, for those conditions where there is sufficient evidence that this level of proof is satisfied, the disease is 'prescribed', i.e. attributable in the individual case to the particular cause in relation to clearly-specified circumstances of exposure.

5. In the individual case, attribution is usually based on sufficient evidence to answer the questions:

    - Does the particular agent or exposure cause the disease, at least in some circumstances?

    - If so, were the circumstances of the individual case such that the agent or exposure is more likely than not to have been the cause of the disease?

6. Recognition of a particular agent as the cause of a disease, and attribution in the individual case, is most clear when the cause is specific to the disease, or nearly so, and the probability of causation is high. Such conditions are now relatively uncommon but a relevant example is occupational asthma, where the primary cause is an agent inhaled at work. The majority of

cases of occupational asthma are due to the development of an allergic reaction to the specific cause encountered in the workplace (e.g. flour in a bakery). Asthma develops after an initial symptom-free period of exposure and recurs on re- exposure to the specific cause, in concentrations which do not cause respiratory symptoms in others similarly exposed or previously in the affected individual. Inhalation testing with the specific agent will provoke an asthmatic reaction in the sensitised individual (but not in others not sensitised). Also, for many agents, evidence of a specific immunological reaction (i.e. specific IgE antibody) will be found. In principle the specific cause of asthma can be demonstrated in the individual case.

7. The majority of diseases, however, are not specific to a particular cause. A particular cause may increase the frequency of occurrence of a disease, which can have other recognised causes. As an example, lung cancer is well known to be caused by smoking cigarettes. More than 90% of cases in the general population occur in cigarette smokers. A smoker of 20 cigarettes a day during adult life will increase his or her chances of developing lung cancer by some twenty-fold. In the case of lung cancer in a smoker of 20 cigarettes a day for 40 years we can say with confidence that it is likely that the lung cancer is attributable to the smoking of cigarettes.

8. However, there are also other causes of lung cancer, such as asbestos and ionising radiation. When are we entitled to attribute lung cancer in an individual to asbestos exposure? The lung cancer caused by asbestos is indistinguishable from lung cancer from another cause, such as smoking, so it has no specific distinguishing features. We have to ask the question: in what circumstances would it be more likely than not that the lung cancer was caused by exposure to asbestos? As the individual case has no distinguishing (or specific) features, we have to look at populations of people exposed in their work to asbestos. Among these, are there any circumstances where the frequency of the disease has increased sufficiently to make it more likely than not in the individual case that the lung cancer would be unlikely to have occurred in the absence of occupational exposure to asbestos? The answer is that, among other circumstances, the frequency (or incidence) of lung cancer was more than doubled in asbestos textile workers, both smokers and non-smokers, who worked for 20 years or more in an asbestos textile factory. In these circumstances we can conclude it is more likely than not the lung cancer is attributable to asbestos.

9. Why is a greater than doubling in the frequency of the disease so critical in determining attribution to a particular cause? We can consider a hypothetical 100 men working in a particular occupation (figure 1). Among these 100 men, as in the general population, the number of new cases of a particular disease is ten each year, i.e. no different:

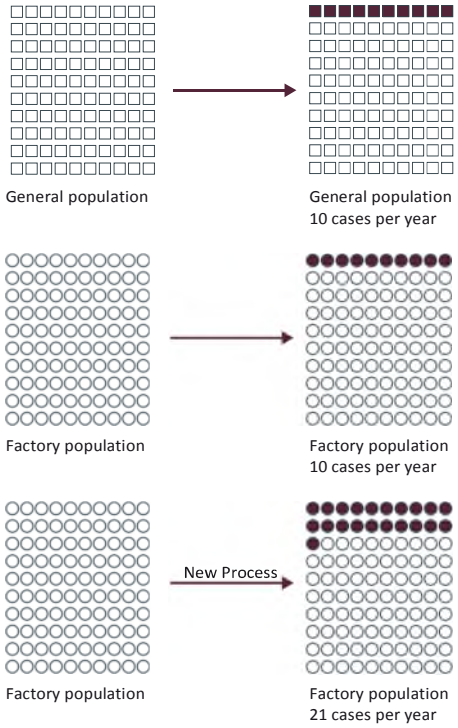

Fig 1. Increased incidence of disease from ten per year to 21 per year in factory population following the introduction of a new process.

Sometime later, after the introduction of a new process, the number of cases of the disease in these 100 men increases to 21 each year, i.e. more than two times the previous frequency. We cannot distinguish the additional 11 cases from the 10 in whom the disease would otherwise have occurred. What we can say is that in any particular individual among the 21 cases, there is a more than 50:50 chance, or a greater than doubling of risk, that the disease would not have occurred without exposure to the particular cause. On the balance of probabilities it is therefore more likely than not that the disease is attributable to the particular cause in the individual case. We can say that 'but for' his working in this factory it is unlikely the man would have developed the disease. The balance of probabilities has shifted to "more likely than not" and in this circumstance the disease can be attributed to the particular cause.

10. In the case of Recognised Diseases in the AFCS, we are therefore looking for evidence that service in the Armed Forces is consistently associated with an increase in the frequency of a particular disease or illness and whether there are circumstances where the frequency is more than doubled, making it more likely than not in the individual case that the disease was attributable to a cause in service.

11. It is also important to distinguish "all or none" diseases from "more or less" diseases. A well-recognised "all or none" physiological condition is pregnancy: one cannot be a bit pregnant. In contrast, many important conditions including high blood pressure, hearing loss and mental health disorders are "more or less" conditions. These have a continuum of frequency of symptoms without a clear distinction subject to expert opinion.

12. The epidemiological evidence informing these determinations should be of high quality, drawn from several independent studies and sufficiently consistent and robust that further research at a later date would be unlikely to overturn it.

Ultraviolet Radiation (UVR) and Skin Cancers

Clinical Issues

1. Skin cancers, the most common cancers in white-skinned populations, are usually divided into non-melanoma skin cancers (NMSC) and cutaneous malignant melanoma (CMM). The most important types of NMSC are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Over the last 50 years the incidence of skin cancers of all types has increased and continues to do so. In Europe, the US and Canada the average increase incidence is about 3-8% a year (1). Precise rates of NMSC are difficult to compute because not all skin cancers are registered, and in some countries data is only collected on all NMSC (undifferentiated into SCC or BCC). Other issues with NMSC estimation include the occurrence of multiple lesions and recurrence. Skin cancers occur both in Caucasian and darker skins where incidence is lower but prognosis often poorer because of delay in detection and diagnosis.

Non-Melanoma Skin Cancers (NMSC)

2. Basal cell carcinoma (BCC) is commonly called rodent ulcer. There are no precursor lesions and the tumour arises from the basal cells of the epidermis and is usually grouped according to histology and clinical course into nodular, micronodular, superficial and morpheaform. The mortality rate is low and they rarely metastasise but the morpheaform and micronodular variants may invade surrounding tissues including cartilage and bone causing significant destruction. BCCs may recur locally. The great majority occur on the head and neck especially in the central section of the face bound by the inner canthus, sides of nose and the forehead. In Australia and other tropical/subtropical sunnier regions they also occur on the trunk and back where they may be multiple.

3. Squamous cell carcinomas (SCC) may arise in scar tissue but the majority arise on sun-damaged exposed skin or in precursor lesions such as Bowen's disease, and most commonly in actinic keratosis (AK). AK is common in white skin on the face, scalp in males and backs of hands in both genders and increases in incidence with age. It develops on sun-damaged skin in the form of raised scaly lesions which may bleed. They are often multiple and it is generally thought that the risk of malignant transformation is low. In the UK, once detected, they are usually treated to prevent development of SCC. It is not known through specific research whether this approach is necessary or cost-effective. It may be difficult to differentiate a large AK from a SCC. Both require similar treatment, surgical excision or radiotherapy. SCC can metastasise and should be followed up after initial treatment.

Cutaneous Malignant Melanoma (CMM)

4. Cutaneous malignant melanoma (CMM) is thought to account for less than 5% of total skin cancers although the incidence is rising in all parts of the world for which data are available (2). Present survival from treated CMM in Europe and the US is about 80% at five years (3) although in the US CMM leads to 75% of all deaths from skin cancer (4). CMM is typically pigmented and may arise in pre-existing naevi (moles). It is divided into four types (5):

    - Superficial spreading – the most common type on white skins accounting for about 70% of cases.

    - Nodular – 15-30% of cases. This may appear anywhere on the body including non-sun exposed sites. Although usually pigmented may be amelanotic. Usually invades the dermis from the start with no apparent horizontal spread. Tends to metastasise.

    - Acral – these make up less than 10% of cases in white skin although more frequent in dark skin. Occurs on palms, soles and nail-beds.

    - Lentigo maligna melanoma – accounts for less than 10% of total CMM and usually diagnosed in older people. Arises in a lentigo maligna and grows superficially over many years before invading the dermis and becoming lentigo maligna melanoma.

5. In men, CMM develops most frequently on the trunk between the shoulders and hips while in women lower limb lesions are more common. The prognosis for thin melanoma (less than 1.5 mm) is good but declines with thickness of the lesion and the associated risk of metastatic spread.

6. The precise aetiology and pathogenesis of CMM and NMSC are not yet understood but there are multiple factors:

    - 2-5% of CMM is familial and work is progressing to identify genetic susceptibility. About a third of CMM families carry mutation CDKN2A on chromosome 9, whose role is to control entry to the cell cycle. This allows damaged melanocytes to proliferate and go on to invade the dermis (6).

    - UVR is a major aetiological factor for CMM (7) with one study suggesting that as many as 65-90% of melanomas are attributable to UVR (8). Although there is a substantial research base investigating the role of UVR in skin cancer in general, particularly CMM, the findings of studies are inconsistent. This relates to study design, reliance on retrospective history, selection of controls and small numbers. There are few cohort studies and all are of short follow-up duration. The larger group of case control studies usually depend on self-recall of UVR exposure with high risk of bias especially in more recent studies, following worldwide campaigns on the dangers of excessive sun exposure. Study controls are often hospital patients and not community-based. In addition studies tend to focus on only one possible

causal factor at a time and do not address possible confounders or interactions e.g. with age and gender, date or pattern of UV exposure.

- Occupational studies – there have been a significant number of occupational studies (9) (10), including military studies (11) (12) but findings are inconsistent (13). This is due to the difficulty in separating out occupational and non-occupational sun exposure. Some studies conclude that outdoor work, e.g. farming, is associated with high risk (14) (15) but negative associations have also been documented (16). Few studies have considered links between CMM and exposure to mineral oils, coal tar, metal working fluids and other agents positively linked with NMSC. Links have been recorded between CMM and high salary earners and professional occupations (17). Using CMM incidence data for 2011 and CMM mortality data for 2012, a recent study calculated the attributable fraction for CMM due to occupational UVR exposure in Britain as 2% (18). This represents about 50 deaths and 250 new cases of CMM annually. Almost half of these deaths relate to the construction industry with agriculture responsible for about a quarter and public administration, defence and land transport accounting for about 10%.

UVR

7. UVR is part of the continuous spectrum of electromagnetic radiation that is sunlight. It is divided arbitrarily into UVA, 315-400 nm, UVB, 280-315nm and UVC, 100-280nm. In terms of skin cancer, natural UVC is not relevant as it is absorbed by the earth's atmosphere but the longer wavelength UVB (1-10% of UVR reaching the earth's surface), and UVA which represents over 90-99% of UVR which might reach the skin are important. UVA can penetrate deep into the skin. Once thought to be innocuous, UVA is now considered very important in carcinogenesis if exposure is prolonged and excessive. UVA causes tanning and skin ageing and leads to indirect damage to DNA through the formation of reactive oxygen species. In turn these cause breaks in DNA, mutations and then cancer. UVB penetrates the upper layers of the epidermis and can cause sunburn, tanning, photoageing and skin cancer much more effectively than UVA through direct damage to DNA. UVC is completely filtered out by oxygen in the atmosphere and the ozone layer and so the main source is not natural sunlight but germicidal lamps where it can cause sunburn and skin cancer (19).

Factors affecting the emission of UVR

8. There are a number of factors that influence the emission of UVR. These include season and time of day. Intensity of UVR is highest in summer and the sun is at its most dangerous between 10.00 and 16.00 when the rays have the shortest distance to travel and UVB levels are at their highest. Latitude is important. The nearer the equator, the higher the UVR exposure. An increase in altitude of 1000m increases UVR intensity by 10-12% (20). Cold, shade and fog reduce UVR levels and snow, sea foam and beach sand can all significantly increase the percentage of UVR reflected on to the skin. Other influences are type of exposure, i.e. chronic as in outdoor occupations, e.g. fishing and agriculture, intermittent or total, i.e. lifetime exposure as well as episodes of sunburn. The increase in skin cancers has been associated with ozone layer depletion caused by chlorofluorocarbons and other ozone - depleting substances. The 2000 Montreal Protocol has led to some regeneration of the ozone layer (21)

Photo protection in the person

9. The natural protection of human skin against the harmful effects of UVR developed millions of years ago and involves the internal conversion of skin molecules (so-called natural photoprotection) which absorb the UV photons, converting them into small harmless amounts of heat. Any UV photon energy which escapes generates reactive oxygen species which may go on to stimulate malignant transformation (22) (23). Skin colour, reflecting epidermal melanin, also provides protection with those with darker skin, and increased eumelanin, living nearer the equator where UVB is highest. The pigment eumelanin is present in all healthy people to an extent and absorbs 99.9% of UVR leaving only a very small fraction of melanin molecules at risk of harmful chemical reactions. As well as **skin pigmentation, skin type** is important. Type 1, freckled skin which tans poorly, is the highest risk category for skin cancer. Another risk factor for skin cancers is the presence of melanocytic **naevi** (moles). These may be congenital or acquired and are common benign neoplasms of complex incompletely understood aetiology. If they are multiple, the risk of CMM is increased. Other influences include a **family history** of CMM, gender, **age at UVR exposure and duration, photoageing changes and gender**. A 2009 multi-centre pooled analysis of about 6000 CMM cases and a similar number of controls looked at CMM sites at different latitudes and concluded that excess sunbathing and total recreational sun exposure increased the risk of CMM of trunk and limbs but not head and neck (24).

10. These factors are all long-standing and they do not explain the rise in skin cancers over the last 50 years. The disease profile suggests that this is much more related to cultural and behavioural changes. Notably, the demand for a tan in Caucasians and changes to employment from rural to indoor work, with paid leave and increased access to international travel, so that white-skinned populations increasingly travel several times a year to much sunnier climes than their genetic endowment envisaged. At the same time artificial tanning sources are now widespread with highly variable types and intensity of UVR output. Overall UVA is usually high relative to UVB. Study findings are conflicting but age at exposure may be important and there is evidence that sunburn at any age, but particularly in youth, may increase the risk of melanoma (25). It is important to bear in mind the therapeutic use of phototherapy and PUVA for dermatological disorders: psoriasis, atopic eczema, mycoses fungoides, and vitiligo, etc. Here the short-term benefits need to be carefully balanced against the undoubted longer-term mutagenic and carcinogenic risks. Sunscreen based on organic chemical absorbers or inorganic physical blockers prevents sunburn but has not been conclusively shown to prevent skin cancer. Some studies actually suggest an increase of CMM while others do show a protective effect. There is some evidence that some ingredients in sunscreens protect against direct DNA damage but increase indirect damage (26) (27).

11. Some further useful insight into the changing incidence of melanoma is provided by a 2007 Swedish study based on the Swedish cancer registry for melanoma by body site for age and gender cohorts over the period 1960-2004 (28). This study aimed to identify behavioural changes as factors influencing the relative distribution of melanoma by body site. In total data were available on 46,337 melanomas. Trends were assessed by establishing CMM incidence per site, relative site distribution per age group and calendar period, taking into account UVR exposure pattern for the different body sites.

12. Between 1960-1964 and 2000-2004 in both men and women the study showed CMM increased most rapidly on the upper limbs (men 885%, women 1,216%) on the trunk (men 729%, women 759%) and on the lower limbs (men 418%, women 289%). The increase in head tumour incidence was slower. Across the lifespan, head tumours were more common in those over 70 years, while for those under 70 years, tumours of the trunk and lower limbs were most common. Trunk tumours formed an increasing proportion of all CMM, especially in females over the period 1960-2004. Looking at the pattern of UVR exposure at the different CMM sites, for the head it is continuous; for the trunk, intermittent, and for the legs probably best described as a mixture. There was no preponderance of naevi in any group or site. The study concluded these findings can best be explained by changed behaviours and much increased intentional intermittent exposure to UVR, with most people having indoor employment for most of the year with low exposure to UVR but short periods of intense UVR exposure through paid holiday entitlement/access to affordable air travel and/or access to artificial sun tanning. In Sweden in 1962 there were 70,000 flights south of the 40th parallel compared with 860,000 in 2004, an increase of 1,229%.

13. The AFCS provides awards for injury and disorder due on balance of probabilities to military service on, or after, 6 April 2005. At that date, public health education on the dangers of sun exposure was well developed, including in the UK, amongst the military medical services and the chain of command and Service personnel themselves. The avoidance of direct UVR exposure and sunburn, use of suitable protective clothing, sunglasses and sunscreens was standard practice. While total cumulative lifetime sun exposure is causally associated with AK and SCC, the evidence is that BCCs are more related to short intermittent burning episodes. Most importantly, in mortality terms sun exposure plays a primary role and supporting role in most cases of CMM with the pattern of exposure in the four main sub-types varying. The risk for lentigo maligna seen in older people, developing over many years and of generally lower mortality, is as for SCC, i.e. chronic long-term excess UV exposure. Superficial spreading melanomas, the most common type, are related to short sharp episodes of burning exposure in younger ages.

Conclusion

14. In general, none of these circumstances is likely to be met due to service on or after 6 April 2005 and so most cases of NMSC and CMM claimed under AFCS will be liable to rejection. However each case will be considered on its facts.

References:

(1) Breitbart, E.W. et al (2006) Effectiveness of information campaigns. Prog. Biophys. Mol. Biol. 92:167-92

(2) Mackie, R.M. et al (2002) Incidence of and survival from melanoma in Scotland. Lancet 360:587-659

(3) Young, C. et al (2012) Occupational cancer in Britain. Skin cancer. Brit. J. Cancer 107:S71-75

(4) Gilchrest, B.A. et al (1999) The pathogenesis of melanoma induced by ultraviolet radiation. N. Eng. J. Med. 340:1341-8

(5) Clark, W.H. et al (1969) The histogenesis and biologic behaviour of malignant melanoma of the skin. Cancer Res. 29:705-726

(6) Walker, G.J. et al (1995) Mutations of the CDKN/p161NK4 gene in Australian melanoma kindreds. Human Mol. Genet. 95: 1845-52

(7) Diegen, T. et al (2002) The epidemiology of skin cancer. Brit. J. Dermatol. 61:1-6

(8) Glanz, K. et al (2007) Reducing ultraviolet radiation exposure among outdoor workers: state of the evidence and recommendations. Environ. Health 6:22

(9) Gawkrodger, D.J. et al (2004) Occupational skin cancers. Occ. Med. 54: 458-463

(10) Fritschi, L. et al (1996) Melanoma and occupation: results of a case control study. Occup. Environ. Med. 53(3):168-73

(11) Kitchener, S. (2012) Ultraviolet Radiation Exposure and Melanoma in Australian Naval Personnel. J. Mil. and Vets' Health. v.19.3

(12) Lea, C.S. et al (2014) Melanoma incidence rates in active duty military personnel compared with a population-based registry in the US, 2000-2007. Mil. Med. 179(3):247-53

(13) Vagero, D. et al (1990) Occupation and malignant melanoma; a study based on cancer registration data in England and Wales and in Sweden. Brit. J. Ind. Med. 47:317-24

(14) Garland, F.C. et al (1990) Occupational sunlight exposure and melanoma in the US Navy. Arch. Environ. Health. 45(5:261-7)

(15) Puntoni, R. et al (2005) Increased incidence of cutaneous malignant melanoma among longshoremen in Genoa, Italy: the role of sunlight and occupational exposure. Occup. Environ. Med. 62(4:270-1) xxx

(16) Elwood, J.M. et al (1997) Melanoma and sun exposure: an overview of published studies Int. J. Cancer 73(2:198-203)

(17) Pion, I.A. et al (1995) Occupation and the risk of malignant melanoma. Cancer 75(2 Suppl): 637-44

(18) Rushton, L. et al (2017) The burden of occupationally-related cutaneous malignant melanoma in Britain due to solar radiation. Brit. J. Cancer 116:536-9

(19) Gandini, S. et al (2005) Meta analysis of risk factors for cutaneous melanoma: 11 Sun exposure. Eur. J. Cancer 41:45-60

(20) WHO (2009) UVR and health

(21) Montreal Protocol on substances that deplete the ozone layer. (1987) revised http://ozone.unep. org/Publications/MP handbook/Section1.1

(22) Peon, J. et al (2001) DNA/RNA nucleotides and nucleosides: direct measurement of excited state lifetimes by femtosecond fluorescence up-conversion. Chem. Phys. Lett. 348:255-62

(23) Young, A.R. (1997) Chromophores in human skin. Phys. Med. Biol. 42:789-802

(24) Chang, Y. et al (2009) Sun exposure and melanoma risk at different latitudes: a pooled analysis of 5700 cases and 7216 controls. Int. J. Epidemiol. 38 (3,814-30)

(25) Westerdahl, J. et al (1994) At what age do sunburn episodes play a crucial role for the development of malignant melanoma? Eur. J. Cancer 30A:1647-54

(26) Xu, C. et al (2001) Photosensitisation of the sunscreen octyl-p-dimethylaminobenzoate b UVA in human melancocytes but not in keratinocytes. Photochem. Photobiol. 73:600-604

(27) Damiani, E. et al (1999) Nitroxide radicals protect DNA from damage when illuminated in vitro in the presence of dibenzoylmethane and a common sunscreen ingredient. Free Radic. Biol. Med. 26: 809-16

(28) Dal, H. et al (2007) Does relative melanoma distribution by body site 1960-2 reflect changes in intermittent exposure and intentional tanning in the Swedish population? Eur. J. Dermatol. 17(5):428-34