Noteworthy Decision Summary

Decision: WCAT-2007-00515-RB **Panel**: Randy Lane, Janice Leroy, Lesley Christensen **Decision Date:** February 13, 2007

Whether breast cancer due to the nature of employment – Flight attendant – Analysis of medical opinions

This decision is noteworthy as WCAT allowed the employer's appeal, finding that a flight attendant's breast cancer was not due to the nature of her employment that is, her exposure to ionizing and cosmic radiation during long-haul/intercontinental flights.

The worker, a flight attendant, was diagnosed with infiltrating carcinoma of her left breast. At issue was whether the breast cancer was due to the nature of worker's employment. The Workers' Compensation Board operating as WorkSafeBC (Board), citing an opinion by Dr. W that the chances of an occupational rather than a non occupational cause for breast cancer were fairly evenly balanced, applied section 99 of the *Workers Compensation Act* (Act) and concluded that the worker's breast cancer was due to the nature of her employment.

The Board's decision was appealed by the employer to the Workers' Compensation Review Board (Review Board). However, as the appeal had not been considered by a Review Board panel before March 3, 2003, it was decided as a WCAT appeal pursuant to section 38 of the *Workers Compensation Amendment Act (No. 2), 2002*.

The WCAT panel allowed the employer's appeal, finding that the worker's breast cancer was not due to the nature of her employment. The panel reviewed medical opinions by Dr. W, Dr. Band and Dr. Boyd, and a number of epidemiologic studies, and considered the Bradford Hill criteria in assessing the issue of causation generally. The panel concluded that the evidence was not sufficient to establish that the worker's individual exposure was such that her personal risk was so elevated that the possibility that her breast cancer was due to the nature of her employment was equally balanced with the possibility that it was not.

The panel noted that the worker's exposure would have to have been extraordinary, when compared to a cohort of flight attendants with a similar number of years of employment, to elevate her personal risk to 2.0 or more. (A relative risk of 2.0 is often equated with a 50% likelihood that an exposed person's disease was caused by the agent and a relative risk greater than 2.0 would permit an inference that an individual's disease was more likely than not caused by the implicated agent.) The evidence did not establish that the worker had extraordinary exposure. To the extent that there was a modestly increased risk of breast cancer amongst flight attendants, the panel found that the evidence failed to establish that the worker's circumstances were sufficient to increase her personal relative risk to near 2.0, such that subsection 250(4) (the WCAT equivalent of section 99) of the Act would be applicable to her claim.

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Panel: Randy Lane, Vice Chair
Janice Leroy, Vice Chair
Lesley Christensen, Vice Chair

Introduction

In December 2001 the worker, then a 49-year-old Caucasian flight attendant, was diagnosed with infiltrating carcinoma of her left breast. By decision of December 12, 2002 a claims adjudicator with the Workers' Compensation Board, now operating as WorkSafeBC (Board), accepted the worker's claim on the basis that her cancer was due to the nature of her employment.

The worker's employer appealed the December 12, 2002 decision to the former Workers' Compensation Review Board (Review Board). In March 2003 the appeal was transferred to the Workers' Compensation Appeal Tribunal (WCAT) as a result of the terms of section 38 of the *Workers Compensation Amendment Act (No. 2), 2002*.

As will be outlined below, submissions on the merits of the appeal were not completed until May 2006.

The Chair of WCAT assigned this appeal to a three-person panel under subsection 238(5) of the *Workers Compensation Act* (Act). This is not a precedent panel established under subsection 238(6).

By letter of June 22, 2004 the parties were advised of the decision of the three-person panel that the appeal would proceed by way of written submissions. The lawyer representing the worker has made several requests that an oral hearing be held. We have considered the rule regarding the holding of an oral hearing set out in item #8.90 of WCAT's *Manual of Rules of Practice and Procedure* (MRPP) and the other criteria set out in that item. The rule provides that WCAT will normally grant a request for an oral hearing where the appeal involves a significant issue of credibility. Oral hearings may also be granted where there are significant factual issues to be determined, multiple appeals of a complex nature, complex issues with important implications for the compensation system, or other compelling reasons for convening an oral hearing. The rule provides that WCAT will normally conduct an appeal on a read and review basis where the issues are largely medical, legal, or policy-based and credibility is not at issue.

We have decided this appeal without an oral hearing. We do not consider that there are significant issues of credibility involved in this appeal. As well, there are no significant factual issues to be determined. While we accept that the issue on appeal has great implications for the worker and the employer, we do not consider that it has important implications for the compensation system as a whole. The issue on appeal involves an examination of medical and scientific evidence which can be undertaken on a read and review basis.

Issue(s)

At issue is whether the worker's breast cancer was due to the nature of her employment.

Jurisdiction

On March 3, 2003, the Appeal Division of the Board and the Review Board were replaced by the WCAT. As this appeal had not been considered by a Review Board panel before that date, it has been decided as a WCAT appeal pursuant to section 38 of the *Workers Compensation Amendment Act (No. 2), 2002*.

WCAT has exclusive jurisdiction to inquire into, hear and determine all those matters and questions of fact, law, and discretion arising or required to be determined in an appeal before it (section 254 of the Act). It is not bound by legal precedent (subsection 250(1) of the Act). WCAT must make its decision on the merits and justice of the case, but, in so doing, it must apply a policy of the board of directors of the Board that is applicable in the case.

This is an appeal by way of rehearing, rather than a hearing *de novo* or an appeal on the record. WCAT has jurisdiction to consider new evidence, and to substitute its own decision for the decision under appeal.

Background

In a December 12, 2001 report Dr. Kuusk, a specialist in general surgery, noted that the worker had had nodular breasts for many years and that she had fibroids in the left lateral breast. She noted that menarche occurred when the worker was 15 years of age. The worker had a deep vein thrombosis when she was on birth control pills in her 20s. She had had one pregnancy at age 30. There was no family history of breast disease. As of December 2001 she was pre-menopausal and not on any hormones. The worker had Factor V Leiden which produced superficial thrombophlebitis.

A December 13, 2001 surgical pathology consultation report determined that a biopsy of the worker's left breast showed infiltrating carcinoma, predominantly lobular.

On January 8, 2002 the worker underwent a left axillary dissection and left fine wire localization biopsy. A January 11, 2002 surgical pathology report indicated that the worker had "Invasive tubulolobular carcinoma, grade I/III."
A January 25, 2002 report by Dr. O'Reilly, a medical oncologist with a specialty in internal medicine,[1] noted that the worker began having mammograms when she was 39 years old and felt cysts in her breast. Dr. O'Reilly noted the worker's episode of deep vein thrombosis at age 21 while taking oral contraceptives and noted that the worker was "G2 P1" (which we interpret to mean gravida 2 and para 1)[2]. She also noted the worker's advice that she did not use tobacco or alcohol and that there was no family history of cancer. The report concludes with the following observations of note:

> In addition, the patient had many questions concerning why she got breast cancer and she was reassured that there is no known association with stress in her life or with her job as a flight attendant and that unfortunately, this just happens.
>
> [all quotations in this decision are reproduced as written, save for changes noted]

In her March 25, 2002 application for compensation the worker indicated that she linked her breast cancer to exposure to ionizing radiation and cosmic radiation subsequent to January 1974.

On April 2, 2002 the worker underwent mastectomy, mastopexy, and tissue expander reconstruction.

In her May 8, 2002 claim log entry the claims adjudicator documented, among other matters, the worker's evidence as to her flying activities as a flight attendant since 1974. The claim log contains the following information:

> This claim is for left breast cancer, the worker is employed as a flight attendant with [employer]. She started with [employer] in 1974 in Montreal. She stayed there for approximately six months until August of that year when she was transferred to Winnipeg. She worked out of Winnipeg until 1979 and from there she went to Toronto for approximately one year. After the one year in Toronto she went back to Winnipeg until 1985. In 1985 she went to Vancouver until 1997 at which time she went back to Toronto until 2000. She came back to Vancouver in 2000 and her last day worked under this claim is in December 2001.

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1 While the report indicates that it was signed electronically by Dr. O'Reilly, it appears that it was prepared by a resident in medical oncology. However, given that it was signed electronically by Dr. O'Reilly, we will regard Dr. O'Reilly as the author of the report.

2 According to *Dorland's Illustrated Medical Dictionary, 26th ed.* (W.B. Saunders Company Toronto: 1985) gravida means a pregnant woman and para means a woman who has produced a viable young regardless of whether the child was living at birth.

> The worker indicates that when she first started working in Winnipeg she did mostly domestic flights within Canada. When she worked in Toronto for the one year she again, did domestic flights. In Winnipeg where she worked from approximately 1980 to 1985, she did domestic flights but as well in the summertime she would fly from Winnipeg to London. She thinks it was her Winnipeg to London route that played a big part in her cancer. She states that during the domestic flights she would fly on a DC9 or a 727. When she did the summertime routes from Winnipeg to London she flew on an L-10/11 which is the plane that she believes may have played a role in her exposure. She indicates that prior to doing the Winnipeg to London route she would occasionally fly on an L10/11. From 1985 to 1997 in Vancouver she again did mostly domestic flights but a sprinkling of overseas flights to London. During this time she was flying DC-8, 747 and some L-500. In 1997 to the year 2000 she did mostly overseas, which included London, Tel-Aviv, Delhi, Frankfurt, Copenhagen but mostly London. In the year 2000 when she came back to Vancouver until her last day worked in 2001, December, she did one full year of flights to Japan and then mostly flights to Shanghai and Hong Kong. All of her flights from her last bit in Vancouver (2000 to her last day worked) were Asia related flights.

The claims adjudicator noted the worker's advice that for one and one-half years prior to December 2001 she had a lump in her breast. It was considered to be a cyst. In May 2001 the lump became larger, and it started to become more painful. She underwent a mammogram in November 2001. She was advised that there was a lump behind the cyst. A needle biopsy confirmed that both the lump and the cyst were positive for breast cancer.

The worker advised that, other than the cancer, she was in good health and that she maintained a fitness program. She advised that she had Factor V Leiden. She had never been a cigarette smoker, but from age 26 to age 47 she had lived with a smoker who smoked in the home. There was no family history of cancer. She had one child, age 18, whom she breast fed for nine months. She was pre-menopausal when the cancer was diagnosed. She drank alcohol and considered herself a social drinker; she drank wine.

By letter of July 23, 2002 the employer provided the Board with a record of the routes flown by the worker between June 1995 and December 2001 and the total flying hours.

In her August 28, 2002 report Dr. Miller, a gynecologic oncologist, noted that the worker was a non-smoker and only occasionally drank alcohol. She observed that the worker's obstetric history was as follows: "Gravida 1, Para 1, having had one normal vaginal delivery."

In her August 1, 2002 claim log entry the case manager requested a medical opinion regarding whether the worker's breast cancer was due to the nature of her employment. In his September 9, 2002 claim log entry Dr. W, a Board medical advisor in the Board's Occupational Health Section, who holds a DIH (Diploma in Industrial Health) and is a certificant of the Canadian Board of Occupational Medicine, provided the following opinion:

> Breast cancer occurs in the general population and is one of the two most common cancers in females over the age of 40. There is no obvious cause in the vast majority of cases although various risk factors have been identified such as positive family history for breast cancer, use of oral contraceptives, ionizing radiation, cigarette smoke, no pregnancies, overweight, to name a few.
>
> Risk factors relevant to work as a flight attendant include ionizing or cosmic radiation and prior to the mid 1990's, the inhalation of second-hand cigarette smoke.
>
> A review of the medical literature supports female flight attendants being at increased risk for breast cancer as compared to the general population. The risk becomes statistically significant amongst flight attendants with more than 15 years experience, the estimated risk varying between 1.3 and 1.87. In two of the three studies I reviewed, the confidence interval includes the value of 2.0, indicating a possible doubling of risk, i.e., out of every 200 cases, 100 would have occurred anyway and 100 would be work caused.
>
> If I am correct in assuming [the worker] started work as a flight attendant considerably more than 15 years before the diagnosis of her breast cancer was made, there is no strong family history of breast cancer or other non occupational risk factors, I think that the chances of an occupational rather than a non occupational cause are fairly evenly balanced.

Dr. W cited four papers which we have listed in order of their publication date: Pukkala *et al*.,[3] Rafnsson *et al*.,[4] Reynolds *et al*.,[5] and Friedberg *et al*.[6]

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[3] Pukkala, E. *et al*. Incidence of cancer among Finnish airline cabin attendants, 1967-92. *British Medical Journal.* 1995 311: 649-652.

[4] Rafnsson, V. *et al*. Risk of breast cancer in female flight attendants: a population-based study (Iceland). *Cancer Causes and Control.* 2001 12(2): 95-101

[5] Reynolds, P *et al.* Cancer incidence in California flight attendants (United States). *Cancer Causes and Control.* 2002 13(4): 317-24.

[6] Friedberg, W *et al.* Radiation exposure of aircrews. *Occupational Medicine: State of the Art Reviews.* 2002 17(2): 293-309.

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In its September 23, 2002 report of injury or occupational disease the worker's employer indicated that it objected to the claim being accepted, on the basis that there was no evidence to relate the worker's cancer to her employment.
By decision of December 12, 2002 the claims adjudicator advised the employer that the Board had determined that the worker's breast cancer was due to the nature of her employment. The claims adjudicator cited Dr. W's opinion. She indicated that the "probabilities" were evenly balanced such that section 99 of the Act supported a conclusion that the worker's breast cancer was due to the nature of her employment.

On December 20, 2002 the worker underwent bilateral laparoscopic oophorectomies. On January 20, 2003 she underwent implant reconstruction.

The employer filed a January 13, 2003 notice of appeal with the Review Board. Mr. Winter, the employer's lawyer, provided a March 9, 2004 submission which included a February 24, 2004 opinion from Dr. Band. A book of reference materials was received on April 5, 2004. While the worker completed a notice of participation, she did not provide a response by the July 14, 2004 deadline WCAT set for a response to Mr. Winter's submission.

By letters of August 24, 2004 and September 15, 2004 Ms. Symes, a lawyer, indicated that she had been retained by the worker's union. By memorandum of September 17, 2004 the three-person panel assigned to this appeal provided the worker with 12 months in which to respond to the employer's materials. Ms. Symes provided an October 25, 2005 submission which was followed by a November 2, 2005 book of authorities and a November 9, 2005 book of reference materials. Ms. Symes' materials included an October 11, 2005 opinion from Dr. Boyd.

By letter of March 2, 2006 the parties were provided with copies of a meta-analysis[7] by Buja *et al.*[8] of published data regarding cancer incidence among female flight attendants.

Mr. Winter provided a March 14, 2006 submission in response to Ms. Symes' October 28, 2005 submission and a March 22, 2006 submission in response to the meta-analysis distributed by WCAT. On March 23, 2006 he also provided a copy of a chapter from *Textbook of Cancer Epidemiology*, Adami, H-O *et al.* eds., Oxford University Press, 2002.

Ms. Symes provided a May 9, 2006 submission which was accompanied by an undated report by Dr. Boyd. Mr. Winter provided a May 26, 2006 response.

[7] Meta-analysis involves the use of statistical techniques in a systematic review to integrate the results of included studies.

[8] Buja, A *et al.* Cancer incidence among female flight attendants: a meta-analysis of published data. *Journal of Women's Health*. 2006 Jan-Feb;15(1):98-105.

By letter of August 15, 2006 Mr. Winter provided WCAT with a copy of Dr. Band's bill for $11,000.00 and a copy of the employer's cheque to Dr. Band for $11,000.00.

Ms. Symes was provided with a copy of Mr. Winter's letter and asked to provide information as to the expenses associated with Dr. Boyd's reports. By letters of November 14, 2006 she provided that information. By a December 4, 2006 telephone call, Mr. Winter advised that he would not be providing a response.

Reasons and Decision

The Concept of Relative Risk in Epidemiological Studies

Before proceeding further, it is important that readers understand some of the concepts and language used in epidemiological studies and discussions.

As noted in *WCAT Decision #2004-00265-AD* relative risk is calculated by comparing the incidence of disease or death amongst people exposed to an agent with the incidence of disease or death amongst the unexposed. A relative risk of 2.0 is often equated with a 50% likelihood that an exposed person's disease was caused by the agent and a relative risk greater than 2.0 would permit an inference that an individual's disease was more likely than not caused by the implicated agent. In cancer incidence studies where cohort incidence is compared to incidence in the general population, SIR refers to standardized incidence ratio. In cancer mortality studies using the same comparison, SMR refers to standardized mortality ratio. An SIR or SMR may be expressed in two ways: for example, 150 or 1.5.

That WCAT decision also notes that random error reflects the extent to which an estimate is greater or lesser than the true relative risk. Confidence intervals, which also reflect statistical significance, refine the idea of the role of random error:

> A confidence interval is a range of values calculated from the results of a study within which the true value is likely to fall. The width of the interval reflects random error. If the limits of the interval do not include 100 (a relative risk of 1.0) the risk is statistically significant. The larger the sample size in a study (all other things being equal), the narrower the confidence boundaries will be (indicating greater statistical stability), thereby reflecting the decreased likelihood that an association that is found in the study would occur if the true association is actually 1.0. Confidence intervals are often noted in connection with relative risks. A 95 percent confidence interval means that the range set by the interval will contain the true risk 95 percent of the time.

Dr. Band asserted that the relative risk estimated from study data, also referred to as the point estimate, has the highest likelihood of being the true value. The likelihood is less for values that depart from the point estimate, that is, all other values within the confidence interval. (We note that Dr. Boyd did not dispute that contention by Dr. Band).

Review of Dr. Band's Report

As indicated by his *curriculum vitae*, Dr. Band is a medical doctor who is recognized by the College of Physicians and Surgeons of Quebec as a specialist in internal medicine and oncology. His *curriculum vitae* also lists an "F.R.C.P.(C)" which suggests that he is recognized as a specialist by the Royal College of Physicians of Canada; however, it is not clear what specialty designation he may hold in that regard. Between 1982 and 1996 he was the chair of the British Columbia Cancer Agency's Division of Epidemiology, Biometry and Occupational Oncology. In 1995-1996 he was the British Columbia Cancer Agency's vice-president, Epidemiology and Cancer Prevention. Since 1996 he has worked as a senior medical epidemiologist for Health Canada. He is a professor at the McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa. Dr. Band was the lead author of a study concerning airline pilots and cancer.[9]

Dr. Band indicated that established risk factors for breast cancer include, in addition to gender and age, socioeconomic status, reproductive factors such as late age at first birth, benign breast disease, and high-dose radiation. He said current oral contraceptive use is a probable risk factor, but acknowledged there was no evidence that the worker had used oral contraceptives since her deep vein thrombosis at 21 years of age. He said possible risk factors include low-dose radiation. He noted that the respective relative risks were 1.3-3.5, 1.5, and 1.5-1.8 in connection with the risk factors of (i) age at first birth of equal to or greater than 30 years, (ii) benign breast disease, and (iii) benign breast disease, biopsied, respectively.

Dr. Band's opinion is notable for the fact that he provided comments concerning sample size and methodology associated with the 16 studies/documents identified by him with respect to flight attendants and cancer incidence and/or mortality. Such comments are of significant assistance in evaluating the weight to be attached to the results of studies. Also of interest are letters from the authors of such studies in response to letters written to journals following publication of the studies. The 16 documents identified by Dr. Band include a total of four such letters.

Dr. Band identified and discussed seven cohort cancer incidence studies. They are listed in order of their publication as follows (footnotes are not given for studies footnoted above): Pukkala *et al*., Lynge[10], Wartenberg and Stapleton[11], Rafnsson *et al*.,

9 Band, PR *et al.* Cohort study of Air Canada pilots: mortality, cancer incidence, and leukemia risk. *American Journal of Epidemiology*. 1996 Jan 15;143(2):137-43.

10 Lynge, E. Risk of breast cancer is also increased among Danish female airline cabin attendants. *British Medical Journal*. 1996 Jan 27;312(7025):253.

11 Wartenberg, D and Stapleton, CP. Risk of breast cancer is also increased among retired US female airline cabin attendants. *British Medical Journal*. 1998 Jun 20;316(7148):1902.

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Haldorsen *et al*.[12], Reynolds *et al*., and Linnersjö *et al.* [13] He identified and discussed three mortality studies listed in order of their publication as follows: Ballard *et al.*[14], Blettner *et al*.[15] and Zeeb *et al*.[16] He identified and discussed a cancer incidence study based on case-control methodology[17] which was nested in one of the cohort studies: Rafnsson *et al.* (2003)[18]. He also identified a meta-analysis conducted by Ballard *et al*.[19]

As noted by Dr. Band, there was a statistically significant standard incidence ratio of 1.87 for the cohort of Finnish flight attendants studied by Pukkala *et al.* However, the authors noted that the incidence of breast cancer among Finnish women of working age who come from the highest social class is 30% higher than that of the average population and that bias caused by non-occupational lifestyle factors was possible. When they adjusted for "social class", the standardized incidence ratio dropped to 1.4 with a confidence interval[20] of 0.9-2.2. It ceased to be statistically significant.

Dr. Band noted that the study methodology used by Pukkala *et al*. was good, but as stated by the authors, a limitation of the study was the absence of individual data on major confounding. He observed that the correction for social class reduced the standardized incidence ratio by 25% and contended that correcting for other confounding factors would further reduce the ratios. He also drew attention to the authors' comments that, given the small size of the cohort and the young age of the cohort, "the numbers of cancer cases were smaller and the risk estimates subject to large random variation." He also noted the authors' comments that reproductive factors are the strongest known etiological component of breast cancer and account for most of the occupational and social class variation in the incidence of breast cancer in Finland. The authors observed that data for individual cabin attendants were not available and that studies linking individuals' history of exposure and exact data on confounders were required.

[12] Haldorsen, T. *et al.* Cancer incidence among Norwegian airline cabin attendants. *International Journal of Epidemiology*. 2001 Aug;30(4):825-30.

[13] Linnersjö *et al.* Cancer incidence in airline cabin crew: experience from Sweden. *Occupational and Environmental Medicine*. 2003 Nov;60(11):810-4.

[14] Ballard, TJ. A retrospective cohort mortality study of Italian commercial airline cockpit crew and cabin attendants, 1965-96. *International Journal of Occupational and Environmental Health*. 2002 Apr-Jun;8(2):87-96.

[15] Blettner, M *et al*. Mortality from cancer and other causes among airline cabin attendants in Germany, 1960-1997. *American Journal of Epidemiology.* 2002 Sep 15;156(6):556-65.

[16] Zeeb, H *et al.* Mortality from cancer and other causes among airline cabin attendants in Europe: a collaborative cohort study in eight countries. *American Journal of Epidemiology.* 2003 Jul 1;158(1):35-46.

[17] A case-control study involves identifying a group of individuals with the disease of interest and a group of people without that disease. Proportions of cases and controls that were exposed and proportions of cases and controls that were not exposed are then calculated.

[18] Rafnsson, V *et al.* Breast cancer risk in airline cabin attendants: a nested case-control study in Iceland. *Occupational and Environmental Medicine*. 2003 Nov;60(11):807-9.

[19] Ballard, T *et al.* Cancer incidence and mortality among flight personnel: a meta-analysis. *Aviation, Space, and Environmental Medicine*. 2000 Mar;71(3):216-24.

[20] All confidence intervals noted in this decision are 95% confidence intervals unless otherwise specified.

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The study by Pukkala *et al.* was the subject of two letters to the journal in which the study was published. Pukkala *et al* responded.[21] We obtained the two letters and the response by Pukkala *et al.* upon which neither Dr. Band nor Dr. Boyd commented. One letter writer considered that the study made no correction for the healthy worker effect and another letter writer contended that the authors omitted cigarette smoking which might have a role in their findings. Pukkala *et al.* considered that passive smoking was mainly a risk factor for lung cancer and observed that the fact that no clear increase was noted in the incidence of lung cancer and other cancers related to smoking suggested that the cabin crew did not smoke more than average and that passive smoking was not a major problem in that cohort. They observed that the evidence regarding cigarette smoking as a risk factor for breast cancer was weak and inconsistent. They agreed that several factors might explain the excess risk of breast cancer noted by them. They observed that the aim of the study was to detect a possible increase in risk and that more detailed analyses were needed to identify causal factors.

Dr. Band had methodological concerns associated with Wartenberg and Stapleton's standardized incidence ratio of 2.0 with a confidence interval of 1.0-4.3. He observed that the published document is a one-page letter reporting results of an unpublished study. No numbers were provided regarding the size of the population studied and the number of observed and expected cancer cases. Information found in a meta-analysis by Ballard *et al.* confirmed that the population studied by Wartenberg and Stapleton was only 287 flight attendants.[22] Dr. Band noted that Wartenberg and Stapleton supplied no information regarding methodology. Wartenberg and Stapleton declared that "more carefully designed studies were needed." In their letter which replied to two letters to the editor following the publication of the initial document[23], Wartenberg and Stapleton indicated that their preliminary study was too small to rule out or to confirm any risk factors for breast cancer among flight attendants. Of interest is the fact that Auvinen *et al*., the authors of one of the letters, commented that the strongest factors that had been shown empirically to affect the risk of breast cancer were parity and age at first birth. They declared that more research was clearly needed to elucidate the reasons for increased breast cancer among cabin crew. Aside from methodological concerns, the

[21] See the following:

- Roff, Sr. Cancer among airline cabin attendants. Interpretation of study minimises occupational hazards *British Medical Journal* 1996 Jan 6;312(7022):53-4.
- Fogelhorn, R. Cancer among airline cabin attendants. Risk due to active and passive smoking should have been mentioned. *British Medical Journal* 1996 Jan 6;312(7022):53.
- Pukkala *et al*. Authors' reply. *British Medical Journal* 1996 Jan 6;312(7022):53.

[22] In his comments regarding the meta-analysis by Ballard *et al.* Dr. Band noted that those authors obtained data from Wartenberg and Stapleton which indicated that their study involved 287 retired flight attendants in whom seven breast cancer cases were observed.

[23] See the following:

- Badrinath, P and Ramaiah, S. Risk of breast cancer among female airline cabin attendants. Findings may have been due to exposure to cosmic radiation or recall bias. *British Medical Journal*. 1999 Jan 9; 318(7176):125.
- Auvinen, A et al. Large European studies are now carried. *British Medical Journal.* 1999 Jan 9; 318(7176):125-6.
- Wartenberg, D and Stapleton, CP. Authors' Reply. *British Medical Journal.* 1999 Jan 9;318(7176):126.

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confidence interval calculated by Wartenberg and Stapleton includes 1.0. Thus, the standardized incidence ratio was not statistically significant.
Dr. Band commented that two studies were of "borderline significance" (Rafnsson *et al.* and Reynolds *et al.),* with the latter study raising questions from a methodological viewpoint. The standardized incidence ratio of 1.5 with a confidence interval of 1.0-2.1 calculated by Rafnsson *et al*. was reported by the authors as being of "borderline significance." Notably, as observed by Dr. Band, the identification by Rafnsson *et al.* of 26 breast cancer cases when 17.89 cases were expected produces a standardized incidence ratio of 1.45 with the lower limit of the confidence interval being less than 1.0. Even the standardized incidence ratio identified by Rafnsson *et al*. included 1.0; therefore the standardized incidence ratio is not statistically significant.

Dr. Band identified a number of concerns associated with the study by Reynolds *et al.* which linked data from the California Cancer Registry to data from the United States Association of Flight Attendants (AFA) representing 27 airlines. Reynolds *et al.* calculated for breast cancer a standardized incidence ratio of 1.29 with a confidence interval of 0.99-1.66 using non-Hispanic white women for comparison. Using "All races" as a category the standardized incidence ratio was 1.42 with a confidence interval of 1.09-1.83. The authors noted that information received from the AFA included "some data on former union members." Dr. Band queried what was meant by "some data." The state of residence was only available for those flight attendants residing in California in December 1997 and the authors assumed that the members of each AFA council had the same probability of being California residents during the entire study period as they did in December 1997. Dr. Band commented that "…the study lacks detail on age, sex, and ethnicity-specific historical employment, as well as on residential information except for 1 of the 8 years of the study duration." He queried the validity, accuracy and "exhaustiveness" of the AFA files and asked why the files from the 27 airline companies were not used. He asked why breast cancer rates were not shown for the 6,895 female flight attendants known to have resided in California. We note that Reynolds *et al.* did not identify the number of person-years of risk.

Dr. Band indicated that the remaining three studies showed no statistically significant relationship between employment as a flight attendant and breast cancer incidence. The standardized incidence ratio calculated by Lynge was 1.61 with a confidence interval of 0.9-2.7. Dr. Band noted that the document produced by Lynge was a one-page letter with no data on methodology. He observed that the numbers were small, the confidence intervals wide, and the result not statistically significant.

The standardized incidence ratio calculated by Haldorsen *et al.* of 1.1 involved a confidence interval of 0.8-1.5. Dr. Band referred to it as the largest cancer incidence study of flight attendants carried out to date.[24] As well, he noted that Haldorsen *et al.* was the only cancer incidence study that controlled for age at first birth.

[24] The comment by Dr. Band must be understood in terms of ascertainable person-years given that the study by Reynolds *et al.* involved more flight attendants but did not specify the number of person-years.

Haldorsen *et al.*'s study was the subject of commentary by Lynge.[25] She addressed cancers in both male and female cabin attendants. In particular, she summarized the data from Haldorsen *et al*., Pukkala *et al*, Lynge, Rafnsson *et al*., and Wartenberg and Stapleton. She indicated that the summary standardized incidence ratio for breast cancer in female cabin attendants was 1.4.[26] She observed that the breast cancer data were puzzling as breast cancer was numerically by far the most important cancer in women. She observed that it would be difficult epidemiologically to disentangle possible exposures behind the moderately elevated risk. She noted that the studies by Pukkala *et al*. and Rafnsson *et al*. "…argued well for not attributing the excess risk to reproductive factors alone." She indicated that radiation exposure remained a potential explanation together with possible influence from diet and alcohol, disrupted sleep-waking cycles, and exposure to organochlorine pesticides sprayed in cabins.

The standardized incidence ratio calculated by Linnersjö *et al.* was 1.3 with a confidence level of 0.85-1.74. Dr. Band noted that the methodology used by those authors to obtain cancer incidence information was good and that the effect of reproductive factors was assessed indirectly.

Of the six "methodologically adequate studies" (Wartenberg and Stapleton excluded), Dr. Band observed that the two largest studies (Haldorsen *et al*. and Linnersjö *et al.)* showed no statistically significant association. Haldorsen *et al*.'s study of a cohort of 3,105 Norwegian flight attendants involved 60,401 person years. As noted by Dr. Band, the cohorts studied by Pukkala *et al.* and Rafnsson *et al*. totalled 3,109, but those studies only involved 49,198 person-years. Linnersjö *et al*.'s study of 2,324 Swedish flight attendants involved 39,135 person-years.

In his concluding summary comments, Dr. Band observed that the standardized incidence ratios for the seven incidence studies all exceeded 1.0 with a range of 10% to 100%. He observed that in the two studies which showed a statistically significant association with breast cancer risk the standardized incidence ratio in one became non-statistically significant after correction for "social class" (*Pukkala et al*.) and the other study was methodologically questionable (Wartenberg and Stapleton).

Dr. Band indicated that the combined standardized incidence ratios for all seven cohort studies equalled 1.35 with a confidence interval of 1.17-1.55 without any adjustment for confounding factors. The associated attributable risk[27] was 26% (.35 divided by 1.35).

[25] Lynge, E. Commentary: Cancer in the air. *International Journal of Epidemiology*. 2001 Aug;30(4):830-2.
[26] She calculated that figure by dividing the total observed cases by the total expected cases.
[27] As noted by Gordis at page 191 and following in Gordis, L. *Epidemiology*. Third edition. Elsevier Saunders 2004 attributable risk is defined as the amount or proportion of disease incidence (or disease risk) that can be attributed to a specific exposure. Attributable risk is the difference in the incidence between exposed and non-exposed groups. Even in a non-exposed group there is disease incidence. An illustration of this point is that in an assessment of the effect of smoking on the incidence of lung cancer, it must be kept in mind that even some non-smokers develop lung cancer.

Dr. Band commented on the five cancer incidence studies (Lynge and Wartenberg and Stapleton excluded) that addressed risk by employment duration. He observed that "…the relationship between breast cancer risk and employment duration of 15 and/or 20 years and over was significant…" in Pukkala *et al*. His comment regarding Pukkala *et al.* is not accurate as the authors calculated standardized incidence ratios of 3.4 and 2.1 for follow-up categories of 15-19 years and 20 years or more since recruitment. Time since recruitment does not equal duration of employment. This point is explored later in this decision. Pukkala *et al.* indicated that adjustment for "social class" reduced the standardized incidence ratio for the group of 15 years or more since recruitment to 1.9, but it still remained statistically significant.

Dr. Band asserted that no significant association was observed in the other four studies that assessed the relationship between breast cancer risk and employment duration of 15 and/or 20 years. We consider that Dr. Band erred in that assertion. Several pages earlier in his report, he noted that Reynolds *et al.* calculated a standardized incidence ratio for 15 years of service of 1.42 with a confidence interval of 1.05-1.87. A review of the article by Reynolds *et al.* confirms the accuracy of those figures. Thus, Reynolds *et al.* calculated a statistically significant relationship. However, Dr. Band's summary concluding comments as to the standardized incidence ratios by employment duration are based on Table 2 in his report in which he asserted that the breast cancer standardized incidence ratio for 15 years or more of employment duration found in the study by Reynolds *et al.* was 1.32 with a confidence interval of 0.42-3.11. A review of the report by Reynolds *et al*. reveals that those figures concern the standardized incidence ratio for malignant melanoma and 15 years or more of employment duration.

Regarding the other three studies, we accept that Dr. Band has accurately summarized the standardized incidence ratios by employment duration with respect to the employment periods of 15 years and over and/or 20 years and over. In Rafnsson *et al.*'s study the standardized incidence ratio of 1.6 for 20 years and over was not statistically significant with reference to *p* values. Haldorsen *et al.* calculated a standardized incidence ratio of 1.0 with a confidence interval 0.3-3.0 for 15 years or more of employment. That figure is taken from Table 3 in the report by Haldorsen *et al.* which documented adjusted rate ratios from Poisson regression[28] of breast cancer among female flight attendants born after 1934. The standardized incidence ratio for 15 years or more of employment duration associated with the entire cohort studied by Haldorsen *et al.*, found in Table 2 of their report is 0.9 with a confidence level of 0.3-2.2. In Linnersjö *et al.*'s study the standardized incidence ratios for employment duration of less than 10 years, 10 to 19 years, and 20 years were 1.36, 1.26, and 1.39, respectively, and were not statistically significant.
Regarding cancer mortality studies, Dr. Band observed that neither Blettner *et al*. nor Ballard *et al*. calculated a statistically significant association between work as a flight attendant and breast cancer risk. Blettner *et al*.'s standardized mortality ratio for the

[28] A Poisson regression models the occurrence of an event of interest or the rate of occurrence of an event of interest as a function of some independent variables.

whole cohort was 1.28 with a confidence interval 0.27-2.20. The standardized mortality ratio for flight attendants who were first employed after 1970 was 1.27 with a confidence interval of 0.54-2.65. Ballard *et al.*'s standardized mortality ratio was 0.99 with a confidence interval 0.36-2.15. As noted by Dr. Band the results of those two studies were included in the study conducted by Zeeb *et al.* who calculated a standardized mortality ratio, following a correction for missing causes of death, of 1.11 with a confidence interval of 0.82-1.48. For women employed for 10 to 19 years, the standardized mortality ratio was 1.27 with a confidence interval 0.74-2.07.

Dr. Band reached the following conclusion:

> The cancer incidence studies show weak and conflicting evidence for an association between employment as a female flight attendant and breast cancer risk, without any adjustment for confounding risk factors. No significant association was found in the large collaborative cohort mortality study carried out in Europe.
>
> In my opinion, the evidence at this time is insufficient to conclude that work as flight attendants is associated with an established risk of breast cancer from occupational exposure to radiation. With respect to [the worker's] specific case, in my opinion, the probabilities are not evenly balanced that this worker's left breast cancer has been caused by an element of her employment.
>
> [Footnote deleted]

Review of Dr. Boyd's Report

Dr. Boyd is a medical doctor who is certified as a specialist in both internal medicine and haematology by the Royal College of Physicians of Canada. He holds professorships at the University of Toronto in the Department of Medicine (Division of Oncology (Medical)), the Department of Nutritional Sciences, the Department of Medical Biophysics, and the Department of Public Health Sciences. Ms. Symes reported that he holds the Lee K. and Margaret Lau Chair in breast cancer research, Ontario Cancer Institute, University Health Network. The website for the University Health Network indicates that Dr. Boyd is the head, Division of Epidemiology, Statistics & Behaviour, Ontario Cancer Institute and senior scientist, Division of Epidemiology, Statistics & Behaviour, Ontario Cancer Institute. Dr. Boyd's research is concerned with the development of strategies to prevent breast cancer.

From 1989 to 2005 Dr. Boyd was the head, Division of Epidemiology and Statistics, Ontario Cancer Institute. From 1993 to 1997 he was the vice president and director, Division of Preventive Oncology, The Ontario Cancer Treatment and Research Foundation. From 1997 to 2000 he was the director, Research, Division of Preventive Oncology, Cancer Care Ontario.

Dr. Boyd indicated that he had read Dr. Band's report. He described the search strategy he used to locate literature. He indicated that the factors that increased the risk of breast cancer included increasing age, residence in Western countries, extensive mammographic density, an early age of menarche, late age at first birth, fewer number of births, greater height and weight, later age at menopause, and use of combined hormone therapy. Inheritance of mutations was associated with increased risk and exposure to ionizing radiation was also associated with an increased risk. He indicated that the relative risks associated with those factors were usually less than 2.0 and that it was not possible from knowledge of those risk factors to predict precisely who would develop breast cancer and who would not. He indicated that groups of individuals with risk factors that indicate increased risk would, on average, develop more breast cancers, but the individuals within the group who would develop the disease could not be reliably predicted in advance.

Dr. Boyd considered that, with respect to the worker, the following factors were associated with a less than average risk of breast cancer: a late age at menarche, no family history of breast cancer, and a body mass index of 29. The following factors were associated with a greater than average risk: late age at first birth, previous benign breast disease, and occupation. He considered that use of oral contraceptives at age 21 and a previous miscarriage had no known influence on her risk of breast cancer.

Dr. Boyd noted the Gail model[29] which is used to predict individual risk by combining some of the risk factors. He advised that the model uses information about age, ethnicity, age at menarche, family history, previous breast biopsy, and age at first pregnancy. Other risk factors noted above were not included in the model. He indicated that the model calculated that at the age "48"[30] when she was found to have breast cancer, the worker's risk of developing breast cancer over the next five years was 1.2%. The average five-year risk for other white women of her age was stated to be 1.2%.

Dr. Boyd identified the same seven cancer incidence studies identified by Dr. Band, as well as the case-control study of Rafnsson *et al.* and the three cancer mortality studies identified by Dr. Band. He examined studies of incidence and mortality separately. Studies of incidence consider only the factors that influence the development of the disease, whereas mortality from breast cancer is influenced not only by factors that affect the development of the disease, but also by factors that influence survival after the onset of disease.

[29] This breast cancer risk assessment tool may be accessed on the website of the National Cancer Institute: http://www.cancer.gov/bcrisktool/.

[30] While Dr. Boyd used an age of 48 years, the worker, who was born in early November 1952, was 49 years old when the late November 2001 mammogram confirmed the presence of cancer. With the use of an age of 49 years, the Gail model produces a risk of 1.2%, whereas use of an age of 48 years produces a risk of 1.1%. As Dr. Boyd appears to have supplied the risk figure associated with the worker's correct age at diagnosis, it appears that his reference to age 48 was a typographical error.

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Dr. Boyd prepared a table (Table 2) which summarized five cohort incidence studies published in the literature which involved a total of 148,684 person-years of observation. (The documents by Lynge, Wartenberg and Stapleton, and Rafnsson *et al.* (2003) were excluded.) He noted that four of the five studies were population-based (all but Reynolds *et al.)* and that results of population-based studies are much less likely to be distorted by biases arising from selection than studies that are not population-based. He observed it was unlikely that bias in the selection of subjects or in the reporting of cancer played any role in influencing the results associated with the population-based studies.

Dr. Boyd noted that in all five studies of breast cancer incidence referred to by him the standardized incidence ratio was greater than 1.0 and that the point estimates varied from 1.1 to 1.87, which indicated that all studies found that flight attendants were more likely to develop breast cancer than women of the same age in the population in general. He observed, however, that only two of the five point estimates were statistically different from 1.0. That observation refers to the studies by *Pukkala et al.* and Reynolds *et al.* Dr. Boyd did not note that the figure in Pukkala *et al.* ceased to be statistically significant after it was adjusted by social class or that he used the figure in Reynolds *et al.* that related to cancer incidence in the “all races” category rather than the figure that related to the “non-Hispanic white” category which provided a standardized incidence ratio that was not statistically significant. We find that the latter racial category is more relevant to the worker’s case.

Dr. Boyd considered that the role of chance could be assessed by considering the consistency of the findings: He observed that if there was, in reality, no association between the occupation of flight attendant and the risk of breast cancer, the estimates of risk provided by the standardized incidence ratios would be expected to be distributed around 1.0 with some below and others above this value and the average of them would be 1.0. He said that as all point estimates were greater than 1.0, it was unlikely that the true underlying risk was 1.0.

Dr. Boyd prepared a figure (Figure 1) which documented the results of his meta-analysis of the five cohort incidence studies. He observed that the fact that the point estimates of risk all lie on the same side of a vertical line denoting a standardized incidence ratio of 1.0 indicated it was reasonable to combine the results from the studies. He noted that the summary standardized incidence ratio was 1.32 with a confidence interval of 1.14-1.53. (We note that those numbers in the text do not match the numbers found in Figure 1 which shows a standardized incidence ratio of 1.36 with a confidence interval of 1.17-1.58. It is possible that the figure of 1.32 cited by Dr. Boyd was obtained using different data from the study by Reynolds *et al.* If the figure of 46.43 expected cancer breast cases for non-Hispanic whites is used, as compared to the all race figure of 42.17, the summary standardized incidence ratio for the five studies changes from 1.359 to 1.316. With rounding, the latter figure would be 1.32).

Dr. Boyd contended that the summary standardized incidence ratio shows that female flight attendants, when compared to women of the same age in the general population, have a 32% greater risk of developing breast cancer. He indicated that both fixed and random effect statistical models were used and gave very similar results.

Notably, Dr. Boyd did not acknowledge that the two largest studies with respect to identified person-years (those conducted by Haldorsen *et al.* and Linnersjö *et al*. which involved 99,536 of the 148,684 person-years of observation to which he referred earlier in his report) were associated with standardized incidence ratios of 1.1 and 1.3, respectively, neither of which was statistically significant.

We note that the 60 observed cancers associated with the study by Reynolds *et al.* is a significant portion of the 177 cancers associated with the summary standardized incidence ratios of 1.32 or 1.36 noted by Dr. Boyd. We note that Dr. Boyd did not contest Dr. Band's methodological concerns associated with the study by Reynolds *et al*. If one removes the all race data collected by Reynolds *et al.* (a non-population-based study) from the five studies on which Dr. Boyd focussed, the four remaining studies (methodologically adequate according to Dr. Band) produce a summary standardized incidence ratio of 1.33. Thus, the summary standardized incidence ratio does not change significantly when the figure is re-calculated without the Reynolds *et al.* data.

Dr. Boyd indicated that confounding by other factors was a possible explanation for the results and that such confounding might occur if flight attendants as a group had non-occupational attributes that increased the risk of breast cancer. He indicated that if, compared to other women, flight attendants less often had children, had fewer children or had children at a later age, their risk would be slightly greater. He noted that two studies showed that flight attendants had, on average, reproductive histories (later age at first pregnancy or fewer children) that would be expected to increase the risk of breast cancer. He asserted that the expected effect of these factors could not account for the observed increase in risk associated with occupation.

Dr. Boyd indicated that the study by Rafnsson *et al.* (2003), the only study that examined the effects of reproductive variables using a case-control method, showed that adjustment for reproductive factors did not account for the effect of occupation on the risk of breast cancer. He indicated that his meta-analysis carried out on the subset of four studies that assessed the effects of childbearing gave results very similar to those shown in Figure 1 of his report: the summary standardized incidence ratio was 1.33 with a confidence interval of 1.11-1.59.

Dr. Boyd noted that, in addition to the studies described in full and published as peer-reviewed papers, there were two published letters by (i) Lynge and (ii) Wartenberg and Stapleton. He indicated that the standardized incidence ratios for both of those studies were statistically significant and in keeping with the findings of his meta-analysis which was based on the results of full published papers. Dr. Boyd indicated that the standardized incidence ratio associated with the paper by Lynge was 1.87 with a confidence interval of 1.15-2.23. He is incorrect. Lynge identified a standardized incidence ratio of 1.61 with a non-statistically significant confidence interval of 0.9-2.7. Dr. Boyd mistook the data regarding the study by Pukkala *et al*. referred to by Lynge for the results obtained by Lynge. We note that Dr. Boyd did not comment directly on the concerns Dr. Band raised about the documents produced by Lynge and Wartenberg and Stapleton.

Regarding mortality studies, Dr. Boyd indicated that in one study the standardized mortality ratio was 1.0. In the other two studies the standardized mortality ratios were greater than 1.0 but were not statistically significant.

Dr. Boyd said that of seven available estimates of breast cancer incidence in flight attendants (the five incidence studies he identified and the letters from Lynge and Wartenberg and Stapleton) all showed risks greater than 1.0 and that the risks were statistically significant in four of the seven individual studies. That assertion is problematic as it incorporates Dr. Boyd's misstatement as to the results obtained by Lynge; there were only three studies which calculated a statistically significant risk. The remaining three studies include the study by Wartenberg and Stapleton, with which, as Dr. Band noted, there are methodological concerns. As well, Dr. Boyd did not note that the standardized incidence ratio in Pukkala *et al.* ceased to be statistically significant when adjusted by "social class" or that the figure in Reynolds *et al*. was not statistically significant when the "non-Hispanic white" category was used to calculate the standardized incidence ratio.

Dr. Boyd discussed exposure of female flight attendants to potential causes of breast cancer, the health consequences of radiation exposure, radiation exposure during flight, radiation dose and risk of breast cancer, risk of acute leukemia in pilot and flight attendants, and risk of other cancers in pilots and flight attendants. He noted that while exposure to jet fuel, engine emissions, and hydrocarbon pollutants have been discussed as possible risk factors, not one has been established as a risk factor for breast cancer. He indicated that there is evidence that environmental tobacco smoke may increase the risk of breast cancer. He commented that melatonin production abnormalities resulting from sleep disturbance associated with employment as a flight attendant has not been established as a risk factor. Further, as yet, there is no convincing evidence of a link between exposure to electromagnetic fields and breast cancer.

Dr. Boyd noted that a small excess risk of cancer has been associated with exposure to low doses of radiation typically received by workers in the nuclear industry. He indicated that radiologic technologists, an occupational group exposed to protracted low doses of radiation, had been found in a population-based study[31] to have an increased

[31] Sigurdson, AJ. Cancer incidence in the US radiologic technologists health study, 1983-1998. *Cancer*. 2003 Jun 15;97(12):3080-9.

risk of breast cancer (standardized incidence ratio of 1.16 with a confidence interval of 1.09-1.23) which he considered was similar in magnitude to the risk of breast cancer reported in flight attendants. During flight, pilots and flight attendants are exposed to radiation which varies according to altitude, latitude, duration, and route taken. He indicated that a study by Lewis *et al.* [32]established that most Canadian-based domestic and international pilots and flight attendants exceed the proposed annual limit of 1 mSv[33]. The average annual exposure for this group was 2.8 mSv, with a low of 0.74 and a high of 4.74. He contended that a little more than 10 years of exposure at the higher level or 20 years at the average level would result in exposure to more than 50 mSv, the lower limit of protracted exposure that an expert panel[34] considered to be associated with an increased risk of cancer.

Dr. Boyd commented that while the literature concerning breast cancer and flight attendants did not measure the dose of radiation to which flight attendants were exposed, some studies examined duration of employment as a surrogate measure of exposure. He observed that duration of employment alone was an imperfect surrogate as exposure to radiation was influenced by flight characteristics. In Table 4 of his report, he summarized the results of five studies which addressed duration of employment.

Dr. Boyd commented that while Linnersjö *et al*. found no evidence that risk increased with duration of employment, Reynolds *et al.* did find a dose-response relationship. Pukkala *et al.* found no cases of breast cancer with less than 15 years of employment. Rafnsson *et al.* analyzed data with and without consideration of lag time between the start of employment and the development of breast cancer. Although risks were elevated in two of three categories of length of employment when no lag time was considered, all risks increased when 20 years lag time was introduced. It was found that those with eight years or more of employment had, 20 years later, a standardized incidence ratio of nearly 6.0 that was statistically significant. He observed that the study by Rafnsson *et al.* was in keeping with some of the known effects of exposure to radiation but "... it needs to [be] viewed with some caution until it is replicated by others." He observed that it was possible that the high-altitude long-duration flights in which exposure to radiation may be greatest, are a sufficiently recent development and that the full health effects of radiation exposure associated with such fights have not yet been seen.

[32] Lewis, BJ *et al*. Cosmic radiation exposure on Canadian-based commercial airline routes. *Radiation Protection Dosimetry*. 1999;86(1):7-24.

[33] A sievert is a measurement unit that attempts to reflect the biological effects of radiation. mSv is the abbreviation for milliSievert.

[34] Brenner, D *et al.* Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. *Proceedings of the National Academy of Sciences of the United States of America* 2003 Nov 25;100(24):13761-6.

Dr. Boyd noted a report by Kojo *et al.*[35] of flight attendants which was published after Dr. Band prepared his report. He asserted that that study showed established risk factors for breast cancer have the expected influence on the risk of disease. He observed that risk was not influenced by estimated cumulative radiation exposure.

We note that in their case-control study of Finnish cabin attendants, Kojo *et al.* concluded that the risk of breast cancer was not associated with cumulative occupational radiation dose. They observed that the expected magnitude of risk was small and a minor effect could not be excluded. They noted that their study indicated that family history of breast cancer was the strongest determinant of breast cancer (adjusted odds ratio of 5.52 with a confidence interval of 1.44-21.23). Alcohol consumption involved an adjusted odds ratio of 4.11 with a confidence interval of 1.01-16.72. They acknowledged that the small number of cases restricted the statistical power of the study. Another limitation was that information on exposure was collected retrospectively. They also noted a sub-optimal response proportion. They concluded their study with the following observation:

> In conclusion, our results suggest that breast cancer among Finnish cabin attendants is related to general, well established risk factors of breast cancer, such as family history of breast cancer. Occupational factors do not seem to exert an influence on breast cancer risk, but the evidence remains inconclusive.

Notably, Pukkala and Auvinen, who prepared the study along with Kojo, co-authored the study by Pukkala *et al.*

Of interest is the fact that Rafnsson commented on the study by Kojo *et al.* and Kojo *et al.* responded.[36] Those letters were published in January 2006, after Ms. Symes and Mr. Winter provided their initial submissions. We have not taken those letters into account in our analysis.

Dr. Boyd considered that the potential relevance of exposure to ionizing radiation could be examined by reference to the risk of developing other diseases with which a positive link to radiation has been established. Acute leukemia is one of those diseases. He observed that the risk of acute leukemia was known to be increased by exposure to ionizing radiation. He determined that the summary standardized incidence ratio for all 11 studies which reported the risk of acute leukemia in pilots and flight attendants was 1.73 with a confidence interval of 1.21-2.47. He stated that the summary figure showed that the risk of acute leukemia in pilots and flight attendants was about double that of

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35 Kojo, K *et al.* Breast cancer risk among Finnish cabin attendants: a nested case-control study. *Occupational and Environmental Medicine.* 2005 Jul;62(7):*488-93.*

36 See the following:

- Rafnsson, V. Breast cancer among airline cabin attendants. *Occupational and Environmental Medicine.* 2006 Jan;63(1):71.
- Kojo, K *et al*. Authors' reply. *Occupational and Environmental Medicine.* 2006 Jan;63(1):71.

the general population of the same age and sex. He noted that one study which examined the proportion of cases occurring in pilots with a relevant chromosomal rearrangement found the rearrangement in a high proportion of cases. He also observed that an increased risk of melanoma, bone cancer, thyroid cancer, and brain cancer has been described in "some papers."

In the "Summary" section of his report, Dr. Boyd concluded that the risk of breast cancer had "…consistently been found to be increased in female flight attendants compared to women in the population of the same age." He determined that that increased risk "... does not appear to be explained by chance or bias, but confounding by reproductive or other factors cannot entirely be excluded." He considered that studies which assessed potential confounding by reproductive factors determined that such factors "... do not appear to account for the results." He considered the risk of breast cancer was known to be increased by exposure to radiation, both acute and protracted. He concluded that flying in Canadian commercial airlines increased exposure of flight attendants to low doses of radiation and that estimates of average exposure over 10 to 20 years were within the range where epidemiological data indicated the risk of cancer is increased. He considered that exposure to radiation had been shown to increase the risk of at least one other type of cancer in pilots and flight attendants.

Dr. Boyd indicated that, taken together, the available evidence showed that the risks of breast cancer and acute leukemia were increased, respectively, in female flight attendants and in pilots and flight attendants. He considered "It thus appears probable that the increased risk of breast cancer in flight attendants, is due, at least in part, to exposure to radiation during the course of their employment." He considered that the factors that influenced his conclusion were the consistency of the evidence of breast cancer in this occupational group published to date, the evidence suggesting a dose-response relationship, and the evidence for a long latency period between exposure and the occurrence of the disease. Biological plausibility of an association was "strongly supported" by the additional evidence that pilots and flight attendants are at increased risk of acute leukemia and the direct measurements that had been made of radiation exposure in Canadian commercial airlines.

Analysis

We turn first to a consideration of Dr. W's opinion. Mr. Winter raised three specific concerns with respect to Dr. W's opinion:

- Dr. W's opinion was not based on a full consideration of the relevant literature,
- Dr. W attached inappropriate significance to the fact that confidence intervals in two studies included the value of 2.0, and
- Dr. W's opinion was based on an incorrect assumption that the worker had no non-occupational risk factors for breast cancer, save for her gender.

We accept that Dr. W's opinion was not based on a full consideration of the relevant literature. We accept that the opinions of Drs. Band and Boyd contain more complete reviews of the literature than that found in the opinion of Dr. W. While some of the reports cited by Drs. Band and Boyd were published after Dr. W's opinion, some of the reports considered by them were published prior to September 2002 when Dr. W provided his opinion. We find it significant that Dr. W did not indicate that he had considered the study conducted by Haldorsen *et al*. which was published in 2001; this is notable given Dr. Band's assertion that that study was the largest cancer incidence study of flight attendants carried out to date.

Mr. Winter has drawn attention to the following comments made by the panel in *WCAT Decision #2004-00265-AD* which we consider are relevant to Dr. W.'s opinion in the case before us:

> Even with the above caveats in mind, we consider that any opinion that seeks to link cancer to an industry or employment that does not take into account the relevant epidemiological studies will likely not be very persuasive.

We accept Mr. Winter's submission that Dr. W erred, from an epidemiological perspective, by attaching inappropriate significance to the fact that confidence intervals in two of the three studies he reviewed included the value of 2.0.

That a confidence interval obtained by a study includes the value of 2.0 does not establish that the actual relative risk is 2.0. The figure 2.0 merely means that the range of random error includes 2.0. As noted by Dr. Band, smaller sample sizes involve wider confidence intervals (more uncertainty, less confidence), whereas larger sample sizes involve narrower confidence intervals (less uncertainty, more confidence).

It would be problematic that a small sample size that produced a wide confidence interval which included 2.0 would be accepted as being more persuasive as to the likelihood of a causal link between exposure and a disease outcome than a narrower confidence interval which did not include 2.0. Dr. Band made this point quite strikingly by contrasting (i) a confidence interval of 1.01-2.15 associated with a relative risk of 1.5 arising out of a study of 30 cancers with (ii) a confidence interval of 1.16-1.95 associated with a relative risk of 1.5 arising out of the study of 60 cancers. He observed that if a confidence interval upper limit of 2.0 is used to accept a claim, paradoxically this could lead to accepting claims based on studies involving limited numbers of subjects with wide confidence intervals and rejecting claims based on studies involving larger numbers of subjects and narrower confidence intervals.

Mr. Winter made a cogent point with respect to Dr. W's assumption that the worker had no other non-occupational risk factors. As noted by Dr. Band, established non-occupational risk factors for breast cancer relevant to the worker include age at first birth (age 30) and a history of benign breast disease. We note that Ms. Symes does not dispute the presence of such non-occupational risk factors for the worker. Dr. Band also contended that a history of a previous breast biopsy for benign breast disease also embodied a non-occupational risk factor. He acknowledged that the evidence was not clear that the worker had undergone such a biopsy. However, we note that Ms. Symes advised that Dr. Boyd included that factor when he calculated the worker's risk using a risk calculation model. Thus, it appears that the worker does not contest that she had this further non-occupational risk factor.

Dr. Band said that some increased risk of contracting breast cancer was associated with an abortion of, or a miscarriage of, a first pregnancy, and noted that there was some question as to whether the worker had two pregnancies and raised the question of whether one of those ended in termination by miscarriage or by abortion. In that regard, he referred to Dr. O'Reilly's January 25, 2002 report noted above. Dr. Boyd indicated that a miscarriage is not a known risk factor with respect to breast cancer. Ms. Symes commented that it was incorrect for the employer to suggest that "the worker's miscarriage" indicated she would be at an increased risk for breast cancer. We take that statement by Ms. Symes to be an admission that the worker did suffer a miscarriage.

We do not consider it necessary to consider whether a miscarriage is a risk factor for breast cancer. We consider it sufficient that, in addition to gender and age, the worker had non-occupational risk factors for breast cancer, contrary to Dr. W's assumption. The presence of such non-occupational risk factors, and other concerns noted above, supports our determination that Dr. W's opinion should not be given significant weight.

We consider that the resolution of this appeal rests on how we weigh the opinions of Drs. Band and Boyd. While Mr. Winter points to the opinion of Dr. O'Reilly in support of the employer's appeal, we note that Dr. O'Reilly's report does not establish that she has expertise in matters of epidemiology or occupational medicine. We attach little weight to that opinion.

Cancer cases are rarely resolved by opinions that merely canvass the case of a particular worker. In most cases, epidemiologic evidence has been gathered and analyzed, and that evidence provides a relevant background for any opinion specific to the particular worker. The increasing number of cases involving such evidence appears to have been one of the main impetuses for the Board's issuance in 1993 of the *Protocol for the Assessment of Medical/Scientific Information - Industrial Diseases Standing Committee, Workers' Compensation Board of British Columbia* (the Protocol), at 9 W.C.R. 429.

In making our decision in this case, our adjudication will take into account the principles found in section 250 of the Act. We must assess whether the evidence that there is a link between the occupation of flight attendant and the worker's breast cancer is evenly weighted with the evidence that there is no such link. Thus, our inquiry involves assessing whether the evidence is "50-50" in favour of a link.

As previously discussed, a 95% confidence interval is a range of relative risk values within which the true value for the relevant study is likely to fall 95% of the time. In assessing causality in adjudication, we consider that it should be kept in mind that the use of confidence intervals does not mean that scientific evidence derived from epidemiological studies involves 95% certainty that there is a causal association between an exposure and a disease, nor do we mean to suggest that such a degree of certainty is required. The use of confidence intervals does not change the question of whether the evidence as a whole establishes that the relative risk is 2.0 or greater for the worker. A 95% confidence interval does not mean that assessment of causation involves determining whether there is a 95% certainty of a link between an exposure and a disease. Thus, use of confidence intervals does not involve a burden of proof greater than the burden of 50% found in the Act.

Assessing whether that burden of 50% is satisfied involves consideration of all of the evidence, which includes such matters as statistical association, causality, and the worker's individual case; it is not limited to the issue of statistical association and the probability of error. The point estimate, the breadth of the confidence interval, and the inclusion of 1.0 in the confidence interval are all factors that need to be taken into account when considering epidemiologic studies.

We, like other decision-makers in administrative law, and perhaps most other fields of law, are not bound by scientific standards of proof. Judges and quasi-judicial decision-makers utilize different burdens of production and proof. As noted by Cranor and Eastmond[37] scientists guard against random errors producing false positive results by demanding that support for their conclusions be statistically significant. Unthinking commitment to such a goal can increase false negatives, and "thoughtful commentators" are increasingly concerned about rigidly using statistical significance as a decision rule.

We accept that the legal standard of equal to or greater than a 50% likelihood is the guiding standard with respect to an assessment of epidemiological evidence by a decision-maker in the workers' compensation system. This does not relieve us from the duty to evaluate and critically analyze the underlying scientific and statistical methodology when evaluating scientific evidence of causation. We must also keep in mind the source of any comments on the literature, as the viewpoint of the commentator is relevant.

In assessing the issue of causation generally, we consider it appropriate to consider the Bradford Hill criteria which provided the basis for the Board's Protocol. A critical

[37] Cranor, C.F., & Eastmond, D.A. (Autumn 2001) Scientific Ignorance and Reliable Patterns of Evidence in Toxic Tort Causation: Is There a Need for Liability Reform? *64 Law & Contemp. Probs.* 64(4) 5-49.

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analysis of epidemiologic studies includes an analysis of causation based on criteria generally accepted by epidemiologists as factors useful in making judgments about causation. These criteria were initially developed by the U.S. Surgeon General in 1964, to be used to assess the relationship between smoking and lung cancer, and they were expanded upon by Bradford Hill in 1965[38]. They were listed by Bradford Hill as follows:

1. Strength of the association
2. Consistency
3. Specificity of the association
4. Temporal relationship
5. Dose response relationship
6. Biological plausibility
7. Coherence
8. Experiment
9. Analogy

Similar criteria are set out in the Board's Protocol which lists the following:

1. Strength of association
2. Consistency
3. Dose-response
4. Coherence
5. Temporal relationship
6. Specificity
7. Statistical significance.

At the original presentation at which Bradford Hill posited these criteria, he suggested that they be applied when there was a clear-cut association between two variables that was not due to chance, and one wanted to consider aspects of the association before deciding that the most likely interpretation of the association was causation.

The Protocol, which was issued by the former board of governors of the Board, examined the criteria as they related to epidemiological studies in humans. It stressed that the criteria were not rigid rules and indicated that the main value of the criteria was to remind readers of the components of an epidemiological study and to aid in assessing reliability and validity.

There is no requirement in law or in policy that the Board or WCAT apply the Protocol in assessing issues of causation in connection with occupational diseases. That being said, the Protocol was issued by the Board with the intention of advising readers of criteria the Board considered "useful in deciding questions about

[38] A Bradford Hill, The Environment and Disease: Association or Causation? 58 *Proceedings of the Royal Society of Medicine*. 295. Hill acknowledged that his factors could only serve to assist in the inferential process: "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*."

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occupational causation of disease." We are aware, as noted by Phillips and Goodman[39], that Bradford Hill emphasized that the criteria were neither necessary nor sufficient for establishing causation.

We consider that Bradford Hill's reference to a clear-cut association means that the initial consideration is whether there is an association that is not due to chance. Thus, the initial consideration entails an examination of whether the relative risks are above 1.0 and whether tests of statistical significance indicated that the figures above 1.0 were not due to chance.

Other critical factors in the case before us concern consistency and dose-response relationship. Temporal relationship which involves determining that the disease of interest occurred after commencement of exposure to the relevant agent is, of course, of critical importance. We do not consider that the studies raise any concern with respect to this criterion.

- Strength of association and statistical significance

We consider it significant that while Dr. Boyd indicated that he had read Dr. Band's report, he did not expressly indicate that he disagreed with Dr. Band's comments regarding the strengths and weaknesses of the various studies. Further, he did not appear to give any specific consideration to shortcomings concerning studies identified by Dr. Band. While we appreciate that a summary standardized incidence ratio is of use, we also consider that a narrative qualitative analysis of the studies which form the basis of a summary standardized incidence ratio is of significant assistance to decision-makers addressing matters of causation.

Dr. Boyd said that two of the point estimates from the five studies he referred to were statistically significant. However, we note that one of the two studies was by Reynolds *et al.* in which the standardized incidence ratio ceased to be statistically significant when calculated on the basis of the "non-Hispanic white" category which we consider to be more relevant in this case than the "all races" category. Further, Dr. Boyd did not acknowledge concerns with respect to the validity of the results in that study that might be relevant to whether significant weight should be attached to those results. Dr. Boyd himself implied that non-population based studies (Reynolds *et al.* conducted such a study) would likely have biases. However we acknowledge, as noted above, that a recalculation of the summary standardized incidence ratio in the absence of the figures from the study by Reynolds *et al.* did not significantly reduce the summary standardized incidence ratio. Thus, it is questionable whether Dr. Boyd's use of a standardized incidence ratio from Reynolds *et al*. associated with the "all races" category is of great import when it comes to establishing a summary standardized incidence ratio.

[39] Phillips, *VC* and Goodman, KJ. The missed lessons of Sir Austin Bradford Hill. *Epidemiologic Perspectives & Innovations.* 2004; 1:3

The other four studies from which Dr. Boyd calculated the summary incidence ratio of 1.32 were the studies by Pukkala *et al*., Rafnsson *et al*., Haldorsen *et al*., and Linnersjö. Mr. Winter attached significance to the fact that Rafnsson *et al.* declared that the risk for breast cancer was of “borderline significance.” Similarly, Dr. Band referred to the standardized incidence ratio calculated by Rafnsson *et al*. as being of “borderline significance.” While Dr. Boyd did not expressly refer to that standardized incidence ratio as being of “borderline significance”, we note that he considered only the Pukkala *et al*. and Reynolds *et al.* studies to have identified statistically significant standardized incidence ratios. Thus, he was aware that the confidence interval calculated by Rafnsson *et al*. included the figure 1.0.

In Pukkala *et al*., the standardized incidence ratio ceased to be statistically significant once it was adjusted for social class. The standardized incidence ratios calculated by Haldorsen *et al*. and Linnersjö *et al.* were not statistically significant.

We find that the summary standardized incidence ratio for the studies and the individual standardized incidence ratios for the studies do not point to a strong statistically significant relationship between breast cancer and the occupation of flight attendant. The numbers are not large and there are concerns with some of the studies which calculated standardized incidence ratios such as 1.61 found by Lynge, 2.0 found by Wartenberg and Stapleton, and 1.42 found by Reynolds *et al*. Further, as noted above, Dr. Boyd erred with respect to his statement as to the results found in the letter by Lynge. And we accept Mr. Winter’s point that there is no indication that Dr. Boyd gave any consideration to limitations found in the letter by Lynge or in the letter by Wartenberg and Stapleton as part of his conclusions with respect to the likelihood of a causal association between development of breast cancer and the occupation of flight attendant.

Buja *et al.* considered that despite “a relatively short follow-up period” (19.3 years per study) the meta-standardized incidence ratio for breast cancer was “…significantly increased in flight attendants with respect to the general population.” They concluded that further studies were necessary to clarify the exact role of occupational exposure. While they noted that in the study by Rafnsson *et al*. (2003) social class and reproductive factors did not explain the magnitude of excess risk for breast cancer among cabin attendants, the authors did not note the comments of Kojo *et al.* that breast cancer risk among Finnish cabin attendants was related to general, well-established risk factors for breast cancer such as family history, and that occupational factors did not seem to exert an influence on breast cancer risk, although the evidence remained inconclusive.

We find that overall strength of association established by the literature reviewed by Drs. Band and Boyd and Buja *et al*. is not compelling. As noted above, the summary standardized incidence ratio calculated by Dr. Band for seven studies was 1.35 with a confidence interval of 1.17-1.55. The standardized incidence ratios calculated by Dr. Boyd for five studies was 1.32 or 1.36 with confidences intervals of 1.14-1.53 and

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1.17-1.58, respectively. The figure calculated by Buja *et al.* was 1.40 with a confidence interval of 1.19-1.65.

In his undated report which accompanied Ms. Symes' May 9, 2006 submission, Dr. Boyd observed that it was not clear whether Dr. Band's report was solely a qualitative description of the literature or a meta-analysis. He noted that Dr. Band did not mention statistical methods used to perform a meta-analysis and did not mention the use of any statistical test of heterogeneity. While Dr. Boyd indicated that the paper by Buja *et al.* used an alternative statistical method to generate a quantitative summary of the risk estimates and also provided an independent validation of the approach results used in Dr. Boyd's report, the fact remains that Buja *et al.* calculated a meta-standardized incidence ratio of 1.4.

As noted in the Board's Protocol, a relative risk of 1.4 to 1.5 for an occupational group is, by itself, not conclusive because there could be many confounding variables. We note the following comments in a 2004 review article[40] regarding cosmic radiation exposure and cancer risk among flight crew:

> Although more than 30 studies of cockpit and cabin crew have been published since 1990, there still is not a clear cause-and-effect relationship between risk of any site-specific cancer and employment as a pilot or flight attendant. For the cancer associations that appear to be consistent with occupational exposure to cosmic radiation, such as breast cancer and malignant melanoma, it is still possible that confounding risk factors partially or totally explain the observed relationship.

[40] Sigurdson, AJ and Ron, E. Cosmic Radiation Exposure and Cancer Risk Among Flight Crew. *Cancer Investigation.* 2004 22(5): 743-761.

As well, a 2003 editorial[41] concluded with similar comments:

> The evidence that flight crew are at increased risk for certain types of cancer is growing and current concerns about potential hazards in this occupation are not without basis. However, thus far, the epidemiological evidence remains inconclusive due to limitations in exposure assessment, sample size, and characterisation of confounders.

We accept that any of the above summary standardized incidence ratios fall substantially below the "more likely than not" standard of 2.0, and agree with the above commentary that the evidence of association is inconclusive. We now turn to the other criteria set out in the Board's Protocol.

- Dose-response relationship

A dose-response is the change in incidence of the measured event (breast cancer) with increasing exposure to the factor (employment as a flight attendant) the effect of which is being studied. Dose-response is an important criterion in analyzing epidemiological evidence as, generally, if a cause and effect relationship exists, one would expect to find an increase in incidence with increasing exposure.

In considering the factor of dose-response relationship, we are aware that causal association does not necessarily correspond to a linear dose-response relationship. Some causal associations may show a single jump (threshold) rather than a monotonic trend. Further, associations that do show a trend in disease frequency with increasing levels of exposure are not necessarily causal; confounding can result in a relationship between a non-causal risk factor and disease if the confounding factor itself demonstrates a biological gradient in its relationship with disease. Thus, we are aware that absolute monotonic correlations may not be revealed in a study, even where there is a confirmed relationship between an agent and a disease. However, we do consider it appropriate to take into account whether data in a study reveal a dose-response relationship.

Ms. Symes submitted that Dr. Boyd found that in three studies there was a statistically significant positive dose-response relationship between the length of employment as a flight attendant and the incidence of breast cancer. She cited the standardized incidence ratio calculated by Reynolds *et al.* of 1.42 for flight attendants with 15 or more years of experience. She cited the standardized incidence ratios calculated by Pukkala *et al* of 3.4 for flight attendants "who had flown for 15-19 years" and 2.1 for flight attendants "who had flown for over 20 years." She noted that Rafnsson *et al.* found standardized incidence ratios of 2.3, 2.5, 2.4 for flight attendants who had over one, two or eight years of experience, respectively. She submitted that the worker's 25 years as

[41] Whelan, EA. Cancer incidence in airline cabin crew. *Occupational and Environmental Medicine*. 2003; 60: 805-806

a flight attendant put her “squarely” within the longest duration category for all three of those studies. Ms. Symes contended that the data collected by Rafnsson *et al*. are the most relevant as the authors controlled for latency or the lag time between start of employment and diagnosis.

In connection with latency, Ms. Symes drew attention to the figures calculated by Rafnsson *et al.* with the use of a lag time of 20 years between the start of employment and the development of breast cancer. Statistically significant figures of 4.1, 4.0 and 5.7 were calculated for flight attendants with one year of experience, two or more years of experience, and eight or more years of experience, respectively. She submitted that the figure of 5.7 identified by Rafnsson *et al.* “…establishes a strong probability that [the worker’s] breast cancer was caused by her occupation as a flight attendant for over 25 years.”

Ms. Symes indicated that the worker’s employer may argue that a latency period of 20 years is not applicable to the worker because she did not commence regular international flights until 1980 and that there were periods of time when she was flying only on domestic flights. She indicated that it was extremely difficult to quantify the exact radiation exposure of flight attendants and that therefore duration of employment was used instead of severity of exposure to radiation. She reiterated that the worker fell into the longest duration category for each of the studies that controlled for dose and that the worker had over 25 years of experience which was five more years than the lag time controlled for by Rafnsson *et al.* She also referred to a study[42] which found that flight crews on shorter haul flights could receive doses of radiation comparable to that of international flight crews simply due to an increase in flight frequency.

Given the importance of dose-response relationship information, we consider it appropriate to review this information quite closely.

Pukkala *et al.* examined both (i) time elapsed since recruitment and (ii) time spent at work. The figures cited by Ms. Symes were for time elapsed since recruitment. She erred in asserting that these figures concerned flight attendants who had flown for 15 to 19 years or had flown for 20 years or more.

In Pukkala *et al.* the authors noted that the standardized incidence ratio increased only slightly with increasing time spent in exposed work. Those flight attendants with at least two years of exposed work had a standardized incidence ratio of 2.0 with a confidence interval of 1.2-3.2 and those with at least ten years had a standardized incidence ratio of 2.1 with a confidence interval of 0.9-3.9.

[42] Tume, P *et al*. "Canadian Aircrew Radiation Environment Study," Volume 1: Project Summary (p. 1-71), Sponsored by the Air Transport Association of Canada and the Office of the Director General of Nuclear Safety, RMC-CCE-NSE-98-IVI

We consider that time in exposed work is a better measurement of dose-response than time since recruitment. As noted above, Dr. Band did not address this distinction when he referred to the Pukkala *et al*. report in his summary concluding statement. Dr. Boyd also did not address this distinction in his discussion of data gathered by Pukkala *et al*. In fact, in Table 4 of his report in which he addressed dose-response, he did not include the data concerning time in exposed work gathered by Pukkala *et al.* His comment in his report that Pukkala *et al.* “found no cases of breast cancer with less than 15 years of employment” suggests that he may not have understood the distinction made by the authors who pointed out that all cases of breast cancer were diagnosed more than 15 years *after the subjects were recruited*.

The fact that figures gathered by Pukkala *et al.* concerning time in exposed work are at or above 2.0 does point to an increased risk, but the change from 2.0 to 2.1 noted above does not persuasively establish a dose-response. We are aware of comments in the Board’s Protocol that, where a dose-response relationship exists, “limiting factors” can sometimes cause the dose-response relationship to flatten out at higher levels. That observation does not mean that the presence of numbers which do not establish a significantly increasing risk associated with increasing exposure establish that there is, in fact, a dose-response relationship.

The figures calculated by Pukkala *et al.* for standardized incidence ratios associated with time since recruitment of equal to or greater than 15 years are of interest given that they are statistically significant and, even after correcting for social class, involve a near doubling or a doubling of risk. That the standardized incidence ratio dropped considerably when adjusted for social class raises important questions as to whether adjustment for other confounders would reduce the figure even more. A further matter to take into account is the fact that the study by Pukkala *et al.* involved a small cohort with a small number of person-years.

Rafnsson *et al*. produced two tables of figures that are relevant to the issue of dose-response. In Table 3 of their report they noted that the standardized incidence ratios associated with employment categories of two or more years, five or more years, eight or more years, ten or more years, and 20 or more years were 1.7, 1.7, 1.8, 1.6, and 1.6, respectively. Those figures do not indicate a dose-response; they do not consistently rise with years of employment.

In Table 4 of their report Rafnsson *et al*. calculated standardized incidence ratios with use of lag times for employment categories of one or more years, two or more years, and eight or more years. For the first category of one or more years, the statistically significant standardized incidence ratio of 2.3 with no lag time rose to a statistically significant figure of 4.1 when a lag time of 20 years was applied. The statistically significant figure of 2.5 for two or more years associated with a lag time of two years rose to a statistically significant figure of 4.0 when a lag time of 20 years was applied. The non-statistically significant figure of 2.4 for eight or more years associated with a

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lag time of eight years rose to a statistically significant 5.7 figure when a lag time of 20 years was applied.

While Rafnsson *et al*. found no dose-response with the employment categories when no lag time, two years of lag time, and eight years of lag time were used, there was a dose-response when a lag time of 20 years was applied for those durations of employment. As noted above, Dr. Boyd observed that the results needed to be viewed with some caution until replicated. He did comment that it was possible that the high-altitude long duration flights in which exposure to radiation may be greatest are a sufficiently recent development that the health effects of the radiation exposure associated with these flights have not yet been seen.

Using the category of "non-Hispanic white" Reynolds *et al.* calculated a standardized incidence ratio of 0.89 with a confidence interval of 0.44-1.60 for flight attendants with fewer than 15 years of experience which increased to 1.42 with a confidence interval of 1.05-1.87 for 15 or more years of service. The figures suggest a dose-response; however, the figure of 1.42 is not especially compelling. As noted above, Dr. Band erred in his comments with respect to a dose-response assessed by Reynolds *et al.* However, he did make some notable comments with respect to the quality of the study conducted by Reynolds *et al.*

We consider it significant that the two largest cancer incidence studies as determined by identified person-years (Haldorsen *et al.* and Linnersjö *et al*.) did not identify greatly elevated statistically significant dose-response relationships. Linnersjö *et al*. found that the standardized incidence ratios for employment categories of less than ten years of employment, ten to 19 years of employment, and 20 plus years were 1.36, 1.26, and 1.39, respectively. Not one of those standardized incidence ratios was statistically significant. Notably, the authors commented that no clear associations were found between years of employment and cancer incidence overall or for breast cancer among women.

The study by Haldorsen *et al.* is notable for the fact that standardized incidence ratios for employment categories of less than five years, five to 14 years, and 15 plus years were 1.2, 1.1, and 0.9, respectively. Not one of those figures was statistically significant. Among female cabin attendants born after 1934 the standardized incidence ratio for employment categories of zero to four years, five to 14 years, and 15 years or more were 1.0, 1.1, and 1.0, respectively. No dose-response was established. Nor was any dose-response apparent after adjustments were made for individual information about fertility variables.

The case-control study by Rafnsson *et al.* (2003) contains data of note. Those authors analyzed data associated with their earlier study and calculated a significant association (adjusted for reproductive factors) between length of employment, measured as five or more employment years before 1971, and risk of breast cancer. The figures associated with employment after 1971 were very different. Notably, the authors observed that the odds ratio associated with less than five years of employment between 1971 and 1997 was 1.0. That figure dropped to a non-statistically significant figure of 0.82 for the employment category of more than five years between 1971 and 1997, as adjusted for age at first childbirth and length of employment 1970 or earlier. Thus, no dose-response relationship was apparent for the employment category relevant to the case before us in which the worker did not commence employment as a flight attendant until 1974. The authors commented that they could not conclude that the exposure related to increased risk of breast cancer was solely confined to the period before 1971 because a long lag time may be required "for inducing breast cancer." Interestingly, they determined that the highest risk was found in flight attendants who were under the age of 24 when they first gave birth.

Kojo *et al.*'s nested case-control study of Finnish cabin attendants noted above also provided information relevant to the dose-response and cancer incidence. The authors concluded that risk of breast cancer was not associated with cumulative occupational radiation dose.

The mortality studies conducted by Blettner *et al.* and Zeeb *et al.* did not establish dose-response relationships. In the first study the standardized mortality ratios for duration of employment categories of half a year to less than five up to years, five up to ten years, and ten years or more were 1.56, 1.53, and 0.87, respectively. Not one of the figures was statistically significant. In the second study, the standardized mortality ratios for duration of employment categories of less than ten years, ten up to 20 years, and 20 years or more were 1.12, 1.27, and 0.80, respectively. Not one of those figures was statistically significant.

While Ms. Symes argued in her May 9, 2006 submission that "There is a strong dose response relationship between amount of flying and development of breast cancer", we are not persuaded that that is so. We do not consider that the data suggestive of a dose-response are especially compelling. While the Rafnsson *et al.* results are of considerable interest, particularly concerning incidence after time lag, they have not been replicated, and the data compiled by Rafnsson *et al*. (2003), Haldorsen *et al.*, and Linnersjö *et al.* raise significant questions as to the existence of any dose-response relationship.

- Consistency

While the studies calculated standardized incidence ratios which exceeded 1.0, for the reasons given earlier under the strength of association analysis, we consider that the studies are not consistent in establishing an appreciably elevated standardized incidence ratio regarding employment as a flight attendant or regarding employment as a flight attendant over an extended period of time.

- Analogy, biological plausibility, and coherence

Information concerning radiation exposure during flight and acute leukemia is relevant to the above three criteria. Dr. Boyd indicated that a study by Lewis *et al.* demonstrated that most Canadian-based domestic and international pilots and flight attendants exceed the proposed annual limit of 1 mSv. As noted by Mr. Winter, that annual limit proposed by the International Commission on Radiological Protection (ICRP)[43] was for the general public and was below the proposed annual limit for occupations exposed to radiation (a fact not noted by Dr. Boyd). The recommended annual limit for occupational exposure was 20 mSv averaged over five years with not more than 50 mSv in a single year. We attach significance to the fact that Lewis *et al.* observed that air crew would be well below the proposed annual limit.

Mr. Winter submitted that the study by Lewis *et al.* does not support Dr. Boyd's assertion that 20 years at the average level of exposure ascertained by Lewis *et al.* would result in exposure to more than 50 mSv, the lower limit of protracted exposure associated with an increased risk of cancer. Mr. Winter submitted that "The unanswered question is what constitutes <u>protracted</u> exposure." He contended that Dr. Boyd appeared to have interpreted "protracted" to mean lifetime exposure while he asserted that the most reasonable interpretation to place on the word "protracted" was the five-year average exposure set out in the proposal by the ICRP. Based upon the results of the study by Lewis *et al*., he contended that the worker's exposure would be well below such protracted exposure over a five-year period.

Mr. Winter appears to have overlooked the fact that Dr. Boyd was referring to an article by Brenner *et al.* who indicated that epidemiological data suggested that 50 to 100 mSv of protracted exposure increased cancer risk in humans. The authors of that study did not indicate that the figures for protracted exposure were somehow tied to the recommendations made by the ICRP.

That a risk of breast cancer may increase at a level of 50 mSv of protracted radiation exposure is not, by itself, persuasive evidence that cancer occurring in a person exposed to such a radiation level was due to the exposure. An increased risk approximating 2.0 for persons so exposed would have to be present before one could consider that the cancer of a specific member of the exposed group was due to the exposure. Dr. Boyd did not indicate that the risk at 50 mSv or 70 mSv was 2.0. The latter figure uses 2.8 mSv per year calculated by Lewis *et al.* (and cited by Dr. Boyd) multiplied by 25 years. Ms. Symes referred to a figure of 6 mSv per year noted by Band *et al.* (see footnote #9). However, she did not cite any evidence which established that an exposure of 6 mSv per year for 25 years resulted in a relative risk of 2.0 for breast cancer.

[43] The ICRP's recommended levels of exposure may be reviewed in ICRP's Publication 60, a summary of which may be viewed at http://www.icrp.org/index.asp.

Whether airline cabin crews are at an increased risk of developing acute leukemia due to occupational exposure to ionizing radiation is not before this panel for determination. We note that Mr. Winter observed that the evidence supported a conclusion that exposure to ionizing radiation was a known cause of acute leukemia, with the exception of chronic lymphoid leukemia.

Dr. Boyd's calculation of a summary standardized incidence ratio of 1.73 with a confidence interval of 1.21-2.47 for acute leukemia was based on data from 11 case studies regarding flight attendants and other flight crew. Buja *et al.* calculated a figure for female flight attendants and the general category of leukemia of 1.43 with a confidence interval 0.33-2.86. Thus, their calculation produced a non-statistically significant figure that was lower than that calculated by Dr. Boyd.

However, that issue is not before us for determination. We note the comments in the Board's Protocol to the effect that biological plausibility, which concerns how an apparent cause and effect relationship fits with other knowledge, is often of little help in sorting out convincing from unconvincing data because, with ingenuity, one can always find a plausible explanation for whatever is observed.

We question the extent to which any possible link between acute leukemia and employment as a flight attendant may be used to establish a causal link between employment as a flight attendant and breast cancer. Even if there is a link between acute leukemia and employment as a flight attendant, and even if that link is due to exposure to radiation, the question would still remain whether exposure to radiation during employment as a flight attendant was of causative significance with respect to the development of breast cancer. The answer to that question would still have to be supplied by a review and analysis of the literature concerning breast cancer and employment as a flight attendant.

Mr. Winter took issue with Dr. Boyd's reliance on data associated with acute leukemia. Mr. Winter indicated that exposure to ionizing radiation is a known cause of thyroid cancer. He observed that the total number of observed and expected cases of thyroid cancer in the seven studies which reported incidence of thyroid cancer in airline flight crews represented a combined standardized incidence ratio for thyroid cancer of 0.87. He contended that it would appear that there is no increased risk, and therefore no causal association, between the occupation of airline flight crew and the development of thyroid cancer. He submitted that evidence concerning thyroid cancer significantly detracted from the biological plausibility argument relied upon by Dr. Boyd. In response, Ms. Symes contended that Mr. Winter failed to take into account that the text chapter submitted by him established that exposure to radiation increases the risk of thyroid cancer only if the exposure is at an early age.

We do not consider it necessary to resolve any issue with respect to thyroid cancer. Just as the issue of acute leukemia is not before us for determination, the issue of thyroid cancer is not before us for determination. The issue before us involves breast cancer.

Ms. Symes attached significance to the worker's flight records for the period 1995-2001 which show that she flew almost exclusively on international flights which occurred at high altitude and involved many routes that were close to the magnetic pole and involved lengthy flights. While such flights would have involved higher levels of exposure, we accept Mr. Winter's argument that the worker's exposure during that period of time was "essentially irrelevant" to the issue before us. If, as noted by Dr. Boyd, breast cancer may take up to 20 years to become manifest, then given that the worker's breast cancer became manifest within five to six years of the time she was most exposed, 1995 to 2001, it seems likely that the initiation and development stage of the worker's breast cancer was well underway before she started flying almost exclusively on international flights.

Ms. Symes contended that the fact that the worker was at the same risk of contracting breast disease as other women her age (1.2%) meant that her non-occupational risk factors did not put her at "increased risk" as compared to other white women her age. However those circumstances do not mean the worker was without risk regarding breast cancer. Both Dr. Boyd and Dr. Band indicated that the worker had non-occupational risk factors. That she and other white women her age were at a 1.2% risk of developing breast cancer over a five-year period meant that some women of her age would develop breast cancer. We do not accept Ms. Symes' assertion that the only "plausible explanation" for the worker's breast cancer is that it was caused by her occupation as a flight attendant.

After reviewing the matter, and for the reasons set out above, we find that the worker's breast cancer was not due to the nature of her employment. We do not consider that the evidence is sufficient to establish that the worker's individual exposure was such that her personal risk was so elevated that the possibility that her breast cancer was due to the nature of her employment was equally balanced with the possibility that it was not. The worker's exposure would have to have been extraordinary, when compared to a cohort of flight attendants with a similar number of years of employment, to elevate her personal risk to 2.0 or more. The evidence does not establish that the worker had extraordinary exposure. To the extent that there is a modestly increased risk of breast cancer amongst flight attendants, we consider that the evidence fails to establish that the worker's circumstances were sufficient to increase her personal relative risk to near 2.0, such that subsection 250(4) of the Act would be applicable to her claim.

Legal Costs

Ms. Symes requested reimbursement of legal costs pursuant to section 6(c) of the *Workers Compensation Act Appeal Regulation, B.C. Reg. 321/02* (Regulation). She submitted that this case involves exceptional circumstances that would make it unjust to deprive the worker of costs. She submitted that, as this is an important case of first instance, significant costs were incurred in (i) obtaining a qualified expert to provide an expert opinion, (ii) undertaking "copious research" on breast cancer, ionizing radiation, and the legal standard for causality, and (iii) drafting submissions.

In considering this matter we have taken into account the terms of section 6 of the Regulation:

> The appeal tribunal may award costs related to an appeal under Part 4 of the Act to a party only if the appeal tribunal determines that:
>
> (a) another party caused costs to be incurred without reasonable cause, or caused costs to be wasted through delay, neglect or some other fault,
> (b) the conduct of another party has been vexatious, frivolous or abusive, or
> (c) there are exceptional circumstances that make it unjust to deprive the successful party of costs.

As provided for in item #13.10 of the MRPP, an order for payment of costs by one party to another under section 6 will only be made in an "unusual case." Further, an award of costs under section 6(c) may only be made to a "successful party." As we have allowed the employer's appeal, the worker is not a successful party to whom costs could be awarded. We find that the worker is not entitled to costs pursuant to section 6(c) of the Regulation.

Ms. Symes did not request payment of legal costs under section 7 of the Regulation. Such a request would be unsuccessful given that the regulation provides that WCAT "…may not order the Board to reimburse a party's expenses arising from a person representing the party or the attendance of a representative of the party at a hearing or other proceeding related to the appeal."

Conclusion

We allow the employer's appeal. We vary the December 12, 2002 decision of the Board claims adjudicator. We find that the worker's breast cancer was not due to the nature of her employment.

Item #13.23 of the MRPP provides that WCAT will generally order reimbursement of expenses for attendance of witnesses or obtaining written evidence, regardless of the results in the appeal, where (i) the evidence was useful or helpful to the consideration of the appeal or (ii) it was reasonable for the party to have sought such evidence in connection with the appeal. WCAT will generally limit the amount of reimbursement to the rates or tariff established by the Board.

It was reasonable for the parties to have sought the reports of Drs. Band and Boyd. Further, the panel found the reports helpful. The expenses associated with these reports were significant: $11,000.00 and $5,000.00, respectively. (Dr. Boyd did not bill for his second report.) The expertise of the two physicians is significant. We find it appropriate to order full reimbursement for the reports. While there may be cancer cases where full reimbursement of expenses associated with the reports of appropriate specialists is not warranted, we consider that in most cases, full reimbursement is appropriate. Full reimbursement may encourage parties to obtain input from appropriate specialists as part of their submissions concerning appeals on cases concerning cancer. Input from such specialists may be of significant assistance to panels addressing complex issues associated with such claims.

Randy Lane
Vice Chair

Janice Leroy
Vice Chair

Lesley Christensen
Vice Chair

RL/jd