

Chapter 18: Radiation-Related Risk Analysis for Atmospheric Flight Civil Aviation Flight Personnel

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Preface

Human data on low dose rate radiation exposure and consequent effects are not readily available, and this fact generates groundtruth concerns for all risk assessment techniques for possible health effects induced by the space radiation environment, especially for long term missions like those foreseen now and in the near future. A large amount of such data may be obtained through civil aviation flight personnel cohorts, in the form of epidemiological studies on delayed health effects induced by the cosmic-ray generated atmospheric radiation environment, a high-LET low dose and low dose rate ionizing radiation with its typical neutron component, to which flight personnel are exposed all throughout their work activity. In the perspective of worldwide studies on radiation exposure of the civil aviation flight personnel, all the available results from previous studies on flight personnel radiation exposure have been examined in various ways (i.e. literature review, meta-analysis) to evaluate possible significant associations between atmospheric ionizing radiation environment and health risks, and to assess directions for future investigations. The physical characteristics of the atmospheric ionizing radiation environment make the results obtained for atmospheric flight personnel relevant for space exploration.

INTRODUCTION

For future manned space missions, with envisaged stays in Lower Earth Orbit (LEO) (Messerschmid and Bertrand, 1996) or deep space (Nealy et al., 1997; Cucinotta et al, 2001a) environment of at least several months or more (for example, the International Space Station crewmembers (SAAM, 1996)) the risk for possible health effects from low dose rate radiation exposure needs to be assessed (NCRP, 1989). Risk assessment techniques for possible health effects from low dose rate radiation exposure should combine knowledge of both radiation environment and biological response (NCRP, 1987), whose effects (e.g. carcinogenesis) are generally evaluated through mathematical models and/or animal and cell experiments (BEIR V, 1990). Data on human exposure to low dose rate ionizing radiation and its effects are not so readily available, especially with regards to stochastic effects (Jablon, 1984), related to carcinogenesis and therefore to cancer risks, for which the event probability increases with increasing radiation exposure (Kiefer, 1989). In distinction, for deterministic effects the level of injury severity increases with increasing radiation exposure (Kiefer, 1993). The largest source of such low dose rate data might be flight personnel (Foelsche et al., 1974), if considered as enrolled in epidemiological cohorts for studies on health effects induced by the cosmic-ray generated atmospheric ionizing radiation. The crew total dose, increasing over the years, might cause delayed radiation-induced health effects, with the high-LET and highly ionizing neutron component typical of atmospheric radiation (Wilson et al. Chapter 2) contributing so much to the effective dose equivalent (Sinclair, 1985) and being more similar in effects to space radiation than the normal terrestrial low-LET radiation (Singleterry

and Thibeault, 2000), which generally radiobiological studies are based on (Kiefer, 1989). In this way the human response database for low dose rate radiation exposure might be significantly augmented (BEIR V, 1990), with benefic effects on space radiation-related risk assessment techniques, both for LEO scenarios (Wu et al., 1996) and for interplanetary mission cruise phases (e.g., Letaw et al., 1989; Obe et al., 1999; Turner and Badhwar, 1999). Moreover, consideration of significant Solar Particle Events (SPEs), although infrequent (Shea and Smart, 1990), is of paramount importance for risk assessment techniques both for atmospheric flight (Wilson, 1981; O'Brien et al., 1994) and space flight (Petrov et al., 1994; Badhwar, 1997; Tripathi et al., 2001). Such events are to be studied in terms of received doses, generally massive, and possible delayed effects observed on crewmembers (Wilson et al., 1991). Another aspect for the significance of atmospheric flight results for space flight scenarios is the fact that the high altitude aircraft radiation environment is expected to be similar to the radiation environment found at the surface of Mars (Wilson et al., 1999), in spite of the constituent and pressure difference between the two atmospheres, air and 1013 mbar for the Earth, and mainly CO₂ and about 6 mbar for Mars (Zurek, 1992), being of little relevance on this respect (Singleterry and Thibeault, 2000), the neutron component at the surface of Mars being generated mainly due to a surface-generated backward flux (Wilson et al., 1999). Therefore any information gathered about terrestrial atmospheric aircraft flight may be applied to studies for manned Mars targeted missions, particularly with regards to landings on Mars, in the planet exploration phase (Weaver et al., 1993), and for planning habitats suitable to the Martian environment and which therefore can safely host a crew, as shelters, or a permanent base (Hoffman and Kaplan, 1997), or settlements for planet colonization (Zubrin, 1997).

In this study all the available results from previous epidemiological studies on flight personnel exposures have been considered in different ways to evaluate the association between atmospheric flight environment and health risks, with a particular regard to cancer induction, and to assess features and needs of future investigations. The physical characteristics of the atmospheric ionizing radiation environment have been described elsewhere (Wilson et al. Chapter 2), as well as the techniques for the evaluation of the exposure (Wilson et al., 2000), so they will be not further discussed in this paper.

ANALYSIS TECHNIQUES

A) LITERATURE REVIEW

The discussion on aircraft flight personnel radiation-related health issues has started already long ago (Winter, 1968). In 1990, aircraft flight personnel have been given the status of "occupationally exposed to radiation" by the International Commission for Radiation Protection (ICRP, 1991), with a received radiation dose that is at least twice larger than that of the general population (Wilson et al., 1994). Starting from this, in several countries epidemiological studies on the health status of civilian airlines crewmembers were promoted (see, e.g. Band et al., 1990; Kaji et al., 1993; Pukkala et al., 1995). These pioneering studies were limited in scope and cohort size, so no conclusive answers on disease risk were found, as better shown below. Moreover, in all these studies no information whatsoever on radiation occupational exposure (e.g. radiation dose, flight hours, route haul, etc.) were used in the analysis, so no correlation was possible between atmospheric ionizing radiation and (possibly radiation-induced) observed health effects, nor has it been possible to discriminate between radiation-induced effects and those of

potential occupational confounding risk factors, as exposure to jet fuels and volatiles (Seldén and Ahlborg, 1995), to disinfection and disinfestations products (Wartemberg et al., 1998 and 1999), to ozone (Reed et al., 1980), to cabin air pollutants (NRC, 1986), including passive smoking in the past (Ryan, 1991), to electromagnetic fields (Kaune, 1993), circadian rhythms disruption (Suvanto et al., 1990), and other factors related to lifestyle (Haugli et al., 1994) and leisure activities (Vågerö et al., 1990). Conversely no account could have been taken of possible synergies among concomitant exposures to different agents (Wu et al., 1996), in terms of risk increase because of the possible interaction mechanisms between radiation and the involved exposure agent, if the latter shows radiomimetic properties (USEPA, 1986). Spacecraft show the same kind of situation (Wu et al., 1996; James, 1997), with the crew member exposed simultaneously to radiation and to many other possible contamination sources (NRC, 1992), even if for spacecraft the infrequent occurrence and the low concentration of the airborne contaminants suggest minimal risk (NRC, 2000), with the simultaneous effects of these low concentration agents and radiation expected to be less than additive due to the concomitant repair of macromolecular lesions at different target sites (James, 1997).

So all the available information on aircraft flight personnel may be only evaluated on the basis that the exposure to the "flight environment" (i.e. exposure to atmospheric cosmic radiation and other physical or chemical agents not evaluated in more precise terms than the implicit fact of being aircraft flight personnel members who are exposed to the atmospheric ionizing radiation environment and to the civilian airline crew members occupational and leisure lifestyle) may pose health risk for flight personnel members.

Thorough literature reviews on epidemiological studies among pilots and cabin attendants have been published, mostly related to cancer risk (Krauss, 1985; Blettner et al., 1998; Blettner and Zeeb, 1999; Ballard et al., 2000; Boice et al., 2000; De Angelis et al., 2001a). In these reviews are considered studies aiming at obtaining results of incidence and mortality in the form of relative risk (RR), i.e. the ratio of the risk of the exposed population of interest and the risk of a reference population taken as the unexposed one (see, e.g. Kleinbaum et al., 1982), with its confidence limits. As a study design, the cohort study approach is generally selected, i.e. the selection and follow-up of an exposed population to obtain data of incidence and mortality. Case-control studies have played until now a minor role in investigations on aircraft flight personnel (Blettner et al., 1998), apart from nested case-control studies among the US Air Force crew members on brain and nervous system cancer (Grayson, 1996; Grayson and Lyons, 1996), mostly related to electromagnetic field exposure. Hoiberg and Blood (1983) compared hospitalization rates for male US Navy pilots and other flying crewmembers with non-flying officers, with flying officers having higher rates for both total hospital admissions and most of the major diagnostic categories. As for cancer endpoints, hospitalization rates for the Hodgkin disease and testis cancer were higher for the flying crewmembers, but numbers and rates were not reported in the paper. Depending on the study design, and dealing with mortality, the relative risk can be approximated through the odds ratios (see, e.g. Rothmans, 1986), namely the Standardized Mortality Ratio (SMR), when it is possible to calculate the ratio between the observed number of deaths in the cohort and the expected number of deaths in the cohort, the latter obtained through mortality data available for the reference population, or the Proportional Mortality Ratio (PMR), when only the relative frequencies of death in the exposed and the unexposed population are known and can be compared, but no personal information is available. In the case

of incidence results, the mortality data are just replaced by the incidence data to obtain the Standardized Incidence Ratio (SIR).

From these comprehensive reviews no clear picture with regards to disease patterns emerges, with individual studies being unrelated to exposures from the flight environment, lacking statistical power to indicate clear trends due to the small number of people enrolled in the considered cohorts, with the consequence of having cancer site-specific incidence increased in some studies and not increased in other ones due just to random effects due to the too small a sample size. The problem is complicated by the fact that for the flight personnel as a group the health risks of this selected group of individuals are low (“healthy worker effect”, for the specific case of aircrew members see De Angelis et al., 2001a). The authors of a recent work on mortality for USA pilots and flight engineers (Nicholas et al., 1998), besides showing with their PMR analysis a significantly increased mortality for kidney and renal pelvis cancer, motor neuron disease, and various external causes, along with not statistically significant indications for mortality rate increase for various other causes, put into evidence the impossibility to obtain meaningful results on radiation without considering in detail both environment and work history. In their paper it is clearly stated: “...to determine if these health outcomes are related to occupational exposures, it will be necessary to quantify each exposure separately, to study the potential synergy of effects, and to couple this information with disease data on an individual basis”.

In more recent studies, not yet included in most reviews, use has been made of some information related to exposure of the individual crewmember, although in most cases obtained in rudimentary ways. Irvine and Davies (1999) used a ‘long/short haul’ route characterization, Gundestrup and Storm (1999) used overall flight hours and a ‘jet/non-jet’ aircraft type characterization, Haldorsen et al. (2000, 2001) and Hammar et al. (2002) overall flight hours and specific aircraft type characterization, and Rafnsson et al. (2000) ‘>5h/<5h flight length’ route characterization, overall flight hours and full aircraft type characterization. In the papers by Haldorsen et al. (2000, 2001) and Rafnsson et al. (2000, 2001) a tentative evaluation of the individual cumulative dose equivalent has been performed with the statistical approach proposed in Tveten (1997), but unfortunately the obtained values for radiation doses and exposures cannot be used for radiation-related investigations, because in Haldorsen et al. (2000, 2001) for dose evaluation the authors used the FAA CARI-3N software package (Friedberg et al., 1992), a version which does not include in the calculations and therefore in the dose results most of the atmospheric neutron component, i.e. about or more than 50% of the observed dose equivalent (O’Brien et al., 1994) depending on time and the considered flight path, whereas in Rafnsson et al. (2000, 2001) the dose is obtained by multiplying individual block-hours with mean hourly dose values averaged on flights of an airline company different from that whose aircrew members have been considered in the analysis.

From the health effects point of view, Rafnsson et al. (2000, 2001) have to cope with extremely small aircrew and reference populations like those of Iceland, and therefore they report only a significant incidence increase for malignant melanoma for both cockpit and cabin personnel, but on the basis of only few cases detected, in Haldorsen et al. (2000, 2001) significant excess risks is reported for only few cancer sites, which the authors interpret as due to leisure lifestyle, and incidence rates for other cancer sites very close to those of the Norwegian general population

they used as a reference. Irvine and Davies (1999) and Hammar et al. (2002) report only excess risk for melanoma skin cancer, and in Gundestrup and Storm (1999) the authors report significant excess risk for malignant melanoma and non-melanoma skin cancer, which they also attribute to leisure activities rather than occupational exposure, and increased risks for acute myeloid leukemia and total cancer incidence for crew members with more than 5000 hours of flight time. Even if these excess risks are to be considered as very slight due to the so large confidence intervals shown by these results (both very close to RR=1 on the confidence interval left side), this phenomenon due to the small numbers for incident cases for each different cause due to the rather small sample enrolled in their Danish flight personnel cohort. In a previous study on Danish cabin attendants, Lynge (1996) found a non-significant excess risk for breast cancer, 1.6(0.9-2.7).

As for more recent US studies, Wartenberg and Stapleton (1998, 1999) reported a very slightly significant excess risk for breast cancer among female cabin attendant, and suggested it was due to the use of disinfectants products and pesticides as dicophane (DDT) used to get rid of insects onboard planes. The frequency and magnitude of exposures to pesticides for aircrew members are unknown, but probably limited (Pukkala et al., 1995), used only on international flights to very few destinations, so this exposure was certainly rare and is unlikely to have contributed to the observed incidence. Nicholas et al. (2001) performed a study on self-reported diseases from a health and lifestyle survey on active and retired commercial airline pilots. A questionnaire was mailed to 10678 pilots, of which only 6609 answered, the overwhelming majority (99.1%) being men. For cancer endpoints the main outcome was a self-reported age-adjusted incidence rate, whereas for non-cancer endpoints the main outcome was a self-reported prevalence rate. Increased morbidity with respect to the general population was found only for melanoma skin cancer, motor neuron disease, already found in Nicholas et al. (1998) with a PMR analysis, and ocular cataracts. Recently, a positive association between cataracts and space radiation exposure, both as increased incidence and earlier onset with respect to the general population, has been reported for US astronauts by Cucinotta et al. (2001b). Reynolds et al. (2002) performed a study based on the California cancer registry and including both male and female cabin crewmembers. They report an excess risk among female cohort members for breast cancer and skin melanoma, and, like in Haldorsen et al. (2001), an excess risk among male flight attendants for Kaposi's sarcoma skin cancer, in both papers considered as related to lifestyle only. In the paper by Haldorsen et al. (2001) the same can be said about the reported excess risks for esophagus and liver cancers.

In the Italian national study (De Angelis et al., 2001; Ballard et al., 2002) a retrospective cohort mortality study, still unrelated to radiation exposure evaluation, was conducted among Italian commercial airline cockpit crewmembers and cabin attendants with work history within the 1965-1996 years. The cohort was composed of 3,022 male cockpit crewmembers, and 3,418 male and 3,428 female cabin attendants. Cause-specific standardized mortality ratios (SMR) and 95% confidence intervals (CI) were calculated as estimates of the relative risk. No exposure variables other than length of employment was used in this mortality study. Causes of death were grouped into three mutually exclusive categories – (1) malignant neoplasms (ICD9 codes 140-209), (2) non-cancer and non-injury causes including infectious diseases, benign tumors, chronic diseases, and unknown causes (ICD9 codes 001-139, 210-799), and (3) external causes (ICD9 codes E800-E999). Cancer mortality was reduced for both male cockpit crew and cabin attendants (SMR 0.58 and 0.67 respectively) with respect to the Italian general population,

but only slightly less than expected for female cabin attendants (SMR 0.90). These are the first reported results about mortality for cabin attendants. No significant excess risk has been found for mortality for any cancer site. There was no increasing trend of the SMR for all-sites cancer or for breast cancer by duration of employment at any exposure lag. The SMR for leukemia was somewhat elevated (SMR 1.72; CI: 0.74-3.40) among male flight personnel based on 8 deaths, with a positive but non-significant trend by length of employment. No excess mortality was noted for non-cancer and non-injury causes, and, with the exception of acute myocardial infarction, SMRs for most other causes were well below one. Mortality from aircraft crashes was highly elevated (SMR 102.7; CI: 60.8-162), which is not surprising given the rarity of this cause of death in the general population. Additionally, an excess of death by suicide was seen among female cabin attendants (SMR 3.38; CI: 1.24-7.35). Other studies on the cohort of the Italian flight personnel are underway, including a detailed assessment of cosmic radiation exposure, a prospective study on disease incidence, an investigation of occupational risk factors for non-tumor outcomes, including psychological distress and circadian rhythms disruption, and an investigation on reproductive disorders and outcomes of female cabin attendants, similar in both philosophy and practice to that by NIOSH/FAA discussed below (Grajewski et al. 1994, 2002; Whelan 2002).

All cancer sites with significant positive association for civilian airline flight personnel crewmembers found in published studies are reported in Table 1 as from each study with its confidence limits (90 or 95 percent, depending on study).

B) FLIGHT PERSONNEL MORTALITY AND CANCER INCIDENCE META-ANALYSIS

As mentioned above, increased cancer risk among flight personnel have been noted in individual studies, but without the statistical power to identify increased risks with any statistical significance. In order to increase the precision of the estimated association between occupation as flight personnel crew member and observed morbidity patterns, different aircrew member cohorts have been selected for a meta-analysis process, in the way proposed in Blair et al. (1995). The studies to be considered were mortality and incidence cohort studies, divided into studies targeted to male pilots and female flight attendants. No proportional mortality studies were included in the analysis, and the same for military pilots studies. The results of the individual selected studies were combined by study outcome (mortality or incidence) for cause of death and/or cancer incidence sites with an excess risk in at least one of the individual studies and for which there were at least five cases in total among eligible studies. Calculations for combined relative risks for selected causes have been performed with a fixed effect model with inverse variance weighting of the log risk ratios (Greenland, 1987), with an evaluation of potential selection biases and heterogeneity among the combined groups, and with estimate and adjustment for possible sources of confounding, e.g. by socioeconomic status (SES). For male pilots, results from two to four individual studies per subcategory have been included to estimate the combined risks for nine cause of death or cancer incident sites, resulting in increased adjusted relative risks for mortality from melanoma and brain cancer and for incidence from prostate and brain cancer. For female cabin attendants, results from two individual studies were combined for incidence of all cancers, of melanoma and breast cancer, and excess risks were found for all sites. The results showing only excess risks are shown in Table 2. However even in the meta-analysis process for both male and female crew members the obtained

RRs show quite large confidence intervals, very close to $RR=1$ and even well below this on the confidence interval left side, so the results must be interpreted with caution. This work has been published in Ballard et al. (2000).

DISCUSSION

From all the above studies, a need comes out of further investigations to be performed over much larger cohorts, to reduce all uncertainties, and with a much better description of the flight environment to which aircrew members are exposed, in terms of a dose reconstruction as accurate as possible. The latter implies an in-depth knowledge of the atmospheric ionizing radiation environment and of its variation with location, altitude and time, a knowledge as detailed as possible for each individual crew member of his flight history, possibly in terms of the details for each work day of the individual flights on which each considered crew member was onboard, and a knowledge as detailed as possible on the flight paths of each individual flight in terms of timing, geographic coordinates, and altitudes, to calculate the dose along the profiles. The use of proxies for exposure evaluation like the use of the overall work hours (i.e. length of employment) instead of radiation doses gives only partly satisfactory results (Hammer et al., 2000).

As for health risk issues, also in individual small size studies excess disease risks have been found, but it has never been possible to confirm these results due to the lack of power of these studies (De Angelis et al., 2001b). Much larger enrolled cohorts such as those composed of the whole flight personnel of a civilian airline are needed to provide more conclusive answers and results, with consideration in detail of the flight environment, in terms of atmospheric ionizing radiation environment, crew employment history, and aircraft route profiles, to reconstruct individual doses. This can provide more solid clues on disease morbidity patterns by exposure to atmospheric ionizing radiation and on risk analysis. A need for a multi-part or an international study in order to obtain a much larger cohort size with the radiation exposure patterns considered in detail came out long ago (see e.g. Friedberg et al., 1991). Two collaborative multi-national efforts are underway, one, called ESCAPE (European Study on Cancer risk among Airline Pilots and cabin crEw), with the participation of nine European countries (namely Denmark, Finland, Germany, Greece, Iceland, Italy, Norway, Sweden and United Kingdom), as composed of individual national-level projects, then pooled together in a joint analysis following a jointly agreed protocol (as sketched in Blettner et al., 1998), with about 30 000 pilots and 45 000 cabin crews as cohort members, with the mortality from cancer as goal. The other study, the Nordic one, called NO-ESCAPE (Northern European Study on Cancer risk among Airline Pilots and cabin crEw), is composed of cohorts from five northern European countries (namely Denmark, Finland, Iceland, Norway and Sweden), with smaller numbers of cases, and incidence of cancer as the end point (all Nordic countries have national cancer registries with full national coverage). These studies are expected to provide results with reduced incertitude on the issue. Most of the national-level studies are presently completed or close to completion, at least in their basic contents. The joint data analysis phase for the two above mentioned studies is close to completion. As for US research project, the only large effort currently underway is the NIOSH/FAA Study of Reproductive Disorders in Female Flight Attendants. This study, in which female primary school teachers of the same age distribution as the female cabin attendant are used as a control group, is performed in three parts: a questionnaire to be filled by each cabin attendant on reproductive outcomes, the study of the

ovulation function by using hormone testing, and an environmental assessment of the cabin space (Whelan 2002). In the framework of the same study, Grajewski et al. (2002) developed an algorithm to evaluate whether effects of cumulative doses could be distinguished analytically from effects of circadian rhythm disruption for crewmembers as cabin attendants, for which generally only limited flight history details are available. An evaluation in terms of radiation doses of the exposure for pregnant female cabin attendant has been performed by Nicholas et al. (2000a), with the technique presented in Nicholas et al. (2000b), in which the mother's body has been modeled with a soft-tissue slab phantom at various thicknesses (from 0 to 30 cm); the results was that in this model the body of the mother provides no significant shielding to the embryo from atmospheric ionizing radiation

The obtained data sets would provide potentialities for interesting side studies, like an assessment on effects of prenatal exposure, to obtain clues about possible embryonic damages and/or lethality (and/or possible association with childhood disease) and radiation exposure deterministic effects during organogenesis, especially due to high-LET radiation (see e.g. BEIR V, 1990), onset of radiation-related ocular cataract (Grahn, 1973; Cucinotta et al., 2001b), and an association to cellular studies to associate observed cell damages or chromosomal aberrations to a quantitative and qualitative evaluation of radiation exposure, to assess on possible evaluation of radiation doses on an individual level on the basis of lymphocyte chromosomal analysis (for recent reviews and discussions on these topics see e.g. Edwards, 1997, Wolf et al., 1999), in particular on possible radiation myelopoiesis and lymphopoiesis alterations (see, e.g. Jones et al., 1991). Recently Gundestrup et al. (2000), basing their analysis on 7 cases only, reported aircrew members who had myelodysplasia or acute myeloid leukemia showing the same cytogenetic abnormalities as non-aircrew-members patients of the same disease treated with radiotherapy alone, suggesting that these abnormalities could be indicators of previous radiation exposure.

ACKNOWLEDGEMENTS

The authors are grateful to Prof. V. Rafnsson for his invaluable help and support.

This work is dedicated to the memory of Maria Teresa Nicoletti.

REFERENCES

- Badhwar, G. D. (1997). The Radiation Environment in Low Earth Orbit. *Radiat. Res.*, **148 (Suppl.)**, S3-S10.
- Ballard, T.J., S. Lagorio, G. De Angelis, and A. Verdecchia (2000). Cancer Incidence and Mortality among Flight Personnel: A Meta-Analysis. *Aviat. Space Environ. Med.*, **71**, 216-224.
- Ballard, T.J., S. Lagorio, M. De Santis, G. De Angelis, M. Santaquilani, M. Caldora, and A. Verdecchia (2002). A Retrospective Cohort Mortality Study of Italian Commercial Airline Cockpit Crew and Cabin Attendants 1965-96. *Int. J. Occup. Environ. Health* **8**, 87-96.
- Band, P.R., J.J. Spinelli, V.T.Y. Ng, J. Moody, and R.P. Gallagher (1990). Mortality and Cancer Incidence in a Cohort of Commercial Airline Pilots. *Aviat. Space & Environ. Med.*, **61**, 299-302.
- Band, P.R., N.D. Le, R. Fang, M. Deschamps, A.J. Coldman, R.P. Gallagher, and J. Moody (1996). Cohort Study of Air Canada Pilots: Mortality, Cancer Incidence, and Leukemia Risk. *Am. J. Epidemiol.*, **143**, 137-143.

- BEIR V (5th Committee on the Biological Effects of Ionizing Radiations) (1990). *Health Effects of Exposure to Low Levels of Ionizing Radiation*. National Academy Press, Washington DC.
- Blair, A., J. Burg, J. Foran, et al. (1995). Guidelines for Application of Meta-Analysis in Environmental Epidemiology. *Reg. Toxicol. Pharmacol.*, **22**, 189-197.
- Blettner, M., and H. Zeeb (1999). Epidemiological Studies among Pilots and Cabin Crew. *Radiat. Prot. Dos.*, **86**, 269-273.
- Blettner, M., B. Grosche, and H. Zeeb (1998). Occupational Cancer Risk in Pilots and Flight Attendants: Current Epidemiologic Knowledge. *Radiat. Environ. Biophys.*, **37**, 75-80.
- Boice, J.D., Jr., M. Blettner, and A. Auvinen (2000). Epidemiologic Studies of Pilots and Aircrew. *Health Phys.*, **79**, 576-584.
- Cucinotta, F.A., W. Schimmerling, J.W., Wilson, L.E. Peterson, G.D. Badhwar, P. Saganti, and J.F. Dicello (2001a). Space Radiation Cancer Risks and Uncertainties for Mars Missions. *Radiat. Res.*, **156**, 682-688.
- Cucinotta, F.A., F.K. Manuel, J. Jones, G. Iszard, J. Murrey, B. Djojonegro, and M. Wear (2001b). Space Radiation and Cataracts in Astronauts. *Radiat. Res.*, **156**, 460-466.
- De Angelis, G., M. Caldora, M. Santaquilani, R. Scipione, and A. Verdecchia (2001a). Health Risks from Radiation Exposure for Civilian Aviation Flight Personnel: a Study of Italian Airline Crew Members. *Radiat. Res.*, **156**, 689-694.
- De Angelis, G., M. Caldora, M. Santaquilani, R. Scipione, and A. Verdecchia (2001b). Radiation-Induced Biological Effects on Crew Members: A Combined Analysis on Atmospheric Flight Personnel. *Phys. Med.*, **17**, **Suppl. 1**, 175-176.
- Edwards, A. A. (1997). The Use of Chromosome Aberrations in Human Lymphocytes for Biological Dosimetry. *Radiat. Res.*, **148 (Suppl.)**, S39-S44.
- Foelsche, T., R.B. Mendell, and J.W. Wilson (1974). *Measured and Calculated Neutron Spectra and Dose Equivalent Rates at High Altitudes: Relevance to SST Operations and Space Research*. NASA Technical Note TN D-7715.
- Friedberg, W., D.N. Faulkner, L. Snyder, et al. (1991). The Cosmic Radiation Environment at Air Carrier Altitudes and Possible Associated Health Risks. In *Proceedings of the Workshop 'Radiation Exposure of Civil Aircrew'* (Reitz, G., K. Schnuer, and K. Shaw, Eds.), **EUR 14964**, Luxembourg.
- Friedberg, W., D.N. Faulkner, L. Snyder, E.B. Darden, and K. O'Brien (1992). *Radiation Exposure of Air Carrier Crewmembers*. Federal Aviation Administration, Office of Aviation Medicine, Report No. DOT/FAA/AM-92/2.
- Grahn, D. (Ed.) (1973). *HZE Particle Effects in Manned Space Flight*. National Academy of Sciences, Washington, DC.
- Grajewski, B., E.A. Whelan, M.A. Waters, J.S. Kesner, and T.M. Schnorr (1994). Overview of the Proposed NIOSH-FAA Study of Reproductive Disorders in Female Flight Attendants. Paper presented at the 42nd Annual Meeting of the Radiation Research Society, Nashville, TN.
- Grajewski, B., M.A. Waters, E.A. Whelan, and T.F. Bloom (2002). Radiation Dose Estimation for Epidemiologic Studies of Flight Attendants. *Am. J. Industr. Med.* **41**, 27-37.
- Grayson, J.K. (1996). Radiation Exposure, Socioeconomic Status, and Brain Tumor Risk in the US Air Force: a Nested Case-Control Study. *Am. J. Epidemiol.*, **143**, 480-486.

- Grayson, J.K., and T.J. Lyons (1996). Brain Cancer, Flying, and Socioeconomic Status: a Nested Case-Control Study of USAF Aircrew. *Aviat. Space Environ. Med.*, **67**, 1152-1154.
- Greenland, S. (1987). Quantitative Methods in the Review of Epidemiologic Literature. *Epidemiol. Rev.*, **9**, 1-30.
- Gundestrup, M., and H.H. Storm (1999). Radiation-Induced Acute Myeloid Leukaemia and Other Cancers in Commercial Jet Cockpit Crew: A Population-Based Cohort Studies. *Lancet*, **354**, 2029-2031.
- Gundestrup, M, M. Klarskov Andersen, E. Sveinbjornsdottir, V. Rafnsson, H.H. Storm, and J. Pedersen-Bjergaard (2000). Cytogenetics of Myelodysplasia and Acute Myeloid Leukaemia in Aircrew and People Treated with Radiotherapy. *Lancet*, **356**, 2158 (letter).
- Haldorsen, T., J.B. Reitan, and U. Tveten (2000). Cancer Incidence among Norwegian Airline Pilots, *Scand. J. Work Envir. Health*. **26**, 106-111.
- Haldorsen, T., J. Reitan, and U. Tveten (2001). Cancer Incidence among Norwegian Airline Cabin Attendants. *Int. J.Epidemiol.* **30**,825-830.
- Hammar, N., A. Linnarsjö, L. Alfredsson, B.-G. Dammstrom, M. Johansson, and H. Eliasch (2002). Cancer Incidence in Airline and Military Pilots in Sweden 1961-1996. *Aviat. Space Environ. Med.*, **73**, 2-7.
- Hammer G.P., H. Zeeb, U. Tveten, and M. Blettner (2000). Comparing Different Methods of Estimating Cosmic Radiation Exposure of Airline Personnel. *Radiat. Environ. Biophys.*, **39**, 227-231.
- Haugli, L., A. Skogstadt, and O.H. Hellesoy (1994). Health, Sleep and Mood Perceptions Reported by Airline Crews Flying Short and Long Hauls. *Aviat. Space Environ. Med.*, **65**, 27-34.
- Hoffman, S.J., and D.L. Kaplan (Eds.) (1997). *Human Exploration of Mars: The Reference Mission of the NASA Mars Exploration Study Team*. NASA SP-6107.
- Hoiberg, A., and C. Blood (1983). Age-Specific Morbidity among Navy Pilots. *Aviat. Space Environ. Med.* **54**, 912-918.
- ICRP (International Commission on Radiological Protection) (1991). *1990 Recommendations of the International Commission of Radiological Protection*. ICRP Publication **60**, Pergamon Press, Oxford, United Kingdom.
- Irvine, D., and D.M. Davies (1999). British Airways Flightdeck Mortality Study. *Aviat. Space Environ. Med.*, **70**, 548-555.
- Jablon, S. (1984). Epidemiologic Perspectives in Radiation Carcinogenesis. In *Radiation Carcinogenesis: Epidemiology and Biological Significance* (Boice, J.D., and J.F. Fraumeni Jr, Eds.), Raven Press, New York, NY.
- James, J.T. (1997). Carcinogens in Spacecraft Air. *Radiat. Res.*, **148 (Suppl.)**, S11-S16.
- Jones, T.D., M.D. Morris, and R.W. Young (1991). A Mathematical Model for Radiation-Induced Myelopoiesis. *Radiat. Res.*, **128**, 258-266.
- Kaji, M., T. Tango, I. Asukata, et al. (1993). Mortality Experience of Cockpit Crewmembers from Japan Airlines. *Aviat. Space Environ. Med.*, **64**, 748-750.
- Kaune, W.T. (1993). Introduction to Power-Frequency Electric and Magnetic Fields. *Environmental Health Perspective Supplements*, **101 (Suppl. 4)**, 73-81.
- Kiefer, J. (1989). *Biological Radiation Effects*. Springer-Verlag, Berlin, Germany.

- Kiefer, J. (1993). On the Biological Significance of Radiation Exposure in Air Transport. *Radiat. Prot. Dos.*, **48**, 107-110.
- Kleinbaum, D., L. Kupper, and H. Morgerstern (1982). *Epidemiological Research*. Lifetime Learning Publications, Belmont, CA.
- Kraus, J.F. (1985). Epidemiological Studies on Health Effects in Commercial Pilots and Flight Attendants: A Review. *Sangyo Ika Dagaiku Zasshi*, **7 (Suppl.)**, 32-44.
- Letaw, J.R., R. Silberberg, and C.H. Tsao (1989). Radiation Hazards on Space Missions Outside the Magnetosphere. *Adv. Space Res.*, **9**, 285-291.
- Lyngø, E. (1996). Risk of Breast Cancer is Also Increased among Danish Female Airline Cabin Attendants. *Br. Med. J.*, **312**, 253.
- Messerschmid, E., and R. Bertrand (1999). *Space Stations Systems and Utilization*. Springer-Verlag, Berlin, Germany.
- NCRP (National Council on Radiation Protection and Measurements) (1987). *Recommendations on Limits for Exposure to Ionizing Radiation*. NCRP Report No. 91, Bethesda, MD.
- NCRP (National Council on Radiation Protection and Measurements) (1987). *Guidance on Radiation Received in Space Activities*. NCRP Report No. 98, Bethesda, MD.
- Nealy, J.E., L.C. Simonsen, and G.D. Qualls (1997). SEI Analysis of Deep Space Vehicle Shielding. In *Shielding Strategies for Human Space Exploration (Wilson, J.W., J. Miller, A. Konradi, and F.A. Cucinotta, Eds.)*, NASA CP-3360.
- Nicholas, J.S., D.T. Lackland, M. Dosemeci, L.C. Mohr, Jr., J.B. Dunbar, B. Grosche, and D.G. Hoel (1998). Mortality among US Commercial Pilots and Navigators. *J. Occup. Environ. Med.*, **40**, 980-985.
- Nicholas, J.S., K. Copeland, F.E. Duke, W. Friedberg, and K. O'Brien (2000a). *Galactic Cosmic Radiation Exposure of Pregnant Flight Crewmembers*. *Aviat. Space Environ. Med.*, **71**, 647-648.
- Nicholas, J.S., K. Copeland, F.E. Duke, W. Friedberg, and K. O'Brien (2000b). *Galactic Cosmic Radiation Exposure of Pregnant Aircrew Members*. Federal Aviation Administration, Office of Aviation Medicine, Report No. DOT/FAA/AM-00/33.
- Nicholas, J.S., G.C. Butler, D.T. Lackland, G.S. Tessier, L.C. Mohr Jr., and D.G. Hoel (2001). Health among commercial airline pilots. *Aviat. Space Environ. Med.* **72**, 821-826.
- NRC (National Research Council, Committee on Airliner Cabin Air Quality, Commission for Life Sciences) (1986). *The Airliner Cabin Environment: Air Quality and Safety*. National Academy Press, Washington DC.
- NRC (National Research Council, Committee on Toxicology, Commission for Life Sciences) (1992). *Guidelines for Developing Spacecraft Maximum Allowable Concentrations for Space Station Contaminants*. National Academy Press, Washington DC.
- NRC (National Research Council, Committee on Toxicology, Commission for Life Sciences) (2000). *Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants*. National Academy Press, Washington DC.
- Obe, G., R. Facius, G. Reitz, I. Johannes, and C. Johannes (1999). Manned Missions to Mars and Chromosome Damage. *Int. J. Radiat. Biol.*, **75**, 429-433.
- O'Brien, K., W. Friedberg, H.H. Sauer, and D.F. Smart (1994). Atmospheric Cosmic Rays and Solar Energetic Particles at Aircraft Altitudes. *Environment International*, **22 (Suppl.1)**, S9-S44.

- Petrov, V.M., V.S. Makhmtov, N.A. Panova, V.A. Shurshakov, Ts.P. Dachev, J.V. Semkova, and Yu.P. Matvijchuk (1994). Peculiarities of the Solar Proton Events of 19 October 1989 and 23 March 1991 According to the Measurements onboard the Mir Space Station. *Adv. Space Res.*, **14**, 645-650.
- Pukkala, E., A. Auvinen, and G. Wahlberg (1995). Incidence of Cancer among Finnish Airline Cabin Attendants. *Br. Med. J.*, **311**, 649-652.
- Rafnsson, V., J. Hrafnkelsson, and H. Tulinius (2000). Incidence of Cancer among Commercial Airline Pilots. *Occup. Environ. Med.*, **57**, 175-179.
- Reed, D.S., S. Glaser, and J. Kaldor (1980). Ozone Toxicity Symptoms among Flight Attendants. *Am. J. Ind. Med.*, **1**, 43-54.
- Reynolds P., J. Cone, M. Layfesky, D.E. Goldberg, and S. Hurley (2002). Cancer Incidence in California Flight Attendants (United States). *Cancer Causes Control*, **13**, 317-324.
- Rothman, K. (1986). *Modern Epidemiology*. Little, Brown & Company, Boston, MA.
- Ryan, P. (1991). Smoking and Commercial Airline Flights in Europe. *Eur. J. Cancer*, **27**, 1348-1350.
- SAAM (Subsystem Analysis and Analytical Models) (1996). *ISS Integrated Traffic Model Report (DAC 4 Final)*. Boeing-Report NASA-JSC-Contract NAS15-10000.
- Seldén, A., and G. Ahlberg (1995). Mortality and Cancer Morbidity after Exposure to Military Aircraft Fuel. *Aviat. Space Environ. Med.*, **62**, 789-794.
- Shea, M.A., and D.F. Smart (1990). A Summary of Major Solar Proton Events. *Solar Physics*, **127**, 297-320.
- Sinclair, W.K. (1985). Experimental RBEs of High-LET Radiations at Low Doses and the Implications for Quality Factor Assignment. *J. Rad. Prot. Dos.*, **13**, 319-326.
- Singleterry, R.C., and S.A. Thibeault (2000). *Materials for Low-Energy Neutron Radiation Shielding*. NASA Technical Paper TP-2000-210281.
- Suvanto, S., M. Partinen, M. Haermae, and J. Ilmarinen (1990). Flight Attendants' Desynchronization after Rapid Time Zone Changes. *Aviat. Space Environ. Med.*, **61**, 543-547.
- Tripathi, R.K., Wilson, J.W., Cucinotta, F.A., Nealy, J.E., Cloudsley, M.S., and Kim, M.H.Y. (2001). *Deep Space Mission Shielding Optimization*. Society for Automotive Engineers, Paper SAE 2001-01-2326.
- Turner, R.E., and G.D. Badhwar (1999). Mars 2001 Cruise Phase Radiation Measurements. In "Proceedings of the Workshop on Mars 2001: Integrated Science in Preparation for Sample Return and Human Exploration" (Lunar and Planetary Institute, Houston TX, October 2-4, 1999), Lunar and Planetary Institute, Houston, TX.
- Tveten, U. (1997). *Cosmic Radiation and Airline Pilots: Exposure Patterns of Norwegian SAS Pilots 1960 to 1994*. Report IFE/KR/E-96/008, Institute for Energy Technology, Kjeller, Norway.
- USEPA (United States Environmental Protection Agency) (1986). Guidelines for Carcinogen Risk Assessment, *Fed. Regist.*, **51**, 33992-34003.
- Vågerö, D., A.J. Swerdlow, and V. Beral (1990). Occupation and Malignant Melanoma: A Study Based on Cancer Registration Data in England and Wales and in Sweden, *Br. J. Industr. Med.*, **47**, 317-324.
- Wartenberg D., and C.P. Stapleton (1998). Risk of Breast Cancer is also Increased among Retired US Female Airline Cabin Attendants. *Br. Med. J.*, **316**, 1902 (letter).

- Wartenberg D., and C.P. Stapleton (1999). Risk of Breast Cancer among Female Airline Cabin Attendants. *Br. Med. J.*, **318**, 126 (letter).
- Weaver, D.B., M.B. Duke, and B.R. Roberts (1993). Mars Exploration Strategies: A Reference Design Mission. Paper IAF 93-Q.1.383, presented at the 44th Congress of the International Astronautical Federation, held in Graz, Austria, in 1993.
- Whelan, E.A. (2002). *The Working Women's Health Study: the NIOSH/FAA Study of Reproductive Disorders in Female Flight Attendants*. National Institute for Occupational Safety and Health, Status Reports Q2-2002.
- Wilson, J.W. (1981). Solar Radiation Monitoring for High Altitude Aircraft. *Health Phys.*, **41**, 607-617.
- Wilson, J.W. (2000). Overview of Radiation Environments and Human Exposures. *Health Phys.*, **79**, 470-494.
- Wilson, O.J., B.F. Young, and C.K. Richardson (1994). Cosmic Radiation Doses Received by Australian Commercial Flight Crews and the Implications of ICRP. *Health Physics*, **66**, 493-502.
- Wilson, J.W., L.W. Townsend, W. Schimmerling, G.S. Khandelwal, F. Khan, J.E. Nealy, F.A. Cucinotta, L.C. Simonsen, J.L. Shinn, and J.W. Norbury (1991). *Transport Methods and Interactions for Space Radiations*, NASA Reference Publication #1257.
- Wilson, J.W., M.Y. Kim, M.S. Cloudsley, J.H. Heinbockel, R.K. Tripathi, R.C. Singleterry, J.L. Shinn, and R. Suggs (1999). Mars Surface Ionizing Radiation Environment: A Need for Validation. In "*Proceedings of the Workshop on Mars 2001: Integrated Science in Preparation for Sample Return and Human Exploration*" (Lunar and Planetary Institute, Houston TX, October 2-4, 1999), Lunar and Planetary Institute, Houston, TX.
- Wilson, J.W., D.L. Maiden, P. Goldhagen, H. Tai, and J.L. Shinn, this book. Overview of Atmospheric Ionizing Radiation (AIR). In "*Proceedings of the Workshop Atmospheric Ionizing Radiation (AIR) Investigators' Workshop: Preliminary Results and Lesson Learned from the June 1997 Flights*" (NASA Langley Research Center, Hampton VA, March 30-31, 1998), this book.
- Winter, P.M. (1968). Aviator's Cancer. *Lancet* **2**, 285 (letter).
- Wolf, G., R. Pieper, and G. Obe (1999). Chromosomal Alterations in Peripheral Lymphocytes of Female Cabin Attendants. *Int. J. Radiat. Biol.*, **75**, 829-836.
- Wu, H., W. Atwell, F.A. Cucinotta, and T.C. Yang (1996). *Estimates of Space Radiation-Induced Cancer Risks for International Space Station Orbits*. NASA Technical Memorandum #104818, NASA Center for Aerospace Information, Linthicum Heights, MD.
- Zubrin, R. (1997). *The Case for Mars: the Plan to Settle the Red Planet and Why We Must*. Touchstone Books, Simon & Schuster Publishing, New York, NY.
- Zurek, R.W. (1992). Comparative Aspects of the Climate of Mars: An Introduction to the Current Atmosphere. In *Mars* (Kieffer, H.H., B.M. Jakowsky, C.W. Snyder, and M.S. Matthews, Eds.), Univ. of Arizona Press, Tucson, AZ.

Table 1. Cancer Sites with significant positive association for civilian airline flight personnel crew members. Confidence limits are 90 or 95 percent depending on study.

Cancer Site	Sex	Job	Type	Confidence Limits		Source
All Sites*	M	CA	SIR	1.3	2.2	Haldorsen et al. (2001)
All Sites*	F	CA	SIR	1.0	1.6	Rafnsson et al. (2001)
Bone	F	CA	SIR	1.8	54.4	Pukkala et al. (1995)
Brain	M	P	SIR	1.2	7.9	Band et al. (1990)
Brain	M	P	SMR	1.4	9.5	Band et al. (1990)
Breast	F	CA	SIR	1.2	2.2	Pukkala et al. (1995)
Breast	F	CA	SIR	1.0	4.3	Wartenberg et al. (1998, 1999)
Breast	F	CA	SIR	1.09	1.83	Reynolds et al. (2002)
Esophagus	M	CA	SIR	2.7	11.4	Haldorsen et al. (2001)
Hodgkin Lymphoma	M	P	SIR	1.2	11.7	Band et al. (1990)
Kidney and Pelvis	M+F	P	PMR	1.18	3.06	Nicholas et al. (1998)
Leukemia – AML	M	P	SIR	2.1	9.3	Band et al. (1996)
Leukemia – Myeloid	M	P	SIR	1.4	5.5	Band et al. (1996)
Liver*	M	CA	SIR	1.3	39.2	Haldorsen et al. (2001)
Prostate	M	P	SIR	1.4	2.5	Band et al. (1996)
Rectum	M	P	SMR	1.2	11.2	Band et al. (1990)
Skin – Melanoma	M	P	SMR	1.5	6.3	Irvine & Davies (1999)
Skin – Melanoma	M	P	SIR	1.1	2.7	Haldorsen et al. (2000)
Skin – Melanoma	M	P	SIR	5.0	36.5	Rafnsson et al. (2000)
Skin – Melanoma	M	CA	SIR	1.1	6.4	Haldorsen et al. (2001)
Skin – Melanoma	M	P	SIR	2.85	4.23	Nicholas et al. (2001)
Skin – Melanoma	F	CA	SIR	1.2	6.7	Rafnsson et al. (2001)
Skin -- Melanoma	M	P	SIR	1.27	4.54	Hammar et al. (2002)
Skin -- Melanoma	F	CA	SIR	1.28	4.38	Reynolds et al. (2002)
Skin – Other Cancers	M	P	SIR	1.1	2.2	Band et al. (1990)
Skin – Other Cancers	M	PE (jets)	SIR	2.1	4.2	Gundestrup & Storm (1999)
Skin – Other Cancers	M	P	SIR	1.3	4.0	Haldorsen et al. (2000)
Skin – Other Cancers*	M	CA	SIR	4.5	18.8	Haldorsen et al. (2001)
Skin – Other Cancers*	M	CA	SIR	5.18	15.3	Reynolds et al. (2002)
Prostate#	M	P	SIR	1.19	2.29	Ballard et al. (2000)
Skin – Melanoma#	M	P	SMR	1.02	3.82	Ballard et al. (2000)

*cancer outcome possibly related to lifestyle only;

results from meta-analysis of previous studies, then adjusted for socio-economical status;

AML = Acute Myeloid Leukemia;

CA = Cabin Attendants;

P = Pilots only;

PE = Pilots and flight Engineers;

PMR = Proportional Mortality Ratio;

SIR = Standardized Incidence Ratio;

SMR = Standardized Mortality Ratio

Table 2. Results for cancer sites with adjusted RRs showing excess risk (results from Ballard et al., 2000).

Results for Male Pilots		Results for Female Flight Attendants	
Cancer Site	RR (95% CI)	Cancer Site	RR (95% CI)
COLON (mortality)	1.05 (0.71-1.53) *	ALL-SITES (incidence)	1.29 (0.98-1.70)
MELANOMA (mortality)	1.97 (1.02-3.82) #		
MELANOMA (incidence)	1.07 (0.55-2.10) #	MELANOMA (incidence)	1.54 (0.83-2.87) ^
PROSTATE (mortality)	1.11 (0.70-1.75) *		
PROSTATE (incidence)	1.65 (1.19-2.29) *	BREAST (incidence)	1.35 (1.00-1.83) #
BRAIN (mortality)	1.45 (0.75-2.80) §		
BRAIN (incidence)	1.74 (0.87-3.30) §		

* SES factor 1.1 # SES factor 1.5 § SES factor 1.2 ^ SES factor 1.3