

Cutaneous malignant melanoma and occupational exposure to (natural) UV radiation in pilots and aircrew



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Presented to Parliament by the Secretary of State for Work and Pensions by Command of Her Majesty

May 2020

OGL

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Cutaneous malignant melanoma and occupational exposure to (natural) UV radiation in pilots and aircrew

Dear Secretary of State,

The Industrial Injuries Advisory Council (the Council) undertook an extensive investigation into the risks of developing cutaneous malignant melanoma as a consequence of working as a pilot or cabin crew on commercial aircraft. This came about after the Council received correspondence from a worker who developed skin cancer as a result of spending extended periods of time exposed to natural ultra violet (UV) radiation i.e. sunlight. The current list of prescribed diseases includes 'primary carcinoma of the skin' (PD C21) following exposure to arsenic or arsenic compounds, tar, pitch, bitumen, mineral oil (including paraffin) or soot. It does not include skin cancer arising from exposure to sunlight during the course of outdoor working.

Cutaneous malignant melanoma accounts for 3 to 5 percent of all skin cancers and is responsible for approximately 75 percent of all deaths from skin cancer. Persons with an increased number of moles, dysplastic (also called atypical) nevi, or a family history of the disease are at increased risk compared with the general population. Around 15,000 newly diagnosed cases (cancer registrations) of melanoma occur each year in the UK (half in women) and approximately 2,500 deaths. In both sexes the risk rises with age but a little more so in men. The key triggers leading to malignant transformation of melanocytes (the pigment cells of the skin) have yet to be fully elucidated, but are multifactorial and include UV radiation damage and genetic susceptibility.

The investigation carried out by the Council established that the evidence base for an increased risk of the incidence of melanoma in aircrew – both pilots and cabin crew - is consistent and convincing; the pattern of an excess risk has not substantially changed by date of publication over the last 30 years although the exact magnitude varies between studies. An in-depth analysis of the scientific literature of melanoma incidence conclusively demonstrated a consistent doubling of risk for both pilots and cabin crew, and for pilots in particular, after 5,000 aggregated hours' flying time. This corresponds to approximately 5 or more years aggregated duration of employment.

From currently available evidence, the Council concluded that neither cosmic radiation nor occupational exposures to UV during flights are likely to contribute substantially to the excess risk. The most likely causes are:

(i) UV exposure outside the aircraft, but there is uncertainty about the nature and patterns of UV exposure that might occur during non-flight work and during flight stopovers and the potential contribution of exposure during recreational activities, together with;

(ii) disruption of the circadian rhythm through shift work, although the exact relationship of this combination is as yet uncertain.

This Command Paper sets out how the Council arrived at its conclusion and details the evidence it has reviewed. Given the clearly doubled risk, the Council recommends that malignant melanoma in pilots and cabin crew be added to the list of prescribed diseases for which benefit is payable, following 5 or more years' duration of employment.

Yours sincerely

Dr Lesley Rushton

Chair, Industrial Injuries Advisory Council

Cutaneous malignant melanoma and occupational exposure to (natural) UV radiation in pilots and aircrew.

Summary

The Industrial Injuries Advisory Council (IIAC) undertook an investigation into the risks of developing cutaneous malignant melanoma as a consequence of working as a pilot or cabin crew on commercial aircraft. This study was initiated after the Council identified elevated risks of this workforce developing melanoma following its investigation into skin cancer risks following prolonged sun exposure (Information note: Non-melanoma skin cancer and occupational exposure to (natural) UV radiation).

The Council has established there is substantial and consistent evidence that there is more than double the risk of malignant melanoma in pilots and cabin crew, and for pilots in particular after 5,000 aggregated hours' flying time. This corresponds to approximately 5 or more years aggregated duration of employment. The Council has investigated several relevant exposures which this workforce may experience, including ultra-violet (UV) light (the main risk factor for melanoma), that might potentially contribute to the excess risk.

From currently available evidence, IIAC has concluded that neither cosmic radiation nor occupational exposures to UV during flights are likely to contribute substantially to the excess risk. The most likely causes are:

(i) UV exposure outside the aircraft, but there is uncertainty about the nature and patterns of UV exposure that might occur during non-flight work and during flight stopovers and the potential contribution of exposure during recreational activities, *together with;*

(ii) disruption of the circadian rhythm through shift work, although the exact relationship of this combination is as yet uncertain.

Given the clearly doubled risk, the Council recommends that malignant melanoma in pilots and cabin crew be added to the list of prescribed diseases for which benefit is payable, following 5 or more years duration of employment. This report contains some technical terms, the meanings of which are explained in a concluding glossary.

Background

- A former seaman with long service in hot climates developed a basal cell cancer of the skin and contacted the Industrial Injuries Advisory Council (IIAC) to enquire whether he was eligible to make a claim for Industrial Injuries Disablement Benefit (IIDB).
- The current list of prescribed diseases includes 'primary carcinoma of the skin' (PD C21) following exposure to arsenic or arsenic compounds, tar, pitch, bitumen, mineral oil (including paraffin) or soot. It does not include skin cancer arising from exposure to sunlight during the course of outdoor working.
- 3. The Council therefore decided to consider the case for prescription of skin cancer in workers with high exposure to natural UV radiation in the form of sunlight. Although the Council considered that the risks of both basal cell carcinoma of the skin and squamous cell carcinoma of the skin may be increased by outdoor work such as in farming or construction, the evidence from studies in countries at similar latitudes to the UK suggests that outdoor exposures are generally insufficient to increase the relative risk by as much as two. In addition, the contribution of exposure from leisure activities is uncertain. The Council did not therefore recommend prescription for either of these skin cancers in respect of occupational exposure to sunlight.
- 4. However, evaluation of the literature on cutaneous malignant melanoma ('melanoma') and sun exposure during work highlighted evidence that there was a consistent excess in pilots and aircrew. This paper reviews the evidence in more detail.

The Industrial Injuries Disablement Benefit Scheme

- 5. The IIDB Scheme provides non-contributory, 'no-fault' benefits for disablement because of accidents or prescribed diseases which arise during the course of employed earners' work. The benefit is paid in addition to other incapacity and disability benefits. It is tax-free and administered by the Department for Work and Pensions.
- 6. The legal requirements for prescription are set out in The Social Security Contributions and Benefits Act 1992 which states that the Secretary of State may prescribe a disease where he is satisfied that the disease:
 - (a) ought to be treated, having regard to its causes and incidence and any other relevant considerations, as a risk of the occupation and not as a risk common to all persons; and
 - (b) is such that, in the absence of special circumstances, the attribution of particular cases to the nature of the employment can be established or presumed with reasonable certainty.
- 7. Thus, a disease may only be prescribed if there is a recognised risk to workers in an occupation, and the link between disease and occupation can be established or reasonably presumed in individual cases.

The Role of the Industrial Injuries Advisory Council

- 8. IIAC is an independent statutory body established in 1946 to advise the Secretary of State for Social Security on matters relating to the IIDB scheme. The majority of the Council's time is spent considering whether the list of prescribed diseases for which benefit may be paid should be enlarged or amended.
- In considering the question of prescription the Council searches for a practical way to demonstrate in the individual case that the disease can be attributed to occupational exposure with reasonable confidence; for

this purpose, 'reasonable confidence' is interpreted as being based on the balance of probabilities.

- 10. Some occupational diseases are relatively simple to verify, as the link with occupation is clear-cut. Some only occur due to particular work or are almost always associated with work or have specific medical tests that prove their link with work, or have a rapid link to exposure, or other clinical features that make it easy to confirm the work connection. However, many other diseases are not uniquely occupational, and when caused by occupation, are indistinguishable from the same disease occurring in someone who has not been exposed to a hazard at work. In these circumstances, attribution to occupation depends on research evidence that work in the prescribed job or with the prescribed occupational exposures causes the disease on the balance of probabilities. The Council thus looks for evidence that the risk of developing the disease associated with a particular occupational exposure or circumstance is more than doubled (previous reports of the Council explain why this threshold was chosen).
- 11. The health effects arising from occupational exposure to UV light cannot be distinguished reliably from similar effects from non-occupational UV exposure, so the case for prescription rests on research evidence on the causal probabilities.

Introduction

- 12. Cutaneous malignant melanoma ('melanoma') is a cancer of the pigment cells of the skin. Around 15,000 newly diagnosed cases (cancer registrations) of melanoma occur each year in the UK (half in women) and approximately 2,500 deaths. In both sexes the risk rises with age but a little more so in men.
- 13. Melanoma of the skin arises in different anatomic sites in men and women. The trunk (back, abdomen and chest) is the most common in men, accounting for

38%. Melanoma is most commonly found on the legs (including the hips and thighs) in women, accounting for 42%.

- 14. Melanomas may be treated curatively if they are identified early and are excised in their entirety. If identified late they may have disseminated to other sites of the body where they become more difficult to treat successfully.
- 15. Numbers of newly diagnosed melanomas and deaths from melanoma have increased steadily over the last decade; however, survival rates have also been improving with over 90% of cases now surviving up to 10 years after diagnosis (Cancer Research UK 2020).
- 16. The identification of a melanoma and its distinction from a benign naevus ('mole') - requires an expert opinion and often, surgical biopsy. There is strong and consistent evidence that the incidence of melanoma is greater in those from 'higher' socio-economic classes; while this may reflect greater recreational exposure to UV light, it is possibly related also to more ready access to a dermatologist.
- 17. Benign acquired naevi (those that develop after 6 months of age) and atypical naevi are well-established risk factors for melanoma of the skin. Naevi are most likely to be associated with superficial spreading melanoma rather than other types. Congenital naevi (those present immediately at birth) are categorised by size, which corresponds to the malignant potential, thus cutaneous melanoma arising in small congenital naevi is rare.
- 18. The epidemiological evidence for an association is stronger and more consistent for intermittent, generally recreational, exposures to high intensity UV light from the sun. Exposures early in life, and particularly exposures that are intense enough to cause sunburn, carry the highest risks. This is believed to be an explanation for the high proportion of melanomas that arise on the trunk or limbs (rather than head or neck).

- 19. Less consistent is the evidence in relation to prolonged exposure such as might occur in relation to certain outdoor occupations.
- 20. Data for occupational mortality centred round the 2001 census (Occupational Health Decennial Supplement for the period 1991- 2001) shows that, in men and women aged 20-74 years in England, the risk for melanoma was greatest in compositors (in the printing industry) for men, and architects and surveyors for women. In comparison to the previous supplement based on the 1981 census, sales managers, school teachers and aircraft flight deck officers are the only occupations that re-appear, with lower proportional mortality ratios (PMR) in male sales managers and school teachers and higher PMRs in male aircraft flight deck officers and female school teachers. Other outdoor occupations in 2001 showing significantly elevated PMRs, include professional athletes, sports officials, police officers, builders and building contractors (Coggon *et al*, 2009).
- 21. An occupational mortality supplement was not produced for deaths around the 2011 census. However, PMRs for 2001-2010 are available online. There are no deaths for female aircraft flight deck officers or for men aged 65+. However the second highest PMR for men dying aged between 16 and 64 is for aircraft flight deck officers, based on 11 deaths (PMR= 265 95%CI 132-473, standardised for age and social class) (https://www.ons.gov.uk/people populationandcommunity/healthandsocialcare/healthinequalities/adhocs/0079 58occupationalmortalityinenglandandwales2001to2010).

Epidemiological Evidence

22. Since the 1990s, there have been a large number of studies of the health of aircrew, including cabin crew and pilots. These include cohort and case-control studies of mortality and cancer incidence and several reviews and meta-analyses. In addition, there is a large literature on the dosimetry of cosmic radiation, electromagnetic fields, tobacco smoke exposures, cabin air quality including ozone, and fatigue.

- 23. Hammer et al (2009) carried out a comprehensive review of studies of cancer in pilots and cabin crew, including melanoma, up to the end of 2008. They identified 4 meta-analyses for melanoma that included a varying number of studies. All the meta-risk estimates for melanoma were statistically significantly increased, and all but one more than double; Ballard et al (2000), male pilots mortality meta-relative risk (RR) 11.97 (95%CI 1.02-3.82), female flight attendants incidence meta-RR 11.54 (95%CI 0.83-2.87); Buja et al (2005), civil pilots incidence meta-standardised incidence ratio (SIR) 2.18 (95%CI 1.69-2.80), military pilots incidence meta-SIR 1.43 (95%CI 1.09-1.87), male cabin attendants incidence meta-SIR 3.42 (95% CI 1.94-6.06); Buja et al (2006) female flight attendants incidence meta-SIR 2.15 (95%CI 1.56-2.88); Tokumanu et al (2006) female flight attendants incidence meta-RR 2.13 (95%CI 1.58-2.88).
- 24. A later systematic review and meta-analysis of studies published after 2013 included 1 study of both mortality and incidence in pilots (Bland et al 1996) and a further 11 studies in pilots and 2 in cabin crew of incidence only and a further 3 studies in pilots and in cabin crew of mortality only (San Lorenzo et al 2015a). Most of the studies were carried out among northern Europeans. The SIRs ranged from 1.56 to 10.20 in pilots with a summary risk for incidence of melanoma of 2.22 (95% confidence interval 1.67-2.93); the summary risk for incidence from 2 studies of cabin crew was 2.09 (1.67-2.62). The Standardised mortality ratios (SMR) for mortality for pilots ranged from 1.29 to 3.33 and gave an overall SMR of 1.83 (95%CI 1.27-2.63); the overall SMR for cabin crew based on 2 studies was 1.42 (95%CI 0.89 2.26).
- 25. The Council undertook a further search of literature published after 2013.
- 26. Following the study of Icelandic pilots (Rafnsson et al 2000), an extended follow-up identified 7 cases of melanoma (SIR 3.31 1.33-6.81) (Gudmundsdottir et al 2017).
- 27. A pooled cohort of 93,771 cockpit and cabin crew members (the ESCAPE study; European Study of Cohorts for Air Pollution Effects) from 10 countries

including 16,068 UK cockpit crew (the same cohort as reported by Dos Santos Silva et al (2013)) was followed for a mean of 21.7 years during which 5508 deaths occurred (Hammer et al 2014). The overall mortality was strongly reduced in male cockpit (SMR=0.56) and female cabin crews (SMR=0.73). The mortality from malignant melanoma was elevated; male cockpit crew SMR=1.57, (95% CI 1.06-2.25); male cabin crew SMR=1.20, (95% CI 0.45-2.59); female cabin crew SMR=1.17, (95% CI 0.64-1.97). Non-melanoma skin cancer was also raised for male cabin crew SMR=8.01, (95% CI 2.98-17.33).

- 28. A study by McNeely et al (2018) reported an analysis of data from participants (5366) of the Harvard Flight Attendant Health Study who were surveyed in 2014–2015. The prevalence of their self-reported cancer diagnoses was compared to that of a contemporaneous cohort in the National Health and Nutrition Examination Survey (NHANES 2013–2014) using age-weighted standardized prevalence ratios (SPR). Compared to NHANES participants with a similar socioeconomic status (currently employed adults with a family income to poverty ratio of 1 or greater and at least high school education) (n=2729) flight attendants had a higher prevalence of melanoma and non-melanoma skin cancer among females. SPR for these conditions were 2.27 (95% CI 1.27-4.06) and 4.09 (95% CI 2.70-6.20), respectively; males had lower SPRs for melanoma and non-melanoma skin cancers (SPR=1.47, 95% C 0.72-3.01, and SPR=1.11, 95% CI 0.78–1.59 respectively). Job tenure was positively related (non-significantly) to non-melanoma skin cancer among females, with borderline associations for melanoma and non-melanoma skin cancers among males.
- 29. A recent systematic review and meta-analysis of studies of melanoma in pilots and aircrew restricted inclusion to those studies (12) where diagnosis was confirmed histologically (Muira et al 2018). There is thus some overlap of studies with the San Lorenzo meta-analysis; however, more recent papers such as dos Santos Silva are also included. The pooled SIR for melanoma in pilots was 2.03 (95% CI 1.71–2.40) and in cabin crew was 2.12 (95% CI 1.71–2.62). For pilots, the pooled SMR for melanoma was 1.99 (95% CI 1.17–3.40) and for cabin crew was 1.18 (95% CI 0.73–1.89). There was no evidence of study

heterogeneity. Note: the SIR results used in this meta-analysis for the Gudmundsdottir et al (2017) paper were those for 'other pilots' (SIR = 0.98 (95% CI 0.0-5.45) based on 1 case; the SIR for Icelandic pilots was 5.48 (95%CI 2.0-11.9) based on 6 cases and the SIR for all pilots was 3.31 (95% CI 1.33-6.81). It is not clear why Muira et al selected the SIR for 'other pilots' but inclusion of either of the other estimates would cause their meta-SIR to increase.

- 30. A study has been recently reported of all melanoma cases histologically diagnosed among Australian-licensed commercial pilots in the period 2011–2016 and comparison with corresponding population rates using standardised incidence ratios (SIRs) (Olsen et al, 2019). Only 6% were female. Of the male pilots, 114 developed a melanoma (51 invasive, 63 in situ). More than 50% of melanomas occurred on the trunk, and the predominant subtype was superficial spreading melanoma. The SIR for invasive melanoma was 1.20 (95% CI 0.89-1.55) and for melanoma in situ, 1.39 (95% CI 1.08-1.78). The mean age at diagnosis was 49, lower than that in the general Australian population. The nonelevated risks from this study contrast with many from the northern hemisphere. The authors comment that this 'may reflect the varying proportions of occupational versus recreational UV radiation exposure in comparison with pilots residing in higher latitude locations and with lower ambient UV levels, i.e., the contribution of occupational exposure to total UV exposure is likely to be lower for Australian-certified commercial pilots'.
- 31. Melanoma incidence has also been shown to be increased in studies of military personnel. During a 15-year surveillance period, there were 2,233 incident diagnoses of malignant melanoma among members of the active component of the U.S. military (unadjusted incidence rate 1.08 cases per 10,000 person-years (p-yrs) (Brundage et al 2017). Over the 15-year surveillance period, incidence rates (unadjusted) of malignant melanoma among U.S. military members overall increased in an exponential fashion in relation to years of active service. However, unadjusted incidence rates were highest in pilots and crews of fixed-wing aircraft (e.g. fighters, bombers, cargo/personnel transporters) (2.45 per 10,000 p-yrs). In addition, after several years of service, rates of melanoma diagnoses

increased relatively rapidly among pilots and the crews of fixed-wing aircraft and those in occupations inherently conducted outdoors (e.g., infantry, special operations, combat engineers). In contrast, melanoma diagnosis rates increased relatively slowly among healthcare providers and those in "other" military occupations.

Evidence by length of flying time

- 32. The activities of pilots and cabin crew including flight hours, rest periods, and stopovers are highly regulated and are detailed and complex; they depend on international and national regulations, rostering arrangements, industry agreements and individual employment contracts; records are also required to be kept of these activities. These records have been used in some studies to estimate risk by length of service, cumulative flight hours or block hours.
- 33. Flight hours are defined as hours in the air; block hours are flight hours plus the additional time in the plane from the gate at the departure airport until docking at the arrival airport. In the following studies, unless otherwise stated, cumulative time is defined as an aggregate over a defined period.
- 34. It should be noted however that none of the studies below take account of the time worked in pre- and post-flight duties nor the time for travel to and from home or hotel. Pilot pre-flight duties include looking at fuel planning, weather and briefing the crew. Cabin crew also have pre-flight briefing where workload is organised, details about passengers' requirements are outlined and safety and emergency procedures are gone through; cabin crew are questioned about how they would act in certain scenarios. Pilots and cabin crew have to get to the aircraft early enough to complete their checks and start boarding customers to ensure an on-time departure. Most short haul flights have a flight duty period that would start 1 hour before the flight and long haul is typically 90 minutes before. Post-flight duties for pilots include post-flight checks on-board, filing of any paperwork in the office and clearing customs and immigration. Post-flight duties for cabin crew include discussion of on-board issues and situations which have occurred, performance feedback and document finalisation.

- 35. On long haul flights pilots may be able to take up to 45 minutes inflight rest; there is also a requirement for a local night's rest depending on the length of flight and time zones travelled. A general rule is 12 hours or the length of the preceding duty if it was more than 12 hours (https://www.flightdeckfriend.com/ how-many-hours-can-pilots-work-in-one-day/). If an overnight stay is required after a flight before returning home after a suitable rest-period, then it is normal for the airline to arrange this.
- 36. The largest study in the meta-analysis by San Lorenzo et al examined cancer incidence (including 67 cases of melanoma) in a cohort of around 16,000 British flight crew and 3,165 air traffic controllers (ATCOs) who held professional licenses were enrolled in 1989-1990 and followed until the end of 2008 (dos Santos Silva et al 2013). Information held on their occupational health records was supplemented, in 2001, by a postal questionnaire to obtain more detailed information on certain variables, including UV-related exposures; 7,878 responses from pilots and 1,822 responses from ATCOs were returned. Cancer incidence rates among flight crew and ATCOs were compared to those of the UK general population by calculating standardised incidence ratios (SIRs). The SIR for melanoma for flight crew was 1.87 (95% CI 1.45-2.38). The risk of melanoma increased with cumulative flying hours at study entry (categorised into tertiles) and was doubled (SIR = 2.47 95% CI 1.83-3.33) in those with ≥5,500 hours at time of entry into the cohort or ≥11,700 hours at the later time of the guestionnaire. Skin melanoma rates were also increased for ATCOs (SIR = 2.66 95% CI 1.55–4.25). The earlier paper from this study reporting mortality (De Stavola et al 2012) did not have sufficient deaths from melanoma for an analysis by length of flying time. As melanoma and non-melanoma rates were similar between pilots and ATCOs analyses the two populations were combined for analyses that adjusted for risk factors such as type of skin, hair colour, sunburn, sunbathing and use of sunscreens. Type of skin and ever been sunburnt were strong predictors of melanoma. A trend for an increased risk by flying hours was found when mutual adjustment for all these risk factors was carried out but the risk was less than doubled for those with more than 5,000 flying hours (SIR=1.49 95% CI 0.49-4.51); only 44 of the 67 pilots with

melanoma had complete data and were included in this analysis, thus reducing the power.

- 37. The cohort study of Icelandic pilots reported that the risk of melanoma increased with number of flying hours with 5 of the 7 melanoma cases occurring in pilots with more than 10,000 accumulated air hours (SIR 10.29, 95% CI 1.66-197.12) (Gudmundsdottir et al 2017). The SIR for 15+ years employment, based on 5 cases, was 9.55 (95% CI 1.5-187.5).
- 38. The study by McNeely et al (2018) found borderline associations between each five-year increase in net job tenure as a flight attendant for melanoma among males (OR=1.23, 95% CI 0.94-1.61).
- 39. An earlier study in Denmark of cockpit-crew (pilots and flight engineers) from 1943 to 1995 identified 14 cases of skin melanoma (Gundestrup and Storm 1999). Flight hours were calculated cumulatively by type of aircraft based on the individual licence of the cockpit crew. The cohort was subdivided into three subgroups for total flight hours (<1,000, 1,000-4,999 and >5,000), and further into jet (long-haul) and non-jet crew (short-haul). There were 7 observed cases in both jet and non-jet aircraft crews resulting in SIRs of 2.79 (95% CI 1.0-5.2) and 3.11 (95% CI 0.9-4.7) respectively. Overall there was a significant increase in risk (SIR=2.4, 95% CI 1.3- 4.0), which was present in subjects in the highest flight hours' subgroup, >5,000 hours. (Jet: SIR=2.8, n=7, p<0.05 and non-jet: SIR=4.5, n=4, p<0.05).</p>
- 40. A cohort study of 3,700 male pilots registered in Norway (Haldorsen et al 2000) found an SIR greater than 2.0 (SIR 3.1 95% CI 1.6-5.2; 13 cases) in those with more than 10,000 flying hours.
- 41. A similar study by Haldorsen et al (2001) of Norwegian airline cabin attendants found an overall SIR for melanoma of 2.9 (95% CI 1.1-6.4) for males and 1.7 (95% CI 1.0-2.7) for females. There was a non-significant increased risk for melanoma in men and women combined by duration of

employment (p trend = 0.07) with a significant excess for 15+ years of employment, SIR=3.6 (95% CI 1.4-7.3).

- 42. In a joint analysis of over 10,000 people in cohorts of pilots from Nordic countries (Denmark, Finland, Iceland, Sweden, Norway), an SIR for melanoma of 2.55 (95% CI 1.4-4.28) for male pilots with between 5,000 and 9,999 flight hours and an SIR of 3.05 (95% CI: 2.04–4.38) for male pilots with 10,000 or more flight hours (Pukkala et al., 2003).
- 43. A study of male and female airline cabin attendants (see under cancer site below) found no difference in risk overall between length of employment (defined as total days of having a valid licence) less than 20 years (SIR=2.02 95% CI 1.42-2.79) and length of employment greater than 20 years (SIR=2.04 95% CI 1.45-2.77) (Pukkala *et al* 2012).
- 44. An earlier study by Linnersjö et al. (2003) examined incidence of cancer from 1961-1996 amongst Swedish cabin crew at the Swedish Airline System employed from 1957 to 1994. The study population included 2,956 subjects (2,324 women and 632 men), with 17 cases of malignant melanoma (11 in women, 6 in men). Compared with the general Swedish population there was an increased incidence for both men (SIR=3.66, 95% CI 1.34-7.97) and women (SIR=2.18, 95% CI 1.09-3.90), resulting in a combined SIR of 2.61 (95% CI=1.52-4.17). There was no consistent pattern in relation to length of employment for men (<10 years: SIR=4.15 95% CI 0.50-14.98, n=2, 10-19 years: SIR=6.59, 95% CI 1.36-19.25, n=3 and >20 years: SIR=1.59, 95% CI=0.04-8.86, n=1) or women (<10 years: SIR=2.45, 95% CI 0.90-5.33, n=6, 10-19 years: SIR=1.08, 95% CI 0.13-3.89, n=2 and >20 years: SIR=4.60, 95% CI 0.95-13.44, n=3). In relation to block hours (including inflight and ground time) over 10,000, a risk specifically for men could not be calculated since there were no exposed controls. However, for women and all cabin crew combined, elevated risks were found (OR=2.67, 95% CI 0.20-35.14, n=2 and OR=4.67, 95% CI 0.45-49.14, n=5 respectively).
- 45. A subset of cohorts from the European study of cancer risks among airline pilots and cabin crew (ESCAPE) with time-dependent information on

radiation-related exposure (Denmark, Finland, Germany, Iceland, Italy, Norway, Sweden) gave results for cumulative block hours i.e. hours on board the aircraft including some ground time (Langner et al 2004). An internal analysis using Poisson regression found only a weak association between cumulative block hours and melanoma deaths (Reference <5,000, RR=1, n=4; 5,000-9,999 RR= 1.57 95% CI 0.51-4.90 n=6; 10,000+ RR=0.88 95% CI 0.23-3.34 n=4).

46. A non-significant increase in the risk of melanoma was found for US flight attendants for increasing time spent working in the standard sleep interval (SSI) (midnight to 8am) and for number of time zones crossed; there was no increased risk by duration of employment (Pinkerton et al 2018). A mortality study of pilots by Yong et al (2014) also found no significant increased risk of melanoma overall (SRR=1.48, 95% CI 0.93-2.21) and no consistent increase by duration of employment.

Long-haul and short-haul flights

- 47. Very few of the epidemiological studies analyse their results by the type of flight generally defined as long-haul or short-haul. However, this classification is often used in the estimation of cosmic radiation doses (see section below). The type of aircraft type may be used for this purpose with papers such as Gundestrup et al (1999) and Langner et al (2004) defining jet aircraft as long-haul and non-jet as short-haul. Langner also defines short-haul as < 5 hours flight duration and long haul as > 5 hours flight duration but does not give results for this. Wollschlage et al (2018) comment that a typical career path of a pilot proceeds from acting as first officer on long-haul flights to being captain on short-haul flights before advancing to being captain on long-haul flights again.
- 48. An early mortality cohort study by Irvine and Davis (1999) of BA male pilots and flight deck engineers found an overall SMR for melanoma in pilots of 3.33 (95% CI 1.52-6.32) and state that this risk was 'evenly split' between long and short haul pilots i.e. no difference in the relative risk (the actual results are not given).

49. Gundestrup et al found a similar risk for melanoma related to jet (longhaul) aircraft and non-jet (short-haul) aircraft.

Evidence by melanoma site

- 50. There are only a few studies that give results by the site of the melanomas. Those that do are often unable to estimate risks for head and neck melanoma due to small numbers of cases.
- 51. A study of male Nordic airline pilots identified 56 cases of melanoma, 7 head and neck, 32 trunk and 14 limbs (Pukkala *et al.* (2002). There was significant excess overall (SIR=2.29, 95% CI 1.73-2.98), which was evident in all three anatomic sites (head and neck: SIR=2.49, 95% CI 1.00-5.14, trunk: SIR=2.33, 95% CI 1.60-3.30 and limbs: SIR=2.29, 95% CI 1.25-3.84). The authors comment that as the risk in the head and neck area is similar irrespective whether the person is regularly outdoors or not, whereas skin melanoma in the trunk and limbs is much more common among indoor workers that this might point to factors other than sunbathing.
- 52. A similar study by Pukkala et al (2012) (included in the meta-analysis by San Lorenzo et al (2015)) followed up a cohort of 8,507 female and 1,559 male airline cabin attendants from Finland, Iceland, Norway and Sweden for cancer incidence for a mean follow-up time of 23.6 years through the national cancer registries. The overall SIR for melanoma was 2.03 (95%CI 1.60-2.58); for females the SIR was 1.85 (95% CI 1.41-2.38) and for males was 3.00 (95% CI 1.78-4.74). Both male and female cabin crew had excesses of melanoma of the trunk, female SIR = 2.73 (95% CI 1.81-3.95) (28 cases), male SIR = 4.50 (95% CI 2.52-7.42) (15 cases). There were only 4 cases of melanoma in the head and neck for females and 1 for males and only 1 case of limb melanoma for males. The SIR for limb melanoma for females was 1.55 (95% CI 1.02-2.27) (27 cases). The overall risk for men and women together increased with length of employment for melanoma on the trunk (<20 years SIR=2.60 95% CI</p>

1.51-4.16; >20 years SIR=3.69 95% CI 2.41-5.40). In contrast, opposite trends were found for melanoma on the head and neck and melanoma of the limbs; this contrasts with the earlier study by Pukkala et al (2002) of pilots. It should be noted that this study does not provide separate estimates for upper and lower limbs.

- 53. In the study by dos Santos Silva (2013) the overall linear trend in the rate of melanoma with increasing flight hours was found to be stronger, although not significantly for melanomas occurring on the trunk and lower limbs than for those occurring on the head and neck and upper limbs.
- 54. The study by Linnersjo et al (2003) found raised SIRs for all sites: women head and neck SIR=3.24 (95% CI 0.08-18.04) (1 case); trunk SIR=4.46 (95% CI 1.79-9.19) (7 cases); limbs SIR=1.08 (95% CI 0.22-3.16) (3 cases): men head and neck SIR=6.05 (95% CI 0.15-33.72) (1 case); trunk SIR=5.82 (95% CI 1.89-13.57) (5 cases); no cases on the limbs.

Evidence by cosmic radiation dose (mSv)

55. Cosmic radiation in the common cruising altitudes (8,000–10,000 m) consists mainly of gamma and neutron radiation, with some heavy nuclei (i.e. nuclei heavier than Helium / an alpha particle). Cosmic radiation is one of the forms of naturally occurring ionising radiation on earth. Airline cabin crew are occupationally exposed to ionising radiation with doses 2–6 MilliSieverts (mSv) per year (Bartlett 2004). Pukkala et al (2012) comment that this is roughly twice the average annual dose from natural and medical sources received by the general population. McNeely et al 2018 also state that US 'cabin crew have the largest annual ionising radiation dose of all U.S. workers (e.g. 3.07 mSv vs. 0.59 mSv for U.S. Department of Energy workers)' and that these exposures can exceed guidelines released by the NCRP (National Council on Radiation Protection and Measurements) or the International Commission on Radiological Protection. They note that flight attendants' exposure to ionising radiation is still not monitored or regulated.

- 56. A few studies have estimated risk by cosmic radiation dose (mSv) by variously combining information on the flying hours, type of flight (long/short haul) and employment information (for example, applying annual flight hours with a job- exposure matrix (JEM) containing aircraft and calendar year-specific dose-rates, (Langner et al (2004)) with estimates of cosmic radiation dose by these factors.
- 57. The study by Pukkala *et al.* (2002) used the flight histories of the pilots before the cancer follow-up period when evaluating exposure to radiation. Risk of melanoma increased significantly with increasing estimated exposure to radiation during flight (p=0.008) with SIRs of 1.37 for 1-2,999µSv (95% CI 0.75-2.30, n=14), 3.00 for 3,000-9,999µSv (95% CI 1.37-5.69, n=9), 3.02 for 10,000-19,999µSv (95% CI 1.61-5.14, n=13) and 3.47 for 20,000+µSv (95% CI 2.02-5.55, n=17). This trend was also significant in the trunk (p=0.02) and limbs (p=0.04). Using an internal reference (exposure of 1-2,999µSv) and adjusting for age and calendar period gave a significant trend (p=0.007). The resulting SIRs were 2.10 (95% CI 0.91-4.87), 2.20 (95% CI 1.03-4.72) and 2.78 (95% CI 1.30-5.93) for 3,000-9,999µSv, 10,000-19,999µSv and 20,000+µSv respectively.
- 58. In contrast, the study by Pukkala et al (2012) of airline cabin attendants found no association overall and no dose-response relationship between cosmic radiation and incidence of melanoma.
- In the cohort study of Icelandic pilots 5 of the 7 melanoma cases occurred in pilots with more than 25 mSv cumulative dose of cosmic radiation (SIR 9.88, 95% CI 1.57 - 190.78) (Gudmundsdottir et al 2017).
- 60. In the ESCAPE study, using a sub cohort that excluded Greece and the UK where no annual records for block hours were available, no significant trend for cumulative radiation dose and risk of melanoma by categories of cumulative radiation was found in either the external or internal analyses; risk estimates for the external analysis (SMRs) were all greater than 1 (non-significant) except for exposure greater than 25 mSv but were only greater than 1 for the category 15-24.99 mSv in the internal analysis (Langner et al 2004).

- 61. A study in Finland carried out a self-administered questionnaire survey on occupational, host, and ultraviolet radiation exposure factors among female cabin crew members and females presenting in the general population (Kojo et al 2013). Among the cabin crew, the estimated cumulative cosmic radiation dose was not related to the increased skin cancer risk (OR = 0.75, 95% CI 0.57,1.00) after adjustment for several personal risk factors such as skin type and for behavioural risk factors such as solarium use.
- 62. The cohort study of US female flight attendants also reported no association between melanoma and occupational radiation dose or circadian disruption. (Pinkerton et al 2018).

Ultraviolet radiation exposure in aircraft

- 63. Solar ultraviolet radiation (UV) is defined in the wavelength interval from 100 to 400 nm which is further divided into the sub-intervals of UV-C (100–280 nm), UV-B (280–315 nm), and UV-A (315–400 nm). Whereas UV-A and parts of the UV-B reach the earth's surface, UV-C is almost completely filtered in the upper layers of the atmosphere. At the short UV wavelengths photons carry higher amounts of energy compared to longer wavelengths, as for example the wavelengths of visible light. As a result, UV radiation is potentially more damaging to tissues of humans, animals, and plants than radiation at wavelengths greater than 400 nm. UV radiation with wavelength shorter than 200nm (and therefore having the highest frequency and highest energy) is considered to be ionising radiation and therefore the most dangerous.
- 64. Earlier studies have tended to report that the windshields of aircraft give good protection against UV radiation thus cabin attendants and pilots should not have an increase in exposure e.g. Linnersjö *et al.* (2003).
- 65. These comments are often based on a study published in 1990 by Diffey et al who measured UV radiation exposure of the captain and first officer

during 12 flights, including long and short haul, using a polysulphone film badge worn by pilots. Further measurements were taken with separate badges at ground level around noon from an unshaded horizontal surface in five locations worldwide. The sensitivity of the film was confined to wavelengths less than 320 nm. All badges worn during flight showed minimal exposure to UV radiation and were significantly less than the radiation outside at ground level. However, details regarding measurements procedures, accuracies of the film measurements, or the spectral sensitivities of the films were not given.

- 66. A study in the US investigated airplane windscreen transmittance in the UV (< 380 nm) and visible (380-780 nm) portions of the optical spectrum (Nakagawara et al. 2007). Transmission measurements were performed on eight aircraft windscreens; three from large commercial jets (MD 88, Airbus A320, and Boeing 727/737); two from commercial, propeller-driven passenger planes (Fokker 27 and the ATR 42); one from a small private jet (Raytheon Aircraft Corporation Hawker Horizon); and two from small general aviation (GA), single-engine, propeller-driven planes (Beech Bonanza and Cessna 182). The two GA aircraft windscreens were plastic (polycarbonate); the others were multilayer (laminated) composite glass. UV transmittance for both glass and plastic windscreens was less than 1% for UV-B (280-320 nm) radiation. In the UV-A portion (320-380 nm) of the spectrum, transmittance differences increased from 0.41% to 53.5%, with plastic attenuating more UV radiation than glass.</p>
- 67. A published paper and PhD thesis report findings from an investigation of whether professional pilots are adequately protected from UV and short wavelength light during flight (particularly to the eyes) (Chorley et al 2014 (a), Chorley et al 2014 (b)). Informed by the results of 22 semi-structured interviews, a questionnaire exploring the eye protection habits of professional pilots was developed and completed by 2,967 participants. The results showed a wide variation in pilot use of sunglasses.
- 68. In flight irradiance measurements were captured during 6 airline and 4 helicopter flights. No measurable UV-B was found. UV-A exposure

depended on the transmission properties of the aircraft windshield. Further ground measurements on 15 aircraft showed the majority had windshields which transmit significant levels of UV-A into the cockpit. Older aircraft generally had superior UV-A blocking windshields. Higher irradiance levels of UV-A were found at altitude (2.4 times higher) compared with ground level.

- 69. Patterns of working were investigated regarding the likely number of hours logged per annum of a full time employed pilot and the amount of time spent operating during daylight hours. A number of factors determined the annual number of daylight hours flown by the professional pilot including: the type of operation (seasonal/holiday destinations vs city destinations); short haul vs long haul; number of 'waves' per day i.e. the number of return trips; number of sectors flown per day. Pilots flew either short haul or a mixture of long and short haul. Overall it was estimated that around 80% of short-haul flying is conducted during daylight hours.
- 70. The research found that erythemal weighted irradiance (a weighting of UV radiation that takes into account the different susceptibility of the skin to the wavelength of the radiation) occurring in flight was low due mainly to the UV-B blocking properties of all windshields. Patterns of working were investigated regarding the likely number of hours logged per annum of a full time employed pilot and the amount of time spent operating during daylight hours (see below). The average Standard Erythemal Dose (SED) per hour across all aeroplane flights was estimated to be 0.06 SED/hr giving an estimated annual exposure of 29-47 SED per annum for short haul pilots and approximately 25 SED per annum for long haul pilots. Chorley points out that these figures compare favourably with studies assessing annual exposure in other UV exposed workers such as gardeners in Denmark (median 224 SED) (Thieden, 2008).
- 71. A further study was carried out by Baczynska et al (2019) to measure the UV exposure of pilots flying between the UK and a range of destinations during three different seasons. In-flight UV exposure of pilots was

measured on 322 Monarch Airlines short-haul flights on the Airbus A321-231 and Airbus A320-214 to 31 destinations in Europe from 4 UK airports in September 2016 - August 2017. The erythema effective and UV-A doses were compared with the International Commission on Non-Ionising Radiation Protection (ICNIRP) guidance and typical recreational weekend exposure of UK office workers. The erythema effective radiant doses were negligible in all flights and did not exceed 0.1 SED. For the majority of the flights the UV-A exposure was also low. On 27 out of 322 single sector flights UV-A exposure exceeded the ICNIRP guidance. The UV exposure in a cockpit was influenced by the presence of the direct sunlight, duration of a flight, altitude, solar elevation and season. The average monthly exposures were low and significantly below weekend recreational exposures of UK office workers over a similar period.

72. Following the meta-analysis by San Lorenzo et al (2015a) a study was undertaken to measure the amount of UV radiation in airplane cockpits during flight and compared them with measurements performed in tanning beds (San Lorenzo et al 2015b). UV radiation measurements from 280 to 400 nm were performed using a Solartech UV index meter and a Solartech UV index meter designed to measure UV-B only (280-322 nm) (Solartech Inc). UV radiation was measured in the pilot seat inside a general aviation turboprop airplane (Socata TBM850) through the acrylic plastic windshield (1.6-cm thick) at ground level and at 2,500, 6,000, 10,000, 15,000, 20,000, 25,000, and 30,000 feet above sea level. The measurements were taken in 2 locations with different solar exposures: San Jose, California, and Las Vegas, Nevada, around midday in April. The same meters were used to measure UV radiation levels in an Omega UV-A tanning bed. The windshields blocked UV-B but allowed UV-A transmission. The amount of UV-A at 30,000 feet measured in Las Vegas, Nevada, was approximately 242 µW/cm₂. The UV-A dose in a UV-A-only tanning bed was 706 μ W/cm₂. The authors estimated that pilots flying for 56.6 minutes at 30,000 feet receive the same amount of UV-A carcinogenic effective radiation as that from a 20minute tanning bed session.

- 73. A simulation modelling study compared UV irradiances and UV doses inside and outside the aircraft cockpit under various conditions such as atmospheric parameters, aircraft direction in relation to the position of the sun, and aircraft windscreen design parameters (Meerkotter 2017). Available measurement data on these parameters were utilised, including the data from Nakagawara (2007). The modelling demonstrated that the intensity of UV radiation inside a cockpit depends on whether direct or diffuse sun is entering the cockpit or not. For diffuse UV radiation only about 5% of the irradiances outside the aircraft reached the interior. For direct UV radiation, UV irradiances in the cockpit varied between 50–100% the irradiances outside. Other factors influencing variation included solar zenith angle, cloud cover, flight route, altitude, time of year and reflecting snow surfaces.
- 74. In a study by Cadhilac et al (2017) measurements were taken with a three sensor-integrated electronics UV radiometer (A, B, and C) during 14 flights from July to October 2016. They were performed during daylight hours once the airliner had reached cruising altitude. UV-A and UV-B radiation was not detected in any parts of the cabins of the planes tested, nor in the Airbus cockpits. UV-A radiation was however found in the cockpit of Boeing 777s. UV-A levels remained well below the values found at ground level and were also strongly reduced (more than 10 times) by cockpit sun visors.

General studies of ionising radiation exposure and melanoma

75. An association between radiation exposure and malignant melanoma has not been consistently observed in a range of studies. Several papers concerning studies on employees of the Lawrence Livermore National Laboratory (LLNL) have shown an association between radiation exposure and malignant melanoma (Austin et al 1997, Donald et al 2004, Moore et al 1997). In contrast a radiation laboratory at Los Alamos, which had similar activities as LLNL, found no clear association between radiation and the risk of malignant melanoma (Aquavella et al. 1983). The IARC monograph on radiation highlights only 4 studies of X and γ radiation in relation to melanoma (Table 2.8 in IARC, 2012). They state that there are few indications of excess risk except for a France–UK study of patients treated with radiotherapy for childhood cancer which found a statistically borderline association (excess OR ratio/Gray₁, 0.07; 95% CI: 0.00– 0.14) (Guerin et al 2007).

Carcinogenicity of UV radiation

- 76. UV radiation is classified by the International Agency for Research on Cancer (IARC) as a group1, definite human carcinogen. UV radiation is a complete carcinogen, as it acts both as an initiator through general toxicity and a promoter, for example through immunosuppression. UV-A comprises 90–95% of UV radiation from sunlight and can reach the dermal layer of human skin. In contrast, UV-B only affects cells within the epidermal layer of the skin and comprises only a relatively small amount of the total UV radiation from the sun (Khan et al 2018). In addition to epidemiological studies, there is evidence for the carcinogenicity of UV exposure from mechanistic studies, mainly in vitro (with human derived tumour cell lines and skin biopsies) and animal studies (HGF/SF transgenic mice), which have shown the induction of melanoma from both UV-A and UV-B radiation. Both UV-A and UV-B have been shown to be involved in processes leading to DNA damage and consequent mutation induction. In addition, there is increasing evidence that epigenetic changes, which play a crucial role in (skin) cancer induction and development, are also induced via UV-A and UV-B.
- 77. Several *in vivo* experimental studies conducted on neonatal HGF/SF transgenic mice irradiated with UV-B have shown the induction of melanoma (Hacker *et al.*, 2005 and 2006; Kannan *et al.*, 2003, De Fabo *et al.*, 2004). A study with irradiation with UV-A has also shown the induction of melanoma (Noonan *et al.*, 2012). The existence of two distinct pathways for melanoma has been suggested: i) an UV-B-dependent pathway independent of pigmentation associated with direct UV-B-type DNA damage and ii) an UV-A pathway that requires melanin which is associated with indirect oxidative DNA damage in

¹ Gray: the absorption of one joule of radiation energy per kilogram of matter

melanocytes. In addition, both UV-B and UV-A have been shown to cause immunosuppression (Khan 2018).

78. There have been many studies of chromosome damage in association with ionising radiation exposure. One study of male US pilots also included measures of circadian disruption (cumulative time zones crossed and median travel time during the standard sleep interval (SSI) (defined as 10pm- 8am at the resident of the pilot) (Grajewski et al. 2018). There was a non-significant trend for increased chromosome translocations across median SSI and also for some of the measures of ionising radiation dose. However, there was a high correlation between cumulative time zones crossed and ionising radiation estimates so that the independent effects of these variables could not be adequately assessed.

Perturbation of circadian rhythm

79. The epidemiological evidence evaluating risk of melanoma, perturbance of the circadian rhythm and consequent melatonin disturbance, through variable shift patterns in pilots and air cabin crew is circumstantial only. In the cohort of Icelandic pilots (13) the SIR for melanoma was higher (25.00; 6.73-64.00: 4 cases) in those who had ever flown over five time zones than in those who had never done so (9.09; 0.12-50.58: 1 case) although the difference was not statistically significant. Among British ATCOs there was no relationship between melanoma risk and cumulative number of night shifts. In addition, a large prospective cohort study of shift work and cancer in nurses found a significant decreased risk of skin cancer related to rotating shift work that was strongest for melanoma; working 10 or more years of rotating night shifts was associated with a 44% decreased risk of melanoma after adjustment for melanoma risk factors (Schernhammer et al, 2011). The strongest decrease was found in women with black or brown hair; no effect modification was shown by sunlight exposure at baseline, geographical residence, or melanoma site. These results support those found in an earlier Swedish registry-based cohort study (Schwarzbaum et al 2007) where no association was found between night shifts and risk of melanoma (based on only 11 cases). Schernhammer et al comment that their findings are in contrast with evidence from other studies (e.g. Hansen 2001, Megdal et al 2005) which suggest that lower levels of melatonin among night shift workers attributable to longer duration of exposure to artificial light at night, could be responsible for the positive associations with the risk of cancers other than melanoma observed in these studies.

- 80. There is a considerable literature demonstrating that fatigue, sleep-loss, and circadian disruption due to flight operations can affect both crew performance and flight safety although there are regulatory limits on maximum daily, monthly and yearly flight and duty hours, and required minimum breaks within and between duty periods. Work patterns of pilots, cabin crew and also ATCOs appear to vary substantially. Circadian disruption can potentially occur not only from long haul flights across different time zones but from the early starts and late finishes of some short-haul flights, when travel time to and from work is taken into account. Interviews with pilots have indicated dissatisfaction with some scheduling as being unreasonable or unstable/irregular (Lee & Kim 2018; Chang et al 2019). Lee & Kim used a detailed guestionnaire and surveyed over 900 pilots regarding factors that might influence fatigue including flight direction, crew scheduling, partnership (interaction with other crew members who they may not have worked with previously), aircraft environment (noise, temperature, humidity etc.), job assignment and ethnicity. Increased pilot fatigue and reduced flight operational performance was shown to be associated with several factors including inadequate schedule operations (no pilot input, early departures etc.); flight direction (west rather than east); incorrect partnerships resulting from culture (duty styles and rest patterns); inadequate aircraft environments; inappropriate job assignments (multiple flight legs and layovers, duty length etc.); and inadequate hotel environments.
- 81. Similar results were found in a study of over 400 Brazilian pilots. The prevalence of sleep complaints was 34.9%, daytime sleepiness 59.3% and fatigue 90.6% (Reis et al 2015); 72% of the pilots flew short or medium-haul flights and were more highly affected than the long-haul pilots. Higher levels of fatigue were associated with type of flight, duty hours, number of sectors flown

(a sector is a flight between two airports e.g. Gatwick to Edinburgh; pilots could fly more than one of these during a working day), early starts and night shifts.

- 82. ATCOs are also reported to experience high rates of fatigue with the risk of this being affected by unbalanced day shift work hours in the morning and afternoon, causing more fatigue with some specific shift types; timing of the breaks (long work hours before a break); and time on task and inadequate environments in rest areas such as poor equipment and poor sound insulation, in addition to frequent emergencies (Chang et al 2019).
- 83. Shift work patterns such as those experienced by pilots and flight crew have the potential for disruption of the circadian rhythm, a natural, internal process that regulates the sleep-wake cycle and repeats roughly every 24 hours. The circadian rhythm is controlled by the central regulator located in the brain. Peripheral organs, such as the skin, also contribute to the circadian rhythm and possess endogenous rhythmicity. A major regulator of circadian rhythm is the pineal gland which secretes melatonin; melatonin is also synthesized at several peripheral sites including the skin. The synthesis of melatonin is regulated by light; melatonin synthesis and release from the pineal gland increases at night and is lower during the day, with light at night causing melatonin levels to drop.
- 84. Experimental studies, both *in vivo* and *in vitro*, provide evidence that melatonin can inhibit cancer development. Melatonin has been reported to reduce the growth of cell lines of malignant melanoma although the results are not always consistent. In one study, low (or "physiological") melatonin concentrations appeared to inhibit melanoma cell proliferation in vitro, whereas higher levels of melatonin had either no effect on melanoma cell growth or exerted stimulatory activity (Otalora et al 2008). In another study, pharmacological doses of melatonin were associated with increased melanoma cell proliferation, but lower doses had no effect (Izykowska et al. 2009). Nocturnal melatonin supplementation in mice that were exposed to constant light was associated with increased melanoma progression, compared with control mice where a 12-hour dark, 12-hour light regime was used; the circadian rhythm of core body temperature was also abolished (Otalora et al 2008). The effects of melatonin

depend on photoperiod and time of day. Melatonin production appears to vary by phenotypes such as hair colour, with dark hair associated with higher melatonin levels.

85. Melatonin has also been shown to be associated with suppression of DNA damage in skin cells. Studies have shown that repair of DNA-damaged skin cells, as a result of UV exposure, peaks at night (Yosipovitch et al 1998). Additionally, previous exposure to UV light can continue to damage skin DNA for up to three hours following exposure; exposure to UV light causes DNA damage in all skin cells, but only melanocytes continue to accumulate DNA damage in the absence of light (Premi et al 2015). Lyons et al (2019) cite a study by Manzella et al (2015) that found that oxidative damage followed a circadian rhythm where the DNA damage was less in the morning hours than later on in the day and DNA repair activity was higher in the morning. This same study found that night-shift workers had decreased levels of DNA repair expression compared with the control group. Lyons et al (2019) comment that this suggests that during the early morning hours, the body best performs DNA repair and that optimal DNA repair occurs with optimal sleep.

Summary of the Evidence

- 86. The evidence base for an increased risk of the incidence of melanoma in aircrew – both pilots and cabin crew - is consistent and convincing; the pattern of an excess risk has not substantially changed by date of publication over the last 30 years although the exact magnitude varies between studies.
- 87. The meta-analyses of melanoma incidence show a consistent doubling of risk for both pilots and cabin crew.
- 88. There are fewer studies of melanoma mortality but again the risks are consistently raised for both pilots and cabin crew, although not always doubled.

- 89. The risk appears to increase by length of employment or flying hours although the studies are less consistent. The large study of British pilots (dos Santos Silva et al 2013), reports a doubling or more of risk at an accumulated dose of over 5,000 flying hours as does the Danish study by Gundestrup and Storm (1999); others report doubling of risk at 10,000 hours, for example Haldorsen et al (2000).
- 90. Few studies investigate risk by site of the melanoma; the majority of cases in the studies occur on the trunk or limbs with very few occurring on the neck and head. Two studies have found increased risk for head and neck melanoma, one in pilots and the other in cabin crew.
- 91. Some studies have combined data on length of employment or flying hours with estimates of cosmic radiation to estimate cosmic radiation dose (mSv); the cosmic radiation measurements are often average doses e.g. aircraft and calendar year-specific dose-rates. Risk of melanoma by cosmic radiation has been found to be increased in some studies but not in others. Although cosmic radiation is not apparently routinely monitored for pilots or cabin crew cumulative doses ranging between 2–6 mSv per year have been suggested.
- 92. None of the epidemiological studies measure or estimate UV exposure during work, either inflight or during non-flight work periods. Studies on the transmittance of UVR of aircraft windscreens are in agreement that UV-B is almost completely blocked. However, there is evidence that UV-A can be transmitted through windscreens; this varies depending on the windscreen material, atmospheric parameters, aircraft direction in relation to the position of the sun etc. However, erythemal dose from this inflight exposure is estimated to be small.
- 93. UV radiation is a complete carcinogen, as it acts both as an initiator through general toxicity and a promoter, for example through immunosuppression.

94. The evidence from both animal and epidemiological studies investigating circadian disruption and the development of melanoma is inconsistent with variable conclusions. However, the circadian control of melatonin and, in particular, DNA repair mechanisms, provides more robust evidence for supporting the link between circadian dysrhythmia and skin cancer development although this is a complex issue and it is difficult to ascertain the exact relationship between circadian rhythm disruptions and skin oncogenesis (Gutierrez 2016).

General Comments

- 95. Not all the published studies adjust for lifestyle or inherent risk factors for melanoma such as skin type, number of common and atypical nevi, family history of melanoma, history of severe sunburn, use of tanning beds, and socioeconomic status (Shanta et al 2015). These data are also unlikely to be available for the comparison populations used in the study particularly if the national population is used. The study by McNeely which compared pilots and aircrew with a similar socioeconomic comparison population found a risk of more than two for the pilots and aircrew. A comparison by Rafnsson et al (2003) of the constitutional and behavioural risk factors for malignant melanoma between aircrews and a population sample found no substantial difference, although aircrews had more often used sunscreen and had taken more sunny vacations.
- 96. There is also the potential for detection bias when comparing pilots to the general population since pilots are subject to regular medical screening; frequent physical examinations may increase the detection of early-stage melanoma thus increasing the reported incidence; early detection may be the reason the risks of melanoma deaths in many studies and meta-analyses tend to be lower than that for incidence. However, these issues are reduced where internal comparisons of well characterised exposure categories have been carried out, for example in dos Santos Silva et al (2012).
- 97. Potential mechanism(s) for the increase in risk of melanoma in pilots and flight crew:

- i. Exposure to UV light in cockpit: more recent studies have confirmed that whilst UV-B does not penetrate windshields, some UV-A exposure may occur in cockpits depending on weather conditions, altitude etc. However, the average annual erythemal dose from this inflight exposure has been estimated to be small. No epidemiological studies of pilots have evaluated the contribution of cockpit exposure to risk of melanoma. This exposure might potentially increase the risk in pilots more than in other aircrew and to favour an increased risk of melanoma on the head, neck and upper limbs. However, the metaanalyses report similar summary risks in pilots and cabin crew.
- ii. Exposure to UV light incurred as part of non-flight duties and, potentially, as a consequence of access to low-cost leisure air travel. There is no direct evidence to show that pilots and cabin crew have increased UV exposure either during stopovers or through leisure activities (Muira et al 2019). None of the epidemiological studies have evaluated the contribution of non-flight UV or leisure exposure to the risk of melanoma in pilots and flight crew. One study found that around 80% of short-haul flying took place during daylight hours; exposure to UV light during non-flight activities might thus be limited, particularly in short-haul work. One expert consulted by the Council also pointed out that many of the sectors and destinations included in published studies were at medium or high latitudes.
- iii. High doses of cosmic ionising radiation incurred through repeated exposures at high altitudes: the evidence base for increased risk of melanoma is not consistent across studies and tends to mirror results for length of employment or flying hours. In addition, experts consulted by the Council have pointed out that cosmic radiation is higher energy radiation that would be more likely to penetrate the skin and affect internal organs in contrast to UV radiation which has weaker penetration and thus can affect the skin.

iv. Perturbance of the circadian rhythm and consequent melatonin disturbance, through variable shift patterns: epidemiological evidence relating to shift work and development of skin cancer in pilots and air cabin crew is scarce and animal evidence is inconsistent. However, there is a large body of evidence investigating work patterns and fatigue indicating varied shift work patterns leading to sleep disturbance, and fatigue. Although complex, recent mechanistic studies suggest that there is a relationship between circadian disruption together with UV sunlight exposure and disruption to the production of melatonin and subsequent repair of skin DNA damage.

Conclusions and Recommendations

- 98. There is substantial and consistent evidence that there is more than double the risk of malignant melanoma in pilots and cabin crew and for pilots in particular, after 5,000 aggregated hours' flying time. This corresponds to approximately 5 or more years aggregated duration of employment. The Council has investigated several relevant exposures that this workforce may experience, including UV light (the main risk factor for melanoma), that might potentially contribute to the excess risk. From currently available evidence, they have concluded that neither cosmic radiation nor occupational exposures to UV during flights are likely to contribute substantially to the excess risk. The most likely causes are: (i) UV exposure outside the aircraft, but there is uncertainty about the nature and patterns of UV exposure that might occur during non-flight work and during flight stopovers and the potential contribution of exposure during recreational activities; together with (ii) disruption of the circadian rhythm through shift work, although the exact relationship of this combination is as yet uncertain.
- 99. Given the clearly doubled risk, the Council recommends that malignant melanoma in pilots and cabin crew be added to the list of prescribed diseases for which benefit is payable, following 5 or more years aggregated duration of employment.

100. The recommendations for prescription are described in the table below:

Disease	Occupation
Cutaneous malignant	Pilots and cabin crew of commercial aircraft following 5 or more years aggregated duration of employment as
melanoma	air-crew.

101. The Council also noted that one study found increased risk of melanoma in air traffic controllers. The Council will continue to monitor the literature for further studies of these workers.

Prevention note:

- 102. The Health and Safety Executive (HSE) provides advice on how those work outside can protect their skin from excessive exposure to sunlight (http://www.hse.gov.uk/skin/sunprotect.htm). Resources on taking action on sun safety at work are available at the Institute of Occupational Safety and Health (IOSH) website (https://www.notimetolose.org.uk/free-resources/solar-pack-taster/). Cancer Research UK has comprehensive information about the risks of skin cancer from UV sunlight exposure and guidance on preventing this (https://www.cancerresearchuk.org/about-cancer/causes-of-cancer/sun-uv-and-cancer).
- 103. Information on managing shift work and reducing the health impacts of shift work can also be found on the HSE website (https://www.hse.gov.uk/ pUbns/priced/hsg256.pdf), together with hints and tips for shift workers (https://www.hse.gov.uk/humanfactors/topics/shift-workers.htm). HSE has also produced guidance for employers and employees on fatigue (https://www.hse.gov.uk/humanfactors/topics/fatigue.htm).

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Glossary

Types of study

Cohort study: A study which follows up a population of individuals (usually defined by a workplace) over time and compared the incidence rate of disease or mortality among those within the cohort or with an external comparison population. The outcome is expressed as a Rate Ratio or Relative Risk, Standardised Incidence Ratio, Standardised Registration Ratio, or Standardised Mortality Ratio, depending on the type of analysis and the disease outcome being studied.

Case-control study: A study which compares people who have a given disease (cases) with people who do not (non-cases, also known as controls) in terms of exposure to one or more risk factors of interest. Have cases been exposed more than non-cases? The outcome is expressed as an Odds Ratio, a form of Relative Risk. In a nested-case control study, cases and controls are sampled from the members in a cohort study – often, all the cases occurring in the cohort and a sample of non-cases.

Measures of association

Statistical significance and P values: Statistical significance refers to the probability that a result as large as that observed, or more extreme still, could have arisen simply by chance. The smaller the probability, the less likely it is that the findings arise by chance alone and the more likely they are to be 'true'. A 'statistically significant' result is one for which the chance alone probability is suitably small, as judged by reference to a pre-defined cut-point. (Conventionally, this is often less than 5% (p<0.05)).

Relative Risk (RR): A measure of the strength of association between exposure and disease. RR is the ratio of the risk of disease in one group to that in another. Often the first group is exposed and the second unexposed or less exposed. A value greater than 1.0 indicates a positive association between exposure and disease. (This may be causal, or have other explanations, such as bias, chance or confounding.) RR is measured or approximated by other measures in this glossary, such as the Odds Ratio, Standardised Incidence Ratio and Standardised

Mortality Ratio.

Odds Ratio (OR): A measure of the strength of association between exposure and disease. It is the odds of exposure in those with disease relative to the odds of exposure in those without disease, expressed as a ratio. For rare exposures, odds and risks are numerically very similar, so the OR can be thought of as a Relative Risk. A value greater than 1.0 indicates a positive association between exposure and disease. (This may be causal, or have other explanations, such as bias, chance or confounding.)

Standardized Incidence Ratio (**SIR**): used to determine if the occurrence of cancer in a relatively small population is high or low. An SIR analysis can tell if the number of observed cancer cases in a particular geographic area is higher or lower than expected, given the population and age distribution for that community

Standardised Mortality Ratio (SMR): A measure of the strength of association between exposure and mortality; a form of Relative Risk in which the outcome is death. The SMR is the ratio of the number of deaths (due to a given disease arising from exposure to a specific risk factor) that occurs within the study population to the number of deaths that would be expected if the study population had the same rate of mortality as the general population (the standard).

By convention, SMRs (and proportional mortality ratios, as described below) are usually multiplied by 100. Thus, an SMR (or PMR) of 200 corresponds to a RR of 2.0. For ease of understanding in this report, SMRs (or PMRs) are quoted as if RRs, and are not multiplied by 100. Thus, a value greater than 1.0 indicates a positive association between exposure and disease. (This may be causal, or have other explanations, such as bias, chance or confounding.)

Proportional Mortality Ratio (PMR): A PMR is the proportion of observed deaths from a given cause in a given population divided by the proportion of deaths from that cause expected (in a standard population). The value is often

expressed on an age-specific basis or after age adjustment. It is a form of Relative Risk.

Other terms

Prevalence: is the proportion of a particular population found to be affected by a medical condition (typically a disease or a risk factor such as smoking). It is derived by comparing the number of people found to have the condition with the total number of people studied, and is usually expressed as a fraction, as a percentage, or as the number of cases per 10,000 or 100,000 people. It is the total number of cases of a disease in a given area during a given time period.

Standardised Prevalence Ratio (SPR): indicates how large is the prevalence of an event/outcome in one group of subjects (with characteristics/attribute) relative to another group (without the characteristics/attributes).

Poisson Regression: a generalized linear model form of regression analysis used to model count data and contingency tables. Poisson regression assumes the response variable Y has a Poisson distribution and assumes the logarithm of its expected value can be modeled by a linear combination of unknown parameters.

Meta-analysis: A statistical procedure for combining data from multiple studies. When the treatment effect (or effect size) is consistent from one study to the next, meta-analysis can be used to identify this common effect. The effect may be summarised as a meta-estimate of relative risk.

Risk: The probability that an event will occur (e.g., that an individual will develop disease within a stated period of time or by a certain age).

Incidence rate or incidence: The rate of occurrence of a new event of interest (e.g. cancer) in a given population over a given time period. (The rate is often expressed in terms of cases per year of 'person-time', and so incorporates the numbers at risk of the event, the time for which they are at risk and the numbers that go on to develop that event.)

Confidence Interval (CI): The Relative Risk reported in a study is only an estimate of the true value of relative risk in the underlying population; a different sample may give a somewhat different estimate. The CI defines a plausible range in which the true population value lies, given the extent of statistical uncertainty in the data. The commonly chosen 95% CIs give a range in which there is a 95% chance that the true value will be found (in the absence of bias and confounding). Small studies generate much uncertainty and a wide range, whereas very large studies provide a narrower band of compatible values.

Job-exposure matrix (JEM): a tool used to assess exposure to potential health hazards in occupational epidemiological studies. A JEM comprises a list of levels of exposure to a variety of harmful (or potentially harmful) agents for selected occupational titles. In large population-based epidemiological studies, JEMs may be used as a quick and systematic means of converting coded occupational data (job titles) into a matrix of possible exposures, obviating the need to assess each individual's exposure in detail.

Erythema: redness of the skin or mucous membranes, caused by increased blood flow in superficial capillaries, one cause being solar radiation (sunburn).

SED (standard erythemal dose): has been developed as an erythemally weighted measure of radiant exposure. The SED is independent of skin type and a particular exposure dose in SED may cause erythema in fair skin but none in darker skin.

Bias: A systematic tendency to over- or under-estimate the size of a measure of interest in a study.

Confounding: Arises when the association between exposure and disease is explained in whole or part by a third factor (confounder), itself a cause of the disease that occurs to a different extent in the groups being compared.

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