Specialist Medical Review Council

Reasons for Decisions

Section 196W
Veterans' Entitlements Act 1986

Re: Statements of Principles concerning Malignant Neoplasm of the Brain Nos. 58 and 59 of 2008 as amended by Amendment Statements of Principles Nos. 37 and 38 of 2011

Request for Review Declaration No. 20

SUMMATION

1. In relation to the Repatriation Medical Authority (the RMA) Statement of Principles concerning malignant neoplasm of the brain No. 58 of 2008 as amended by Amendment Statement of Principles No. 37 of 2011 made under subsections 196B (2) and (8) of the *Veterans' Entitlements Act 1986* (the VEA), the Specialist Medical Review Council (the Council) under subsection 196W of the VEA:

    DECLARES that the sound medical-scientific evidence available to the RMA is insufficient to justify an amendment to include a factor or factors for exposure to heat beyond fever temperature, melatonin depletion due to sleep deprivation, alcohol consumption, exposure to non-ionising electromagnetic radiation emitted from radio equipment (as used in aircraft) or exposure to non-ionising electromagnetic radiation emitted from radar equipment.

2. In relation to the Repatriation Medical Authority (the RMA) Statement of Principles concerning malignant neoplasm of the brain No. 59 of 2008 as amended by Amendment Statement of Principles No. 38 of 2011, made under subsections 196B (3) and (8) of the VEA, the Specialist Medical Review Council (the Council) under subsection 196W of the VEA:

    DECLARES that the sound medical-scientific evidence available to the RMA is insufficient to justify an amendment to include a factor or factors for exposure to heat beyond fever temperature, melatonin depletion due to sleep deprivation, alcohol consumption, exposure to non-ionising electromagnetic radiation emitted from radio equipment (as used in aircraft) or exposure to non-ionising electromagnetic radiation emitted from radar equipment.

THE SPECIALIST MEDICAL REVIEW COUNCIL

3. The Council is a body corporate established under section 196V of the VEA, and consists of such number of members as the Minister for Veterans' Affairs determines from time to time to be necessary for the proper exercise of the function of the Council as set out in the VEA. The Minister must appoint one of the Councillors to be the Convener. When appointing Councillors, the Minister is required to have regard to the branches of medical-science that would be necessary for deciding matters referred to the Council for review.

4. Convener constitute the Council When a review is undertaken, three to five Councillors selected by the. If the Review Council for the purposes of a review does not include the Convener, the Convener must appoint one of the

Councillors selected for the review to preside at all meetings as Presiding Councillor.[1]

5. Professor Ken Ho was appointed by the then Convener, Professor Jonathan Phillips, as Presiding Councillor for this review. Professor Ho is chair of the Princess Alexandra Hospital's coordinating body of research and the centres for health research. His major interests are in endocrine disease, specifically in the understanding of how hormones control metabolism, body composition, and function.

The other members of the Council were:

(i) Professor Adèle Green AC

Professor Green is a Senior Scientist at the Queensland Institute of Medical Research and a former Deputy Director and Head of the Institute's Cancer and Population Studies Group.

She has been a chair or member of several committees at the International Agency for Research on Cancer (IARC) in Lyon, France, including member of the Working Party for the Monograph on Radiation and Cancer in 2009. Professor Green is a Member of the International Commission on Non-Ionising Radiation Protection.

(ii) Dr Michael Izard

Dr Michael Izard is a radiation oncologist. He is the lead radiation oncologist and one of three in Australia who run the Gamma Knife at Macquarie University Hospital; a machine designed specifically to treat brain tumours with radiation. His interests include prostate and breast cancers, with a particular interest in brachytherapy. Dr Izard is Clinical Senior Lecturer at the Australian School of Advanced Medicine and Macquarie University and the Sydney Medical School.

(iii) Dr Glenn McCulloch

Dr McCulloch is former head of neurosurgery at the Queen Elizabeth hospital in South Australia, and former president of the Neurosurgical Society of Australasia. He is currently the clinical director of the South Australian audit of peri operative mortality.

(iv) Dr David Newman

Dr Newman spent over 12 years in the Royal Australian Air Force as a medical officer and aviation medicine specialist. He is currently Senior Lecturer and Head of Research in the Aviation Discipline in the Faculty of Engineering and Industrial Sciences at Swinburne University in Victoria and

[1] Section 196ZK of the VEA.

Head of the Aviation Medicine Unit in the Department of Epidemiology and Preventive Medicine at Monash University.

THE LEGISLATION

6. The legislative scheme for the making of Statements of Principles is set out in Parts XIA and XIB of the VEA. Statements of Principles operate as templates, which are ultimately applied by decision-makers in determining individual claims for benefits under the VEA and the *Military Rehabilitation and Compensation Act 2004* (the MRCA)[2].

7. Fundamental to Statements of Principles is the concept of 'sound medical-scientific evidence', which is defined in section 5AB (2) of the VEA. Information about a particular kind of injury, disease or death is taken to be sound medical-scientific evidence if:

a) the information

(i) is consistent with material relating to medical science that has been published in a medical or scientific publication and has been, in the opinion of the Repatriation Medical Authority, subjected to a peer review process; or

(ii) in accordance with generally accepted medical practice, would serve as the basis for the diagnosis and management of a medical condition; and

b) in the case of information about how that injury, disease or death may be caused - meets the applicable criteria for assessing causation currently applied in the field of epidemiology. [3]

8. The functions of the Council are set out in section 196W of the VEA. In this case, the Council was asked (under section 196Y of the VEA) by a person eligible to make a claim for a pension, to review the contents of:

8.1. Statement of Principles No. 58 of 2008 as amended by Statement of Principles No. 37 of 2011 concerning malignant neoplasm of the brain and death from malignant neoplasm of the brain, being a Statement of Principles determined by the RMA under section 196B(2)[4] of the VEA ('the **reasonable hypothesis** test') and

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2 See sections 120, 120A and 120B of the VEA and sections 335, 338 and 339 of the MRCA.

3 This has been held to mean 'information which epidemiologists would consider appropriate to take into account' see *Repatriation Commission v Vietnam Veterans' Association of Australia NSW Branch Inc* (2000) 48 NSWLR 548 (the New South Wales Court of Appeal decision) per Spigelman CJ at paragraph 117.

4 196B(2) provides;

If the Authority is of the view that there is sound medical-scientific evidence that indicates that a particular kind of injury, disease or death can be related to:

(a) operational service rendered by veterans; or

(b) peacekeeping service rendered by members of Peacekeeping Forces; or

(c) hazardous service rendered by members of the Forces; or

(caa) British nuclear test defence service rendered by members of the Forces; or

8.2. Statement of Principles No. 59 of 2008 as amended by Statement of Principles No. 38 of 2011 concerning malignant neoplasm of the brain and death from malignant neoplasm of the brain being a Statement of Principles determined by the RMA under section 196B(3) of the VEA ('the **balance of probabilities test**').

9. Specifically, the Applicant contended that there was sound medical-scientific evidence on which the RMA could have relied to include as a factor or factors in Statements of Principles Nos. 58 and 59 of 2008 as amended by Statement of Principles Nos. 37 and 38 of 2011:

- Exposure to heat beyond fever temperature
- Melatonin depletion due to sleep deprivation
- Smoking consumption
- Alcohol consumption
- Exposure to cosmic radiation
- Exposure to electromagnetic fields

10. In conducting its review, the Council must review all the information that was available to (before) the RMA at the time it determined, amended, or last amended the Statements of Principles (the relevant times) and is constrained to conduct its review by reference to that information only.[5]

11. Under section 196W of the VEA, the Council can only reach the view that a Statement of Principles should be amended on the basis of sound medical-scientific evidence.

BACKGROUND

First Application for review by the Council

12. On 20 August 2008 the RMA under subsections 196B(2) and (3) of the VEA determined Statements of Principles concerning malignant neoplasm of the

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(ca) warlike or non-warlike service rendered by members;

the Authority must determine a Statement of Principles in respect of that kind of injury, disease or death setting out:

(d) the factors that must as a minimum exist; and

(e) which of those factors must be related to service rendered by a person;

before it can be said that a reasonable hypothesis has been raised connecting an injury, disease or death of that kind with the circumstances of that service.

5 *Vietnam Veterans' Association (NSW Branch) Inc v Specialist Medical Review Council and Anor* (full Federal Court decision) (2002) 72 ALD 378 at paragraph 35 per Branson J.

brain Nos. 58 and 59 of 2008 (**the Statements of Principles**). The Statements of Principles took effect from 3 September 2008.

13. On 22 August 2008 the Statements of Principles were registered on the Federal Register of Legislative Instruments.

14. On 3 September 2008 in accordance with section 42 of the *Legislative Instruments Act 2003* the Statements of Principles were tabled in the House of Representatives and in the Senate.

15. An Application for Review of the Statements of Principles was received by the Council on 28 October 2008. The Application sought review of the Statements of Principles on the grounds that:

> 1. Heat beyond fever temperature is oncogenic (increases cancer risk, including brain tumours) …
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> 2. Fighter pilots in the UK were known to fly up to 35,000 feet. Cosmic radiation is now recognised as a health hazard for Pilots … Ionizing radiation is a known precursor of brain cancer.
>
> 3. Melatonin depletion occurs in Pilots who fly at night… Melatonin is a known oncostatic hormone.
>
> 4. Fighter Pilots were known to suffer extreme fatigue and stress and were supplied with free cigarettes and cheap liquor. Both these drugs are oncogenic.

16. Pursuant to section 196ZB of the VEA, the Council published in the Gazette a Notice of its Intention to Carry Out a Review of all the information available to the RMA about malignant neoplasm of the brain and invited eligible persons or organisations so authorised to make submissions to the Council.[6] The Council gazetted subsequent notices as to the dates by which written submissions must be received by the Council.[7]

The information sent by the RMA to the Council - First Application

17. By email dated 12 December 2008 the RMA, under section 196K of the VEA, sent to the Council the information the RMA advised was available to (before) it at the relevant times, as listed in Appendix B.

18. By agreement between the RMA and the Council, information the RMA advised was available to (before) it at the relevant times is posted on a secure website (referred to as FILEForce). It is made accessible by the Council to the Repatriation Commission and the Military Rehabilitation and Compensation Commission (the Commissions), the Applicant, and other

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6 Gazette Notice No. 6 of 18/02/2009.

7 Gazette Notices No. 30 of 05/08/2009; No. 2 of 20/01 2010; No. S231 of 30/12/2010; No. 16 of 27/04/2011.

participants in the review via confidential password. The information that was available to (before) the RMA at the relevant times was posted on FILEForce on 29 March 2009.

Amendment Statements of Principles Nos 58 and 59 of 2011

19. On 1 September 2010 the RMA gave notice under section 196G of the VEA of its intention to carry out an investigation pursuant to subsection 196B(7A) in respect of diagnostic radiation in Statements of Principles concerning, amongst others, malignant neoplasm of the brain.

20. On 9 May 2011 the RMA, under subsection 196B (8) of the VEA, amended the Statements of Principles. The Instruments, Amendment Statements of Principles concerning Malignant Neoplasm of the Brain Nos. 37 and 38 of 2011, took effect from 25 May 2011.The amendments included removal of an atomic radiation factor from the Statements of Principles and replacement with an ionising radiation factor in clause 6(b) as follows:

    - Having received a cumulative equivalent dose of at least 0.1 sievert of ionising radiation to the brain at least two years before the clinical onset of malignant neoplasm of the brain.

    and definition of:

    - 'Cumulative equivalent dose' means the total dose of ionising radiation received by the particular organ or tissue. The formula used to calculate the cumulative equivalent dose allows doses from multiple types of ionising radiation to be combined, by accounting for their differing biological effect. The unit of equivalent dose is the sievert. For the purposes of this Statement of Principles, the calculation of cumulative equivalent dose excludes doses received from normal background radiation, but includes therapeutic radiation, diagnostic radiation, cosmic radiation at high altitude, radiation from occupation related sources and radiation from nuclear explosions or accidents;'

21. The RMA published its consideration of ionising radiation[8] and described the amendments, so far as they relate to malignant neoplasm of the brain to:

    - cover exposure to all forms of ionising radiation, including diagnostic radiation, radiation from medical therapeutic procedures, cosmic radiation at high altitudes, and radiation from occupation-related sources, but excluding natural background radiation. Where diagnostic radiation factors or therapeutic radiation factors were already included in a Statement of Principles, they are now included in the ionising radiation factor.

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8 Repatriation Medical Authority, RMA consideration of ionising radiation, 9 May 2011 available at http://www.rma.gov.au/new/Radiation/RMA%20consideration%20of%20ionising%20radiation.pdf

- increase the cumulative equivalent dose of ionising radiation required to raise a reasonable hypothesis connecting the disease with eligible operational or equivalent service (reasonable hypothesis standard) from 0.05 sievert to 0.1 sievert.

- reduce the latency period between exposure to ionising radiation and onset of malignant neoplasm of the brain from five years to two years in the reasonable hypothesis standard

- reduce the latency period between exposure to ionising radiation and onset of malignant neoplasm of the brain from ten years to five years in the balance of probabilities standard.

22. On 13 May 2011, Amendment Statements of Principles concerning malignant neoplasm of the brain Nos. 37 and 38 of 2011 were registered on the Federal Register of Legislative Instruments.

23. On 23 May 2011 in accordance with section 42 of the *Legislative Instruments Act 2003* the Amendment Statements of Principles Nos. 37 and 38 of 2011 were tabled in the House of Representatives and on 15 June 2011 in the Senate.

Second Application for review by the Council

24. On 14 July 2011, a second Application for Review of Statements of Principles concerning malignant neoplasm of the brain Nos. 58 and 59 of 2008 as amended by Amendment Statements of Principles Nos. 37 and 38 of 2011 (**the amended Statements of Principles**) was received by the Council from the Applicant. The Applicant referred to the First Application for review by the Council and relied upon the grounds mentioned therein.

25. Pursuant to section 196ZB of the VEA the Council published in the Gazette a Further Notification of its Intention to Carry Out a Review of all the information available to the RMA about malignant neoplasm of the brain and invited eligible persons or organisations so authorised to make written submissions to the Council by 16 December 2011.[9]

The information sent by the RMA to the Council – Second Application

26. By email dated 13 September 2011, the RMA, under section 196K of the VEA, sent to the Council the information the RMA advised was available to (before) it at the relevant times, as listed in Appendix B.

27. The information which was available to (before) the RMA at the relevant times was posted on FILEForce, as described in [18] above, on 14 September 2011.

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9 Gazette Notice. No. GN 35 of 7/09/ 2011.

Notification of Preliminary Decisions on Proposed Scope of Review and Proposed Pool of Information

28. In separate letters, dated 13 June 2011, to each of the Applicant and the Commissions, the Council:

- advised of the Council's preliminary decisions on the proposed scope of the review and proposed pool of information;
- advised of the Council's reasons for limiting the proposed scope of the review in respect of exposure to non-ionising electromagnetic radiation to radiation emitted from radio equipment (as used in aircraft) or radiation emitted from radar equipment.
- invited the Applicant and Commissions to make any written comments as to the Council's preliminary decisions by close of business on 16 July 2011; and
- advised that if any written comments were made, any complementary oral comments could be made at a hearing of oral submissions complementing the written submissions.

29. The Council's preliminary decision on the scope of the review, as advised to the Applicant and Commissions, was as follows

> Without limiting the scope of the Council's review of (some or the whole of) the contents of Statements of Principles Nos. No. 58 of 2008 and 59 of 2008 as amended by Instruments Nos. 37 and 38 of 2011 in respect of malignant neoplasm of the brain, the Council presently proposes to have particular regard to whether there was sound medical-scientific evidence upon which the Repatriation Medical Authority (the RMA) could have relied to amend either or both of the Statements of Principles by the possible inclusion of a factor or factors for:
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> - Exposure to heat beyond fever temperature
> - Melatonin depletion due to sleep deprivation
> - Smoking consumption
> - Alcohol consumption
> - Exposure to non-ionising electromagnetic radiation emitted from radio equipment (as used in aircraft)
> - Exposure to non-ionising electromagnetic radiation emitted from radar equipment.

30. The Council decided that consideration of factors contended by the applications in respect of exposure to non-ionising electromagnetic radiation would be limited to the types of radiation relevant to the Applicant; that is, radio frequency radiation of the type specific to radio waves (i.e. from radio

equipment utilised in aircraft) and radar, of the type and level to which WWII pilots may have been exposed.

31. The Council's reasons for so limiting its consideration of non-ionising radiation, as advised to the Applicant and the Commissions in the separate letters, dated 13 June 2011 were:

31.1. The Council noted that within the electromagnetic spectrum, radio, and radar radiation fall within a specific frequency range; from 3 kHz to 300 GHz.

31.2. The Council considered that research into a putative association between mobile phone use and malignant brain cancers, referred to by the Applicant in a written submission is not relevant to any putative association between radio or radar radiation and malignant brain cancers. Although the frequency of mobile phones (3 to 300 MHz) falls within the radiofrequency range, as do radio and radar, the dose levels of radiation delivered by mobile phones are not comparable to those in the contended factors. The dose levels received from radio or radar would have been much lower. Extremely low doses of this kind fall below the threshold measured in mobile phone studies.

31.3. The Council noted that there is a threshold of radiation volume/dose below which there is no plausible connection between the waves and potential tumour development. Furthermore, below those thresholds, very low levels of radiation have been postulated to have beneficial health effects, and there is a body of science called Radiation Hormesis that investigates this.

31.4. The Council further noted that the strength of radiation received falls off very quickly when any distance is put between the direct source and the person using it.[10] The radio receiver for aircrew was a unit mounted into the aircraft fuselage, and was a distance away from the head of the pilot. Earphones worn by pilots acted as basic, very small, loudspeakers that worked off a direct electric current (DC) provided by the engine(s) of the aircraft, and as such the energy of any magnetic field generated would not be of significance. Earphones are not, as mobile phones are, receivers and emitters of radio waves directly.

32. In its consideration of the sound medical scientific evidence, the Council acknowledged that there is debate about the relationship between carcinogenesis and radiation exposure but decided the debate does not change the Council's view about revising the proposed scope of the review, nor does it justify any change to the proposed scope.

[10] The Inverse-Square Law: the intensity of a wave is inversely proportional to the square of the distance from the source.

Proposed Pool of Information

33. As mentioned above, the RMA is obliged under section 196K of the VEA to send to the Council all the information that was available to it (the RMA) at the relevant times. That comprises all the information that was available to the RMA when it first determined Statements of Principles concerning malignant neoplasm of the brain in 1995 and all the information subsequently available at all times when the Statements of Principles have been amended, or revoked and replaced, up to and including the information that was available in 2011 when the RMA determined Amendment Statements of Principles Nos. 37 and 38 of 2011. In other words, within 28 days after being notified that the Council has been asked to conduct a review, the RMA must send to the Council all the information in respect of malignant neoplasm of the brain that was in the possession of the RMA at the time it (the RMA) made the decision that triggered the Council's review.

34. The chronology of the RMA sending the information to the Council is detailed in [17] and [26] above. As mentioned above, all the information that was available to the RMA at the relevant times was made available to the Applicant and the Commissions for the purposes of the review.

35. In determining its preliminary view on the proposed pool of information the Council applied the methodology it had advised the Applicant and Commissions on 13 June 2011 i.e. that the pool of information should comprise the information:

- that was available to (before) the RMA at the relevant times;
- which was sent by the RMA to the Council under section 196K of the VEA;
- which was considered by the Council to be sound medical-scientific evidence as defined in section 5AB(2) of the VEA being information that:

  (1) epidemiologists would consider appropriate to take into account; and

  (2) in the Council's view 'touches on' (is relevant to) exposure to any of the factors within the scope of the review and
- that has been evaluated by the Council according to epidemiological criteria, including the Bradford Hill criteria.[11]

36. Information that the RMA advised was not available to (not before) the RMA at the relevant times, was not taken into account by the Council for the purposes of the review, as it could only be considered as 'new information'.

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[11] See Bradford Hill, A 1965, 'The Environment and Disease: Association or Causation?', *Proceedings of the Royal Society of Medicine* Section of Occupational Medicine, Meeting January 14, pp. 295 - 300.

37. A copy of the Council's preliminary list of the proposed pool of information was forwarded to the Applicant and the Commissions.

38. In the letters to each of the Applicant and the Commissions dated 13 June 2011, the Council informed them that, given the different delivery methods and levels of radiation delivered by mobile phones, the Council considered the medical literature on mobile phones does not touch upon the putative association between malignant neoplasm of the brain and radio or radar radiation.

39. The Council also excluded from the pool of information, studies which focussed only on potential effects of radiation from electric power lines, as this radiation falls within extremely low frequency (ELF) range of the electromagnetic spectrum, at frequencies of 30-300 Hertz.

40. No comments were received in respect of the Council's preliminary decisions on the proposed scope of review or the proposed pool of information.

Notification of RMA Investigation

41. By Notice of Investigation dated 21 June 2012[12] the RMA gave notice that it intended to carry out an investigation in respect of:

- Carbon monoxide, benzene and other chemicals associated with exhaust fumes; and

- Smoking

as factors in malignant neoplasm of the brain (**RMA's new investigation**)

42. By that Notice, the RMA invited persons, and organisations eligible to do so, to make written submissions to the RMA in respect of the new investigation by 28 September 2012, and gave notice that its first meeting for the purposes of the investigation would be on 2 October 2012.

Revised Preliminary Decision on Proposed Scope of Review and Proposed Pool of Information

43. The Council subsequently reviewed its preliminary decision on the scope of the review taking into account the gazettal of the RMA's new investigation.

[12] Commonwealth of Australia Gazette No. GN 25, 27 June 2012

44. The Council noted:

- The Applicant contends for a number of factors, one of which was smoking;
- the RMA's new investigation may uncover sound medical scientific information on which the RMA could rely to include smoking as a factor in either or both statements of principles concerning malignant neoplasm of the brain (**new information**);
- any new information obtained by the RMA in its investigation cannot be taken into account by the Council in determining the outcome of the review (this Council's task being to review the information available to the RMA when it last amended these statements of principles);
- Persons interested in this Council's review have the rights to make submissions to the RMA in its investigation as set out in Division 1 Part XIA of the VEA ;
- On conclusion of the RMA's new investigation, persons interested have such rights, as set out in Division 1 of Part XIB of the VEA, to apply to the SMRC for review of the Statements of Principles or the RMA's decision in its investigation as applicable.

45. Given these matters, the Council tentatively determined that the contended smoking factor for clinical onset and/or clinical worsening of malignant neoplasm of the brain in one or both of the Statements of Principles should no longer be within the proposed scope of the review. The Council decided, subject to hearing from the Applicant and the Commissions, to confirm its proposed scope of review as described at paragraph [29] above in respect of the possible inclusion of five factors, excluding the possible inclusion of a factor or factors for smoking consumption (the **revised proposed scope of review**)

46. In separate letters, dated 16 July 2012, to each of the Applicant and the Commissions, the Council, in summary:

- advised of the Council's preliminary decisions on the revised proposed scope of the review and proposed pool of information;
- invited the Applicant and Commissions to make any written comments as to the Council's revised preliminary decisions by close of business on 9 August 2011; and
- advised that if any written comments were made, any complementary oral comments could be made at a hearing of oral submissions complementing the written submissions.

47. No comments were received on the Council's preliminary decisions on the revised proposed scope of the review and revised proposed pool of information. The Applicant did however, deliver a document, dated 9 August

2012 described as Supplementary Submissions. In this document, the Applicant addressed five factors, which she submits could have been relevant to the causation or propagation of malignant brain tumours, particularly in her husband's case. The five factors addressed in the supplementary submission were not precisely the same in all respects as the five contended factors described in the Council's revised proposed scope of review.

48. The Council held a meeting on 23 August 2012 to consider all the written submissions and complementary oral submissions.

Revised Proposed Scope of Review

49. The Council's preliminary decision on the revised proposed scope of the review, as advised to the Applicant and Commissions on 16 July 2012, was as follows:

> Without limiting the scope of its review of (some or the whole of) the contents of the Statement of Principles, presently proposes to have particular regard to whether there was sound medical-scientific evidence upon which the RMA could have relied to amend either or both of the Statements of Principles in respect of:
>
> – Exposure to heat beyond fever temperature
>
> – Melatonin depletion due to sleep deprivation
>
> – Alcohol consumption
>
> – Exposure to non-ionising electromagnetic radiation emitted from radio equipment (as used in aircraft)
>
> – Exposure to non-ionising electromagnetic radiation emitted from radar equipment.

50. These five factors are referred to in these reasons as the five contended factors.

Revised Proposed Pool of Information

51. In determining its preliminary view on the revised proposed pool of information the Council applied the methodology it had advised the Applicant and Commissions on 13 June 2011 as set out at paragraph [35] above

52. A copy of the Council's revised preliminary list of the proposed pool of information was forwarded to the Applicant and the Commissions and is attached at **Appendix A.**

53. No comments were received on the Council's revised proposed pool of information.

APPLICANT'S SUBMISSIONS

54. The Applicant made:

- written submissions dated 24 March 2009, 1 April 2009, 5 April 2009, 1 July 2009, and 9 August 2012.
- an oral submission complementing her written submissions on 23 August 2012 which was delivered by the Applicant's daughter.

all of which were taken into account by the Council.[13]

55. In her Applications to the Council of 28 October 2008 and 14 July 2011, the Applicant stated that the grounds for review were as follows:

- Exposure to heat beyond fever temperature is oncogenic, including brain tumours
- Cosmic radiation is now recognised as a health hazard for pilots
- Ionising radiation is a known precursor of brain cancer
- Melatonin depletion occurs in pilots who fly at night. Melatonin is a known oncostatic hormone
- Fighter pilots were known to suffer extreme fatigue and stress and were supplied with free cigarettes and cheap liquor both of which are oncogenic.

56. The Applicant also referred the Council to her submission to the RMA of 21 June 2008.

57. In it, the Applicant refers to her late husband, a World War 2 fighter pilot, who she claims was potentially exposed to significant cosmic radiation during his service of three years in the RAAF, including overseas operational service. The Veteran died of glioblastoma in 2001.

58. The Applicant also raised concerns about her husband's long term use of an infrared lamp in to treat an arm injury and referred to a number of factors which she considered can cause glioblastoma.

59. The Applicant's submission to the RMA was on the basis of her interpretation of a number of articles which she claimed support her contentions.

60. At the oral hearing on 23 August 2012, the Applicant's daughter made oral submissions complementing the Applicant's written submissions. The

[13] The information upon which the Applicant relied, being information which the RMA advised was available to (before) the RMA at the relevant times, is listed in Appendix C.

Council clarified with the Applicant during the course of the oral hearing that the supplementary submission of 9 August 2012 does not contend that the scope of the review should be varied, and she accepted the scope of this review to be the five contended factors as described at paragraph [49] above. The Council has therefore taken account of her submissions in respect of only the five contended factors.

61. The Applicant's submissions included papers that touched on:

61.1. Heat beyond fever temperature

Zhang et al 2001[14], Nylandsted J, Brand K, Jäättelä M. 2000,[15] and Garrido et al 2006[16] which the Applicant submitted evidenced that:

> Heat elicits Heat Shock Protein 70 in Glial tissue. This protein is a potent anti apoptotic oncogenic protein.

Nylandsted et al 2002[17] which the Applicant submitted showed:

> Eradication of **Heat Protein Shock Protein** 70, with antisense HSP 70 causes massive cell death in Glioblastoma Xenografts.

61.2. Dayanc et al 2008[18] and Harada et al 2007[19] which the Applicant submitted evidenced that:

> Natural Killer Cells are also heat sensitive at greater-than-fever temperatures, becoming inactive (allowing uncontrolled growth of cells).

61.3. Ohnishi et al 1995[20]. The Applicant referred to heat sources including microwave infrared ultrasound and infrared ray therapy which she contended

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14 Zhang, W.L. Tsuneishi, S. and Nakamura, H 2001, 'Induction of heat shock proteins and its effects on glial differentiation in rat C6 glioblastoma cells', *Kobe J Med Sci*. vol.47, no. 2, pp.77-95. (RMA ID 49052)

15 Nylandsted, J. Brand, K. & Jäättelä, M 2000, 'Heat shock protein 70 is required for the survival of cancer cells', *Ann N Y Acad Sci*, vol. 926, pp.122-5. (RMA ID 49043)

16 Garrido, C. Brunet, M. Didelot, C. Zermati, Y. Schmitt, E & Kroemer, G 2006, 'Heat shock proteins 27 and 70: anti-apoptotic proteins with tumorigenic properties', *Cell Cycle*, vol. 5, no. 22, pp.2592-601. (RMA ID 49044)

17 Nylandsted, J. Wick, W. Hirt, U.A. Brand, K. Rohde, M. Leist, M. Weller, M. and Jäättelä, M. 2002, 'Eradication of glioblastoma, and breast and colon carcinoma xenografts by Hsp70 depletion', *Cancer Res,* vol. 62, no. 24, pp.7139-42. (RMA ID 49045)

18 Dayanc et al 2008, 'Dissecting the role of hyperthermia in natural killer cell mediated anti-tumor responses', *Int J Hyperthermia*, vol. 24, no.1, pp.41-56. (RMA ID 49046)

19 Harada, H. Murakami, T. Tea, S.S. Takeuchi, A. Koga, T. Okada, S. Suico, M.A. Shuto, T. and Kai, H 2007, 'Heat shock suppresses human NK cell cytotoxicity via regulation of perforin', *Int J Hyperthermia*. vol. 8, pp.657-65. (RMA ID 49047)

20 Ohnishi, T. Matsumoto, H. Takahashi, A. Shimura, M. & Majima, H.J 1995, 'Accumulation of mutant p53 and hsp72 by heat treatment, and their association in a human glioblastoma cell line', *International Journal of Hyperthermia*, vol. 11, no. 5, pp. 663-71. (Abstract Only - RMA ID 49048)

was used commonly in the 1950s and later to increase the blood supply and accelerate the healing of injuries. She submitted that Ohnishi et al showed:

> Tumour Suppressor gene is also heat sensitive. Heat causes mutations in the gene, which renders it inactive. The effect also allows uncontrolled growth of cells. (P53)

62. In her oral submission, the Applicant submitted that:

> Heat shock proteins are designed to protect the cells from the effect of heat and in conditions of heat shock, which is higher than normal heat. They are over expressed in the cells.

63. The Applicant also referred to information on GLOLITE luminous infrared ray lamps 1950[21], which she submitted evidenced that:

> The infrared lamps in use at that time were more powerful than those in use today, and ranged from 450 Watts to 1450 Watts in power.

64. The Applicant contended that:

> It is conceivable that chronic exposure to heat would have deleterious effects and could result in brain tumours. Increasing blood supply via vasodilation to a tumour would have an accelerant effect.
> …
> Attempts to implicate noxious agents in this group, such as poly-chlorinated bi-phenyls and polychlorinated dibenzo-furans, or other toxic chemicals, have so far failed to explain the increased malignancy.
>
> It is again conceivable that the necessary protective apparel, together with full-face shielding and closed circuit breathing apparatus plus the intense infrared heat of a fire is contributing significantly to the risk of malignancy in Fire fighters. The skin and the lungs are the main avenues for dissipation of heat in the body.

and cited Gerstner et al 2007[22]and Stuhr et al 2007[23] Youakim S 2006[24], and Krishnan et al 2003[25] and Kelly et al 2002[26] in support.

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21 'GLOLITE luminous infrared ray lamps 1950, models 439, 751, 1151, and 1451', accepted. *J Am Med Assoc*. vol. 144, no. 13, p.1093. (RMA ID 49049)

22 Gerstner et al 2007, 'Antiangiogenic agents for the treatment of glioblastoma', *Expert Opin Investig Drugs*, vol.16, no.12, pp.1895-908. (RMA ID 49050)

23 Stuhr et al 2007, 'Hyperoxia retards growth and induces apoptosis, changes in vascular density and gene expression in transplanted gliomas in nude rats', *J Neurooncol*, vol. 85, no.2, pp.191-202. *Epub* 2007 Jun 8. (RMA ID 49051)

24 Youakim, S 2006, 'Risk of cancer among firefighters: a quantitative review of selected malignancies', *Arch Environ Occup Health*. vol. 61, no. 5, pp. 223-31. (RMA ID 45822)

25 Krishnan et al 2003, 'Occupation and adult gliomas in the San Francisco Bay Area', *J Occup Environ Med,* vol. 45, no. 6, pp.639-47. (RMA ID 45922)

65. In the Applicant's submission of 5 April 2009, she referred the Council to a '60 Minutes' program broadcast on television on 5 April 2009.[27] She claimed that the program was concerned with:

> …the 'exponential' increase in Brain Tumours, of highly malignant type, amongst the young and also adult population, which has coincided with an 'exponential' rise in mobile phone use. Two neurosurgeons voiced concerns; one detractor admitted that mobile phones do increase the temperature of the brain 'but only by 0.1º C'.
>
> This detractor though also said that 'below 1ºC increase in temperature there is no increase in Brain Tumours'.
>
> She added that:
>
> Older heat lamps, of the kind presented for my father by the Repatriation Department, ranged in power from 450 watts to 1450 watts.
>
> Heat at the head is inversely proportional to the square of the distance from the lamp.

66. In her oral submission the Applicant contended that:

> …chronic toxic heat has been suspected for decades as being harmful to the brain.
>
> An Australian neurosurgeon has publicly stated his concerns about even mild increases in brain temperature and brain cancer risk.
>
> She added that:
>
> Ex-vivo experiments on glioblastoma cell lines verify induction of heat shock proteins by heat, and their tumorigenic potential, particularly heat shock protein 70 and 27, although heat shock protein 90 also is involved. And other heat 5 shock proteins perhaps as well.
>
> Heat effects on P53, a major tumour suppressor gene, has flow on effects with other tumour suppressor genes, in activating P10, for instance, which is another very 10 potent tumour suppressor gene protein increasing carcinogenicity by haploinsufficiency. Immune cells are affected by heat, not only natural killer cells, which lies a wide variety of tumour cells, and are important in the natural resistance to tumours.

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26 Kelly et al 2002, 'Assessment of health effects in New York City firefighters after exposure to polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs): the Staten Island Transformer Fire Health Surveillance Project', *Arch Environ Health*. vol. 57, no. 4, pp. 282-93. (RMA ID 49052)

27 Ninemsn, 2009, 'Wake Up Call' , Reporter: Liam Bartlett, Producer: Nick Greenaway http://sixtyminutes.ninemsn.com.au/stories/liambartlett/797215/wake-up-call © 1997-2013 ninemsn Pty Ltd - (New Information)

67. The Applicant claimed that:

An Australian oncologist, recently retired, noted limbs treated for metastatic melanoma isolated limb profusion showed distinct paucity of lymphocytes in the heat efferent blood samples. Heat exists in the form of molecular or atomic vibration, thermal agitation and may be transferred by conduction through a substance – sorry by convection and by radiation as electromagnetic waves. Conversive heat is the heat developed in the tissues by resistance to the passage of high frequency electromagnetic radiation through them. Radiant heat is heat applied to the body by rays from a source of infrared radiation, such as a heat lamp. Fire fighters are exposed potentially to sustained radiant conductive and convection heat, and have cancer clusters, including brain cancer.

68. In relation to firefighters the Applicant argued that:

The way heat is dissipated from the body is through the skin and through the lungs. Attempts to implicate known chemical carcinogens in the causation have failed to explain the higher cancer rates.

69. In relation to Electromagnetic Radiation (Chronic Exposure) the Applicant cited, in her submission to the RMA :

– Wrensch et al 2002[28], Inskip et al 1995[29], Teodoriet al 2002[30] Szmigielski S. 1996[31], Grayson 1996[32], and Richter et al 2003[33].

contending that:

.. Brain Cancer Clusters have occurred in Vietnam Veterans who worked surrounded by hectares of Radar Masts ('Radar Farms').

and Villeneuve et al 2002[34] which the Applicant contended supported her contention that:

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28 Wrensch, M. Minn, Y. Chew, T. Bondy, M & Berger M. S. 2002, 'Epidemiology of primary brain tumors: current concepts and review of the literature', *Neuro-Oncology*, vol. 4, no. 4, pp. 278-99. (New Information)

29 Inskip, D. P. Linet, M. S. & Heineman, E. F. 1995, 'Etiology of brain tumors in adults', *Epidemiol Rev*, no. 17, vol. 2, pp. 382-414. (RMA IID 9926)

30 Teodoriet et al 2002, 'Static magnetic fields affect calcium fluxes and inhibit stress-induced apoptosis in human glioblastoma cells', *Cytometry*, vol. 49, no. 4, pp.143-9. [Abstract Only] RMA ID 49060)

31 Szmigielski S. 1996, 'Cancer morbidity in subjects occupationally exposed to high frequency (radiofrequency and microwave) electromagnetic radiation', *Sci Total Environ,* vol. 180, no. 1, pp. 9-17. (RMA ID 49060)

32 Grayson, J. K. 1996, 'Radiation exposure, socioeconomic status, and brain tumor risk in the US Air Force: a nested case-control study', *Am. J. Epidemiol.* vol. 143, no. 5, pp.480-486. (RMA ID 14032)

33 Richter, E. D. Berman, T. & Levy, O 2003, 'Brain cancer with induction periods of less than 10 years in young military radar workers', *Arch Environ Health,* vol. 57, no. 4, pp. 270-2. (RMA ID 14032)

> Whilst electromagnetic field studies and individual exposures are plagued by inconsistent measurements, concern remains that chronic exposure to low and very low frequency electromagnetic radiation is deleterious to brain function and may increase brain tumour risk.

70. On electromagnetic radiation exposure the Applicant referred to

- Inskip et al 1995[35]

The Applicant claimed that pilots appear to be particularly exposed to EMR occupationally, and cites an RSL Advocate as saying:

> Some WW2 aircraft instrument panels may not have been sufficiently shielded to reduce EMR (eg Wellington Fighter-Bombers).

And said:

> Other workers exposed to Cathode Ray Tubes and Screens occupationally have shown a higher incidence of Brain Tumours.

In her oral submission the Applicant submitted that:

> The concern about chronic exposure to low levels of electromagnetic radiation may also relate to chronic heating of the brain. Indeed, there has been an unexplained increase in brain cancer worldwide, which at least one Australian neurosurgeon suspects may in part relate to the enthusiastic take-up of technology all over the world.
>
> There is a lag period with brain tumours, and the World Health Organisation, the IARC have issued a caution on putting cellular phones right up against the head for long periods, particularly 30 minutes a day is considered not advisable. Other studies countering this result … have found there could have been a bias from vested industry commissioning the study. … So other studies countering this result for electromagnetic radiation and concern about the brain have been criticised for that reason, for their bias.

In relation to WWII Fighter pilots, the Applicant commented:

> They [had] cramped cockpits and conceivably received significant exposure… a study on cathode ray exposure [found] there was an increase in brain cancer with those exposed to cathode ray oscilloscopes.

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34 Villeneuve, P.J. Agnew, D.A. Johnson, K.C. Mao, Y, Canadian Cancer Registries Epidemiology Research Group. 2002, 'Brain cancer and occupational exposure to magnetic fields among men: results from a Canadian population-based case-control study. *Int J Epidemiol.* vol. 31, no. 1, pp. 210-7. (RMA ID 26227)

35 Inskip, D. P. Linet, M. S. & Heineman, E. F. 1995, 'Etiology of brain tumors in adults', *Epidemiol Rev*, vol. 17, no. 2, pp. 382-414. (RMA IID 9926)

71. In respect of Melatonin depletion due to sleep deprivation, the Applicant cited

- Galijasevic S, Abdulhamid I and Abu-Soud HM 2008[36], Altun and Ugur-Altun 2007[37], Anisimov et al 2006[38], and Martín et al 2006[39] Haldorsen et al 2001[40]

about which the Applicant submitted:

> Melatonin is an oncostatic hormone released during normal nocturnal sleeping hours.
> …
> Studies have associated chronic sleep deprivation with increased malignancy.
>
> **…**
> World War 2 Military pilots frequently flew sorties at night. It is conceivable that chronic sleep deprivation was rife among operational servicemen.
>
> This, coupled with added insults of Cosmic Radiation exposure, Electromagnetic Field exposures, missing meals, alcohol ingestion and cigarette smoking (encouraged during wartime) may contribute to malignancy.

72. In her oral submission the Applicant commented that:

> …even though melatonin is produced at night, it's produced maximally during sleep and chronic sleep deficiency.
>
> The pilots, the bomber, and the fighter pilots are flying at night would sleep during the day, which is not as efficient for melatonin production.
>
> It is reasonable to assume that some, or all, of the above factors will apply to operational servicemen during wartime.

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36 Galijasevic, S. Abdulhamid, I. & Abu-Soud, H.M. 2008, 'Melatonin is a potent inhibitor for myeloperoxidase', *Biochemistry*. vol. 47, no. 8, pp. 2668-77. (Abstract Only - RMA ID 49062)

37 Altun, A. & Ugur-Altun, B. 2007, 'Melatonin: therapeutic and clinical utilization', *Int J Clin Pract,* vol. 61, no. 5, pp. 835-45. (Abstract Only - RMA ID 49063)

38 Anisimov, V. N. Popovich, I. G. Zabezhinski, M.A. Anisimov, S.V. Vesnushkin, G.M. & Vinogradova, I.A. 2006, 'Melatonin as antioxidant, geroprotector and anticarcinogen', *Biochim Biophys Acta*. vol.1757, no. 5-6, pp. 573-89. (Abstract Only - RMA ID 49064)

39 Martín, V. Herrera, F. Carrera-Gonzalez, P. García-Santos, G. Antolín, I. Rodriguez-Blanco, J. & Rodriguez, C. 2006, 'Intracellular signaling pathways involved in the cell growth inhibition of glioma cells by melatonin', *Cancer Res,* vol. 66, no. 2, pp.1081-8. (Abstract Only - RMA ID 49065)

40 Haldorsen, T. Reitan, J.B. & Tveten, U. 2001, 'Cancer incidence among Norwegian airline cabin attendants', *Int J Epidemiol*, vol. 30, no. 4, pp. 825-30. (Abstract Only - RMA ID 49057)

73. In relation to alcohol, the Applicant relied on Wrensch et al 2002[41] to contend:

> Immunosuppression is associated with stress, dietary inadequacy, sleep deprivation, cigarette smoking, alcohol excess and inadequate opportunity for daily exercise.

74. In her oral submission, the Applicant submitted that:

> Alcohol excess was relevant to the services, particularly the RAAF.
>
> Alcohol excess was encouraged… as a stress reliever. In World War II, they didn't have anti depressants, and in any case, it might have blunted the actions of the pilots. So the common methods were alcohol and smoking, and both of which do release the stress; alcohol by interrupting short-term memory, and reducing brain 15 function in general in a global sense, and smoking, the carbon monoxide does have a blunting effect on the brain globally

75. In her Oral Submission the Applicant submitted that:

> …alcohol has been known to be a carcinogen for some time, and the acetaldehyde, which is the major carcinogen in alcohol, is absorbed easily by mouth, in the saliva.

76. At the hearing, the Applicant's representative contended for multifactorial influences:

> As with many cancers, multifactorial influences are likely, apart from genetic malignancy syndromes, I believe this is particularly the case with malignant brain tumours. Brain cancer is relatively uncommonly diagnosed compared with the top few cancers.[42]

77. After the hearing, on 23 August 2012, the Council received from the Applicant, another 'supplementary submission' in which she also contended:

> 'I believe the combined assaults and influences I have so far investigated are important as potential factors in the causation and / or the propogation of MNB. Several of these factors interact, and feedback on each other physiologically.'

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41 Wrensch, M. Minn, Y. Chew, T. Bondy, M & Berger M. S. 2002, 'Epidemiology of primary brain tumors: current concepts and review of the literature', Neuro-Oncology, vol. 4, no. 4, pp. 278-99. (New Information)

42 Transcript p.6.15

Council's comments on the contended multifactorial factor for malignant brain cancer

78. Despite the applicant's agreement to the scope of review noted at paragraph 60 above, the Council carefully considered her contention on multifactorial causation.

79. The Dictionary of Epidemiology[43] defines multifactorial aetiology (synonymous with multiple causation) as a concept that a given health state or health-related process may have more than one cause. A combination of causes or alternative combination of causes is often required to produce the health outcome.

80. Thus, a multifactorial aetiology could acknowledge either that a disease has several different causes or that it is a result of a joint combination of causal factors.

81. The Council considered that all malignancies are multifactorial in origin, but it is difficult to generalise beyond the statement that both genetic susceptibility and environmental factors are involved to varying degrees. It is not usually possible to identify the interplay of specific causal factors involved. Any one or more potentially causal agents or each of several agents combined may contribute to the development of the disease, but precisely identifying the contribution or combination of circumstances causative of the condition is complex.

82. Although there is some recognition in the literature of the probability of complex aetiology, the Council found no sound medical scientific evidence in either the available information or the new information provided by the Applicant to support the contention or to indicate the need for current inquiry by the RMA into the possibility of a factor in the Statements of Principles addressing a multifactoral causation.

83. The Council also noted that the Applicant did not raise this issue in her written submissions lodged pursuant to s 196ZA of the VEA. To that extent this multifactoral causation issue, raised for the first time at the hearing, is a new issue on which the Commissions' submissions have not been invited.

84. The Council considered the available literature and the new information provided by the Applicant in the light of these contentions to assess whether to amend the scope of the review to accommodate this further submission from the Applicant. The Council decided in all of the circumstances to limit the scope of the review to the matters at paragraph [49].

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[43] Porta, M (ed) 2008, *Dictionary of Epidemiology*, 5th ed. Oxford University Press, pp.159-160

COMMISSIONS' SUBMISSIONS

85. The Commissions made a written submission dated December 2011. A Medical Officer with the Department of Veterans' Affairs, representing the Commissions, made an oral submission complementing the Commissions' written submission at the Council's meeting on 23 August 2012.[44]

86. The Commissions' submission addressed: Heat; Cosmic, Therapeutic, Occupational, Diagnostic and Atomic radiation; Electromagnetic radiation; Melatonin depletion / sleep deprivation; and Diet and lifestyle, including Smoking and Alcohol consumption. As the Commissions did not contend that all of those matters should be in scope, the Council has had regard to the Commissions' submissions in respect of only the five contend factors.

87. Concerning ***heat***, the Commissions contended that no epidemiological studies were identified in the available information that have examined the risk of developing malignant neoplasm of the brain from exposure to an external heat source or from having a raised body temperature.

> In the Commissions' view there is no basis for the inclusion of any factor in the SOPs relating to the application of external heat.

88. Concerning ***Electromagnetic radiation*** the Commissions submitted that:

> ...WW2 fighter aircraft pilots were exposed to a relatively low technology, low EMR environment compared to many more modern situations and occupations.
>
> …The Commissions' consider that piloting a WW2 fighter aircraft did not entail any increased exposure to electric power frequency EMR.
>
> The Commissions contended further that:
>
> …major methodological shortcomings in the available literature, particularly concerning exposure assessment, make analysis of the information an unrewarding exercise and make any conclusions very difficult to draw.
>
> The Commissions stated that for these reasons, they decided not to address the power frequency or mobile phone evidence in detail in their submission.

89. Of the original studies concerning *high frequency (HF) and very high frequency (VHF) exposure*, the Commissions cited:

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[44] The information upon which the Commissions relied, being information which the RMA advised was available to (before) the RMA at the relevant times, is listed in Appendix A.

89.1. Milham, 1998[45] in respect of which the Commissions submitted the authors:

> …provided some data on mortality in amateur radio operators in the USA. These operators would seem likely to have had some exposure to HF or VHF radiation. However, the report involved small case numbers and contained no details on actual exposure, potential confounding factors, or demographic differences between the subjects and the comparison general population.

and in their oral submission:

> For radio equipment, the only thing specific to that I could find was the Milham et al; there was a letter to the editor in 1998 by Milham … That reported increased brain cancer, standardised mortality ratios in classes of amateur radio operators in the US. They were small numbers and statistically significant results, not much in the way of detail about exposure at all from that study. So I couldn't really draw anything from that.

89.2. Dolk et al 1997[46], Dolk et al 1997[47], and Cooper et all 2001[48], which the Commissions submitted were ecological studies of cancer incidence in persons living near radio and television transmission towers in England and:

> …used distance from the towers as a proxy for exposure level. However, it is evident from the reports that this measure is not useful as a proxy, with variability between different measurement points at any one distance from the transmitter being as great as that related to distance.

90. Of the original studies concerning *exposure to radar*, the Commissions cited:

90.1. Groves *et al* 2002[49], in respect of which the Commissions submitted the authors:

> ….undertook a mortality study of 40,581 US Korean war naval veterans, with 40 years of follow-up. Subjects in this study had potential exposure to high intensity radar. Exposure assessment was based on job title. The relative risk of brain

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45 Milham, S. Jr. 1998, [Comment] 'Mortality by license class in amateur radio operators', *American Journal of Epidemiology*, vol. 127, pp.1175-1176. (RMA ID 14619)

46 Dolk, H. Shaddick, G. Walls, P. et al 1997, 'Cancer incidence near radio and television transmitters in Great Britain I. Sutton Coldfield Transmitter', *American Journal of Epidemiology,* vol. 145, no.1, pp. 1-9. (RMA ID 9621)

47 Dolk, H. Elliot, P. Shaddick, G. Walls, P. & Thakrar, B. 1997, 'Cancer incidence near radio and television transmitters in Great Britain. II. All High Power Transmitters', *American Journal of Epidemiology*, vol. 145, no.1, pp. 10-17. (RMA ID 9621)

48 Cooper, D. Hemmings, K. & Saunders, P. 2001. 'Re 'cancer incidence near radio and television transmitters in Great Britain. 1. Sutton Colfield transmitter; 11. All high power transmitters', *American Journal of Epidemiology*, vol. 153, no. 20, pp. 202-4. (RMA ID 21127)

49 Groves, F.D. Page, W.F., Gridley, G. et al 2002, 'Cancer in Korean War Navy technicians: mortality survey after 40 years', *American Journal of Epidemiology*, vol. 155, no. 9, pp.810-18. (RMA ID 25344)

cancer for men with high radar exposure potential compared to men with low radar exposure potential was 0.65 (95% CI, 0.43 to 1.01).

and in oral submissions that:

The Groves et al paper had four years follow up for the mortality in this cohort [40,000 Navy technicians who were Korean War veterans]. They did their exposure assessment by job category, and they provided results for high versus low exposure, and for three different occupations, each of which were considered to have high exposure, and they didn't find any association between radar exposure and glioma, and there was even a suggestion of a protective effect in that particular study.

91. In oral submissions the Commissions' representative referred, in relation to high frequency (HF) and very high frequency (VHF) exposure and radar, to the following additional papers:

91.1. Richter et al 2002[50], which he contended was:

… just a series of five case reports on young adults with occupational radar exposure in military settings who developed brain tumours, and in each case, there was a notably short latency period, ranging from two to eight years between their first exposure and diagnosis.

… case series [was] not really persuasive in any way when staked against the Groves cohort mortality study.

91.2. Szmigielski 1996[51] about which he submitted:

…this was a 15 year 45 retrospective cohort study of incident cancer in Polish military, looking at the risk from radio frequency and microwave exposure.

I had some serious questions about the numbers in that study, along with a few other issues about the methodology. There was possibly systematic bias because there was extra information available on the cases compared to the controls. There was no post service cancer ascertainment, it was only cases that had arisen while people were serving in the military, and they only looked age in terms of 10-year age groupings. So there was potential for inadequate age matching there I think as well.

91.3. Grayson, 1996[52] about which he submitted:

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50 Richter, E.D. Berman, T. & Levy, O. 2002, 'Brain cancer with induction periods of less than 10 years in young military radar workers', *Arch Environ Health*, vol. 57, no. 4, pp. 270-2. (RMA ID 49061)

51 Szmigielski, S. 1996, 'Cancer morbidity in subjects occupationally exposed to high frequency (radiofrequency and microwave) electromagnetic radiation'*, The Science of the Total Environment*, vol. 180, pp 9-17. (RMA ID 10413)

52 Grayson, J.K. 1996, 'Radiation exposure, socioeconomic status, and brain tumor risk in the US Air Force: a nested case-control study', *American Journal of Epidemiology*, vol. 143, no. 5. pp. 480-486. (RMA ID 14032)

Probably the best study …in favour of an association between exposure to radiofrequency, radiation and glioma…

…this was a nested case control study in quite a large cohort of US male air force personnel, who served during the period 1970 to 1989. Again, case ascertainment was only for people who were actively serving, there was no follow up after service. .. using a job exposure matrix, the exposed were considered to be those in occupations involving maintenance and repair of radiofrequency and microwave emitters, so not pilots but technicians. ...risk was reported for ever versus never exposed, and again, I have some difficulty with [the] categorisation of saying people are never exposed.

[The Authors} ... didn't find any evidence of a dose response effect, but for the ever versus never, they found relative risk of – an odds ratio was a nested case control of 1.39 and a confidence interval of 1.01 to 1.9. So that is the closest you get to positive evidence, but ...there is no dose response evidence on those issues about the exposure assessment, and it's not specifically about radar or radio equipment, but I would think being the air force, there is at least some of that mixed in there, and probably similar frequency type exposures from other sources.

91.4. Karipidis et al 2007[53] contending the authors:

… looked radio frequency radiation exposure, in this case by occupational history using a job exposure matrix and also an expert hygienist review. But the exposed people here were either plastics workers, physiotherapists, wood workers or telephone technicians. So we're not looking at radar or radio equipment. There were 15 cases and 18 controls in this study of about 400 cases overall, who had radiofrequency exposure, and there was no increased risk of glioma across – they attempted to actually quantify exposure into units of exposure, and they looked at exposure across tertiles and found no increased risk.

91.5. Morgan et al in 2000[54] which he submitted was:

...a study in Motorola[55] employees, people making phones and radar equipment and pagers and antennas and various other things, and it was a 20-year retrospective cohort mortality study…

…this study looked at risk of brain cancer from radiofrequency exposure, and did a lot of internal comparisons and [it is] quite hard to classify their people into groupings based on exposure.

---

53 Karipidis, K.K. Benke, G. & Sim, M.R. 2007, 'Occupational exposure to ionizing and non-ionizing radiation and risk of glioma', *Occupational Medicine*, vol. 57, pp.518-24 (RMA ID 58305)

54 Morgan, R.W. Kelsh, M.A. Zhao, K. Exuzides, A. Heringer, S. & Negrete, W. 2000, 'Radiofrequency exposure and mortality from cancer of the brain and lymphatic/ hematopoietic systems', *Epidemiology*, vol. 11, pp. 118-127. (RMA ID 24970)

55 In his oral submission, the Commissions' representative queried the potential for Motorola having a vested interest in this study not finding that their products are associated with cancer risk.

… using job exposure matrix measurement, [the authors] did various analyses showing no association between radio frequency exposure and mortality from brain cancer.

92. The Commissions' representative contended that the usefulness of cluster studies around radio and television transmission towers is doubtful, saying:

I didn't find these to have any useful data. They tried to look at exposure by distance from the towers, but that ...didn't turn out to be a useful way of determining exposure because ...the exposure didn't turn out to be related to distance.

There were all sorts of other factors to do with shielding and other arrangements that made that not a useful measure of exposure.

93. The Commissions' oral submission included that Grayson et al 1996 [91.32 above],

…is the [study] that meets the closest attention and provides, as far as there is any...some positive evidence of an association between radiofrequency radiation exposure and glioma. But ...I have significant problems with both the biology and the exposure assessment for any of these studies.

94. The Commissions contended in relation to Electromagnetic radiation that:

The nature of the general EMR evidence is such that it does not permit a satisfactory evaluation of risk.

In the epidemiological studies inadequate exposure assessment is the major limitation, but there are substantial other methodological shortcomings. The evidence is inconsistent and inconclusive.

There is no clear hypothesis or evidence concerning what parameters of exposure (type, duration, intensity, and frequency) might be hazardous. The laboratory-based evidence doesn't establish that either ELF or radiofrequency radiation is a carcinogen or tumour promoter for neurogenic tumours.

and that in the Commissions' view

…the inclusion of any factor for extremely low frequency or radiofrequency radiation in the malignant neoplasm of the brain SOPs is not warranted.

95. In oral submissions the Commissions' representative contended in relation to non-ionising radiation that:

…there is two major problems [with studies] that makes it very difficult to place any interpretation on the data:

…there is the issue of exposure, as none of these studies have any individual exposure monitoring, they're all reliant on occupational classifications or job

exposure matrices. None of them adequately account for other potentially relevant exposures that could possibly confound, and it's really not possible, from my perspective, to have any confidence in the adequacy of the exposure assessment in these studies.

AND

We have a body of evidence from animal and experimental data, and the mechanistic considerations, and … none of that is at all persuasive that radio frequency radiation is capable of being a carcinogen in human tissues...

...findings [are] generally inconsistent, they're often temporary, they're usually non-specific and they're not specifically about carcinogenesis, they're about other changes in tissues, but when you put it together… it doesn't give me any confidence that radio frequency radiation is capable of being a carcinogen.

96. Concerning *melatonin depletion due to sleep deprivation*, the Commissions submitted:

> …the Commissions can identify no epidemiological studies in the available information that have examined the risk of developing malignant neoplasm of the brain from melatonin depletion or sleep deprivation. In the Commissions' view there is no basis for the inclusion of any factor in the SOPs relating to melatonin depletion or sleep deprivation.

97. Of the original studies concerning *alcohol* consumption, the Commissions cited studies by Preston et al 1989[56], Hurley et al 1996[57], Ryan et al 1992[58], Lee et al 1997[59], Boeing et al 1993[60] submitting:

> These studies found no association between alcohol consumption and glioma overall and for various sub-categories, including for type of alcoholic beverage and, in the Australian studies, by dose.

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56 Preston-Martin, S. Mack, W. and Henderson, B.E. 1989,' Risk factors for gliomas and meningiomas in males in Los Angeles county', *Cancer Research,* vol. 49, pp.6137-6143. (RMA ID 9293)

57 Hurley, S.F. McNeil, J.J. Donnan, G.A. Forbes, A. Salzberg, M. and Giles, G.G. 1996, 'Tobacco smoking and alcohol consumption as risk factors for glioma: a case-control study in Melbourne, Australia', *Journal of Epidemiology and Community Health*, vol. 50, pp. 442-446. (RMA ID 14033)

58 Ryan, P. Lee, M.W. North, J.B. and McMichael, A.J. 1992, ' Risk Factors for Tumours of the Brain and Meninges: Results from the Adelaide Brain Tumour Study', *International Journal of Cancer*, vol.51, pp. 20-27. (RMA ID 1686)

59 Lee, M. Wrensch, M. and Miike, R. 1997, 'Dietary and tobacco risk factors for adult onset glioma in the San Francisco Bay area (California, USA)', *Cancer Causes and Control*, vol.8, pp.13-24. (RMA ID 14066)

60 Boeing, H. Schlehofer, B. Blettner, M. and Wahrendorf, J. 1993, 'Dietary carcinogens and the risk for glioma and meningioma in Germany', *International Journal of Cancer*, vol. 53, pp. 561-5. (RMA ID 15157)

98. The Commissions cited a further series of case-control studies[61] [62] [63] [64] [65] [66]which they argued provided limited data:

> ...with results only for alcohol consumption versus no consumption. Five of the six reported no association and one found a small, non-significant risk, based on nine cases.

99. The Commissions cited a prospective cohort incidence study in Seventh-Day Adventists[67] which they argued:

> …gave results for glioma risk from alcohol consumption, but this was based on only three cases.

100. The Commissions claimed an interview study based on the third national cancer survey in the US[68]:

> …reported no association between alcohol and nervous system tumours for various categories of consumption in men and women.

101. The Commissions claimed that a census-based cohort mortality study in Japan[69]:

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61 Choi, N. W. Schuman, L. M. & Gullen, W. H. 1970, 'Epidemiology of primary central nervous system neoplasms II: case-control study', *American Journal of Epidemiology,* vol. 91, no. 5, pp. 467-85. (RMA ID 25043)

62 Carpenter, A. V. Flanders, W. D. Frome, E. L. Cole, P. & Fry, S. A 1987, 'Brain cancer and non-occupational risk factors: A case-control study among workers at two nuclear facilities', *American Journal of Public Health*, vol. 77, no. 9, pp. 1180-1182. (RMA ID 9292)

63 Hochberg, F. Toniolo, P. & Cole, P. 1990, 'Nonoccupational risk indicators of glioblastoma in adults', *Journal of Neuro-Oncology*, vol. 8, pp. 55-60. (RMA ID 14158)

64 Ahlbom, A. Navier, I.L. Norell, S. Olin, R. & Spannare, B. 1986, 'Nonoccupational risk indicators for astrocytomas in adults', *American Journal of Epidemiology*, vol. 124, no. 2, pp. 334-337. (RMA ID 14284)

65 Musicco, M. Filippini, G. Bordo, B. M. Melotto, A. Morello, G & Berrino, F 1982, 'Gliomas and occupational exposure to carcinogens: case-control study', *American Journal of Epidemiology,* vol. 116, no. 5, pp. 782-790. (RMA ID 14283)

66 Aschengrau, A. Ozonoff, D. Coogan, P. Vezina, R. Heeren, T. & Zhang, Y. 1996, 'Cancer risk and residential proximity to Cranbury cultivation in Massachusetts', *American Journal of Public Health*, vol. 86, no. 9, pp.1289-1296. (RMA ID 14031)

67 Mills, P. K. Preston-Martin, S. Annegers, J. F. Beeson, W. L. Phillips, R.L. & Fraser, G. E. 1989, 'Risk factors for tumors of the brain and cranial meninges in Seventh-Day Adventists', *Neuroepidemiology*, vol. 8, pp. 266-75. (RMA ID 15212)

68 Williams, R. R. & Horm, J. W, 1977, 'Association of Cancer Sites with Tobacco and Alcohol Consumption and Socioeconomic Status of Patients: Interview Study from the Third National Cancer Survey', *Journal of the National Cancer Institute*, vol. 58, no. 3, pp. 525-547. (RMA ID 3613)

69 Hirayama, T 1990, *Life-Style and Mortality - A large scale census-based cohort study in Japan. (Contributions to Epidemiology and Biostatistics, Vol 6),* J Wahrendorf. Karger. Paris-London-New York-New Delhi-Bangkok- Singapore-Tokyo-Sydney. pp. 1-138. (RMA ID 2999)

…found no association between daily consumption of alcohol and brain tumour risk.

102. The Commissions concluded their written submission in relation to alcohol contending that:

...the available information does not indicate any causal role for alcohol in the aetiology of malignant neoplasm of the brain.

103. In oral submissions, the Commissions' representative submitted in relation to Hurley et al 1996[70], that this population case control study with 416 cases:

…had data on average and total alcohol consumption and also some data by beverage type, and it found no associations for any of the parameters measured, and no dose response effect.

He added that:

One drawback of that study was that 44 per cent of the data was collected by proxy [with] … the usual issues about data collected in that way.

104. In oral submissions, the Commissions' representative referred the Council to two studies that were not available to (before) the RMA:[71]

- Baglietto et al 2011[72], and Benson et al 2008[73]

The Commissions' representative submitted that the study by Benson et al did not:

…find any positive associations between alcohol consumption and glioma.

However, he contended that Baglietto et al, a prospective cohort incidence study looking, relevantly in this case, at glioblastoma:

… did find a dose dependent increased risk of glioblastoma from alcohol consumption.

adding that:

…this new information …is quite important in the context of this consideration.

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70 Hurley, S. F. McNeil, J.J. Donnan, G.A. Forbes, A. Salzberg, M. & Giles, G.G. 1996, 'Tobacco smoking and alcohol consumption as risk factors for glioma: a case-control study in Melbourne, Australia', *Journal Epidemiol Community Health*, vol. 50, pp. 442-446. (RMA ID 14033)

71 See [18] and [27] above.

72 Baglietto, L. Giles, G. English, D. Karahalios, A. Hopper, J & Severi, G. 2011, 'Alcohol consumption and risk of glioblastoma; evidence from the Melbourne Collaborative Cohort Study', *Int. J. Cancer*, vol. 128, pp.1929–1934.

73 Benson, V.S. Pirie, K. Green, J. Casabonne, D. and Beral, V. 2008, 'Lifestyle factors and primary glioma and meningioma tumours in the Million Women Study cohort', *British Journal of Cancer*, vol. 99, pp. 185–190.

Commissions' comments on the Revised Proposed Scope of the Review and Revised Proposed Pool of Information decisions

105. The Commissions sought no amendment to the Council's revised proposed scope of review.

106. The Commissions did not propose any alteration to the Council's revised proposed pool of information.

REASONS FOR THE COUNCIL'S DECISION

The Council's Task

107. In conducting a review the Council follows a two-step process. The Council first identified the pool of information, i.e. it identified from all the information that was available to (before) the RMA at the relevant times the sound medical-scientific evidence (as that term is defined in section 5AB(2) of the VEA (see [7] above)) which in its view 'touches on' (i.e. is relevant to) the issue of whether a particular kind of injury, disease or death can be related to service.

108. The second step required the Council to determine whether;

108.1. there is sound medical-scientific evidence in the pool that indicates ('points to' as opposed to merely 'leaves open')[74] the relevant possibility ie whether exposure to any of the five contended factors (if found to exist in a particular case) could provide a link or element in a reasonable hypothesis connecting malignant neoplasm of the brain or death from malignant neoplasm of the brain to relevant[75] service.[76] The Council had to find that the hypothesis contended for was reasonable and not one which was 'obviously fanciful, impossible, incredible or not tenable or too remote or too tenuous.'[77]

108.2. on the sound medical scientific evidence in the pool, exposure to any of the five contended factors (if found to exist in a particular case) could provide a relevant connection between malignant neoplasm of the brain or death from malignant neoplasm of the brain and relevant[78] service according to a

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74 See full Federal Court decision at [49] per Branson J.

75 Relevant service here refers to operational, peacekeeping and hazardous service, British nuclear test defence service, and warlike or non-warlike service as those terms are defined in the VEA and the MRCA.

76 See Vietnam Veterans' Association of Australia (NSW Branch) Inc v Specialist Medical Review Council and Anor (2002) 69 ALD 553 (Moore J decision) per Moore J at [29].

77 See the full Federal Court decision in Repatriation Commission v Bey (1997) 79 FCR 364 which cited with approval these comments from Veterans' Review Board in Stacey (unreported 26 June 1985), all of which were in turn cited with approval in the Moore J decision at [33].

78 Relevant service here refers to eligible war service (other than operational service), defence service (other than hazardous service and British nuclear test defence service) and peacetime service as those terms are defined in the VEA and the MRCA.

standard of satisfaction ‘on the balance of probabilities’, or as being more probable than not.

109. In these Reasons the association for both the reasonable hypothesis test (at [108.1] and the balance of probabilities test at [108.2]) are respectively referred to as the ‘relevant association’.

110. It was with these tests firmly at the forefront, that the Council considered the sound medical-scientific evidence in the pool of information and the submissions made by the Applicant and the Commissions referable to the matters within the scope of review.

111. In forming its judgement on whether there is sound medical-scientific evidence that indicates ('points to’ as opposed to merely 'leaving open') the relevant association, the Council was conscious that the reasonable hypothesis test is ‘a test of possibility’[79] and ‘an unusually light burden.’[80] If the reasonable hypothesis test was found not to be satisfied, the balance of probabilities test necessarily could not be met.

Scope of Review

112. The Council's final decision on the scope of the review was that it comprise the scope that the Council identified on a revised preliminary basis (see [49]).

Pool of Information

113. The Council's final decision on the pool of information was that it should comprise the sound medical-scientific evidence it had identified on a revised preliminary basis as listed in Appendix A.

114. In reaching its decision, the Council took into account the written submissions and complementary oral submissions and considered whether any of the information, to which it was referred, could or should be in the pool.

115. As mentioned above, the Council noted the Applicant's references to and submissions concerning information which was not available to (not before) the RMA (see Appendix C). The Council in its review was unable to (and so did not) consider information which was not available to (not before) the RMA at the relevant times.

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79 See full Federal Court decision at [49] citing with approval Spigelman CJ in the New South Wales Court of Appeal decision at [111].

80 See full Federal Court decision at [55] per Branson J.

THE COUNCIL'S ANALYSIS OF THE INFORMATION BEFORE THE RMA

116. As mentioned above, having settled the pool of information, the second question for the Council to consider was whether sound medical-scientific evidence in the pool of information 'points to' a contended factor, within the scope of the review, as a link or element in a reasonable hypothesis connecting malignant neoplasm of the brain to relevant service (see[8.1] and footnotes), and if so, whether the relevant association exists on the balance of probabilities (see [8.2] and footnotes).

117. The only basis upon which the Council can review the contents of a Statement of Principles is by reviewing all the information that was available to (before) the RMA at the relevant times, in order to ascertain whether there was sound medical-scientific evidence upon which the RMA could have relied to amend either or both of the Statements of Principles.

118. The Council considered all the articles in the pool. However, the Council in these Reasons focused its discussion upon its analysis of those articles which it considered most pertinent to the scope of review.

119. Ultimately, matters of weight are questions for Council in the exercise of its expertise and scientific judgement, noting that Councillors are appointed to a particular review because of their specialist expertise in the particular condition (in this case malignant neoplasm of the brain) and the matters within the scope of the review.

Preliminary comment on malignant neoplasm of the brain

120. Statements of Principles Nos. 58 & 59 of 2008 as amended by Instruments Nos. 37 & 38 of 2011 concerning Malignant Neoplasm of the Brain define malignant neoplasm of the brain for the purposes of the Statement of Principles as:

> a primary malignant neoplasm arising from the cells of the brain, including neuroepithelial tumour and germ cell tumour, but excluding nerve sheath tumour, soft tissue sarcoma, Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, carcinoid tumour, pituitary tumour and tumour of meningeal tissue.

121. The Council noted that malignant neoplasms of the brain include the various types of tumours arising from glial cells (gliomas) including astrocytomas, glioblastoma multiforme, ependymomas, oligodendrogliomas and microgliomas. The Council noted that it does not include tumours arising from structures outside the brain such as pituitary tumours or meningiomas, even though these tumours may display malignant characteristics, (they rarely do), nor does it include metastases to the brain from malignant tumours originating elsewhere in the body.

122. Some studies used the non-specific term 'brain cancer', which the Council considered to mean malignant brain neoplasms, unless otherwise stated.

The Council's analysis of the information it considered most important as being potentially referable to the contended factors

Exposure to heat beyond fever temperature and melatonin depletion due to sleep deprivation.

123. The applicant's submissions were in respect of a number of studies referring to melatonin depletion and exposure to heat beyond fever temperature that primarily rely on animal or laboratory-based research.

124. The Council considered that animal studies may sometimes support the biological plausibility of an association. However, results from animal studies are not readily applicable to humans and are, at best, used as initial research that may indicate a need for further studies on human subjects.

125. Laboratory based studies of human cells are used in medical research for exploring potential pathological mechanisms, such as examining inflammatory responses to toxins. Processes occurring at the cellular level can be misleading as many other processes contribute to the health of an organism and beyond that to long-term human health effects. Whilst such laboratory-based studies may generate further research, they can often produce a range of conflicting results. Such studies can be material which epidemiologists would consider appropriate to take into account, but the weight to be attached to their results when considering diseases is generally very low because of the large gap in knowledge about which of the results have applicability to long-term chronic disease occurrence in humans. Given this, the Council considered that the animal and laboratory studies submitted by the Applicant, taken in isolation, could not indicate a relevant association and for these reasons, these papers are not discussed in detail here.

126. The Council agreed with the Commissions' conclusions that there were no epidemiological studies in the available information that examined malignant neoplasm of the brain and exposure to an external heat source, or from having a raised body temperature. The Council noted that two epidemiological studies relied upon by the Applicant in regard to heat beyond fever temperature [Youakim[81] and Krishnan[82]] addressed potential carcinogenic exposures of fire-fighters to a range of chemical agents. The studies did not examine, or propose, any independent effect of heat.

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81 Youakim, S 2006, 'Risk of cancer among firefighters: a quantitative review of selected malignancies', *Arch Environ Occup Health*. vol. 61, no. 5, pp. 223-31. (RMA ID 45822)

82 Krishnan et al 2003, 'Occupation and adult gliomas in the San Francisco Bay Area', *J Occup Environ Med,* vol. 45, no. 6, pp.639-47. (RMA ID 45922)

127. The Council also agreed with the Commissions' conclusions that there were no epidemiological studies in the available information that examined malignant neoplasm of the brain and melatonin depletion due to sleep deprivation.

128. The Council found no other sound medical scientific evidence in the pool that could indicate a relevant association.

Alcohol Consumption

Cohort Studies

Mills, P.K. Preston-Martin, S. Annegers, J.F. Beeson, W.L., Phillips, R.L & Fraser, G.E 1989, 'Risk factors for tumours of the brain and cranial meninges in Seventh-Day Adventists,' Neuroepidemiology, vol. 8, pp. 266-275. RMA ID 15212

129. The purpose of this prospective cohort study was to evaluate lifestyle factors in relation to the occurrence of tumours of the brain and cranial meninges among a cohort of 34,000 California Seventh-Day Adventists over a six-year period.

130. The authors chose to focus their study on Adventists 25 years or older who were non-Hispanic whites because in a lifestyle census questionnaire sent to approximately 60,000 Seventh-day Adventists in 1976, the non-Hispanic white group had the highest response rate (>75%) in comparison to other ethnic groups.

131. Cancer incidence was monitored only among 34,000 non-Hispanic whites in California who filled out the lifestyle questionnaire in 1976, and followed up over six years until the end of 1982.

132. The six years of follow-up consisted of annual mailings to this cohort group that requested for information on any hospitalizations during the previous 12 months.

133. Once consent was obtained, the Adventist Health Study personnel reviewed the medical records for evidence of a cancer diagnosis. This follow-up was completed for 99% of the cohort.

134. The authors also used population-based tumour registries to detect cases.

135. The relative risks calculated were adjusted for age and sex.

136. Forty-three brain tumours were detected among 193,703 person-years of follow-up, with glioblastoma (n=12), meningioma (n=10) and astrocytoma (n=9) being the most common.[83]

137. The report was based on 21 gliomas and 10 meningiomas, as all non-specified brain tumours were excluded from the analysis.

138. With regard to alcohol use in relation to the occurrence of tumours of the brain or cranial meninges, the authors found:

> No relationship to risk for alcohol use (Alcohol use and glioma RR 1.31, 95%CI 0.29-4.43, p= 0.72; alcohol use and meningioma RR 0.85, 95%CI 0.20-3.59, p=0.99)...[84]

139. The authors considered the prospective design of the study to be a strength, as lifestyle factors were collected before brain tumour diagnosis, thus eliminating recall bias.

140. The authors considered the weaknesses of their study included:

- the small number of cases (only 3 exposed glioma cases)
- the number of variables tested and the possibility that some of the observations occurred by chance
- evaluation of alcohol and tobacco consumption in relation to disease outcome was problematic as these habits are proscribed by church teachings.

141. The authors in summary stated:

> In this cohort study of risk factors for brain tumours several previously identified relationships were confirmed and some new associations were noted.[85]

Council's Comments

142. This cohort study had low power to detect associations with gliomas and indeed none with alcohol was found. The study was complicated by the study population ostensibly consuming little alcohol. Nevertheless, the Council considered this to be a salient paper which addressed the contended alcohol association.

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83 Table 1, p.267

84 p. 270 and Table 5

85 p. 272

143. Council considered the study **leaves open** the relevant association with alcohol consumption.

Robinette, C.D. Hrubec, Z. & Fraumeni, J.F. Jr. 1979, 'Chronic alcoholism and subsequent mortality in World War II veterans', Am J Epidemiol, vol. 109, no.6, pp.687-700. RMA ID 14463

144. The purpose of this study was to compare the mortality of 4401 US Army servicemen admitted to US army hospitals for chronic alcoholism in comparison to 4401 age-matched controls admitted for nasopharyngitis from 1944 to 1945, who were followed-up for 29 years, from 1946 to 1974.

145. The cases of chronic alcoholism, and comparative group of nasopharyngitis, were identified from the medical and administrative records of the Department of Defence and the Veterans Administration for men who had served in the US armed forces. The study sample was drawn from among enlisted men alive on 1 January, 1946.

146. The authors noted that despite matching the two groups for age, the nasopharyngitis subjects included more non-whites than the chronic alcoholism group, and they were less often career military personnel.

147. The observed mortality was compared with expected mortality for the age- and time-specific rates for US male population rates

148. The authors' findings were:

- Among all 4401 admissions for alcoholism, mortality was significantly higher than in the comparison group for a number of diseases, including brain cancer, and all diseases combined.

- For brain cancer, there was significant excess risk in the alcoholism group. There were five versus zero cases of brain cancer, respectively, but relative risks could not be calculated as no deaths occurred in the nasopharyngitis group.[86]

149. The authors considered the strengths of their study included:

- The two study groups were selected from hospital admission files.

150. The authors considered the weaknesses of their study included:

- Possibility of artefact as multiple statistical comparisons were made

- Brain damage in alcoholic patients may complicate differential diagnosis

[86] Table 3, p.43

- Death certificates may be imprecise for brain cancer. [87]

151. The authors in summary about alcoholism and brain cancer stated:

> The study did show a significant excess mortality from cancer of the brain (specified as glioma in three of the five cases), which has not previously been associated with alcohol.[88]

Council's Comments

152. Council considered this paper important for commenting on brain cancer given its focus on a World War II cohort.

153. The Council noted that the study identified only three cases of glioma in a group with extremely high alcohol consumption. The small number of cases provided the study with only low statistical power.

154. There was a significant excess of mortality from brain cancer among WW2 veterans who were alcoholics, but the Council noted that chronic alcoholism can independently damage the brain and thus this condition itself is a source of metabolic and psychological confounding effects.

155. Council considered the study **leaves open** the relevant association with alcohol consumption.

Case-control studies

Ahlbom, A., Navier, I.L., Norell, S., Olin, R., Spännare, B., 1986,'Nonoccupational risk indicators for astrocytomas in adults'*, Am J Epidemiol*, vol. 124, no. 2, pp. 334-337. RMA ID 14284

156. The purpose of this case-control study was to explore previous hypotheses and to generate new ones.

157. There were a total of 367 subjects, 78 cases, 197 clinical controls, and 92 population controls: [89]

- Cases were aged between 20 and 75 years at the time of diagnosis. They were recruited from among patients with a diagnosis of verified supratentorial astrocytomas treated in Stockholm and Uppsala.

- Controls (clinical and population)

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87 p. 698

88 p. 698

89 p. 334

158. The authors recruited control groups from parish registries and matched forage and sex, and a clinical control group was selected from among patients treated in the same departments as were the cases, during the same period, and in the same age range, having a diagnosis of meningioma, pituitary adenoma, or cerebral aneurysm.

159. Each subject was given a questionnaire to complete, covering a broad variety of exposures.

160. In relation to alcohol consumption, separate questions were asked concerning the quantity and frequency of liquor, wine and beer consumption.

161. Daily alcohol consumption was calculated as follows:

> 1 alcohol unit = 1.5 oz liquor = 6 oz wine = 12 oz beer (1 oz =30ml)
>
> Subjects reporting a daily consumption of at least one alcohol unit were considered exposed. [90]

162. To estimate the relative risk of disease for exposed versus unexposed, the authors used the Mantel-Haenszel procedure to estimate a common odds ratio.

163. For the association of astrocytoma with selected risk factors, the authors found elevated but non-significant elevated ORs for having lived in the vicinity of a farm; and for herbicides and insecticides and increased ORs for smoked foods.

164. For other exposures including alcohol:

> For the remaining exposures reported ... the findings are negative…These findings do not… lend their support to previous reports suggesting an association between these exposures and astrocytoma. [91]

165. For alcohol consumption the authors found a non-significant OR of 1.4, (95%CI 0.5-3.8).[92]

166. The authors considered well-defined catchment areas of Swedish hospitals argue against a biased selection of cases or clinical controls due to differences in referral patterns.[93]

167. The authors considered the weaknesses of their study included:[94]

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90 p. 335

91 p. 336 - Table 1

92 p. 336 - Table 1

93 p. 336

- Recall bias caused by a tendency of the cases to over-report or under-report exposure
- Among the cases, a substantial number of questionnaires were filled out by spouses, which could introduce a bias.
- Limited study size.

Council's Comments

168. Council considered that whilst the primary focus of this study was on exposures in the farming environment, it also looked at alcohol as a factor, and was therefore relevant for consideration.

169. The results of this case-control study showed no significant association between alcohol consumption and astrocytoma. The confidence interval crossed the value of one and was so wide that the results are entirely consistent with chance. The study was limited by small sample size (n=78 cases), the possibility of recall bias, and by potential misclassification of exposure due to reports by cases' spouses.

170. Council considered the study **leaves open** the relevant association with alcohol consumption.

Boeing, H. Schlehofer, B. Blettner, M. & Wahrendorf, J 1993, 'Dietary carcinogens and the risk of glioma and meningioma in Germany', Int J Cancer, vol. 53, pp. 561-565. RMA ID 15157

171. The purpose of this study was to investigate the effect of the ingestion of N-nitroso precursors and of food groups known to contain high concentrations of precursors of N-nitroso compounds in relation to the development of glioma and meningioma.

172. This population-based case-control study was conducted in South-West Germany in the period from 1 January 1987 to 31 December 1988 with 115 histological confirmed glioma and 81 meningioma cases and 418 randomly selected controls.

- Cases were residents of the study area and newly diagnosed during the study period.
- Controls were randomly selected from the residential registers of the study area and matched by ages and gender to the distribution of the cases.

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[94] pp. 335-336

173. All information was obtained by standardized interview. The questions covered details about diet, environment, lifestyle factors, occupation and previous medical history.

174. The authors' findings for the relation between alcohol consumption and glioma or meningioma were that:

> No significant association of risk for glioma or meningioma with lifelong consumption of single alcoholic beverages or total alcohol was found. This observation included beer and dark beer. [95]

175. The authors considered the strength/s of their study included:

- Minimised recall bias differential misclassification by including only incident cases and by continuous standardised training and close supervision of interviewers.

- Excluded proxy interviews

176. The authors in conclusion stated that:

> … this study did not provide much evidence that N-nitroso compounds play an important role in the aetiology of glioma or meningioma. On the level of food groups, we were able to identify an association between higher intake of processed meat and increased risk of glioma. [96]

Council's Comments

177. The Council noted that the primary aim of this case-control study was to examine the association of ingested N-nitroso compounds with glioma and meningioma but information on alcohol was also collected.

178. The authors found no significant association of risk for glioma or meningioma with lifelong consumption of specific types of alcohol or total alcohol.

179. The Council considered the study **does not support** the relevant association with alcohol consumption.

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[95] p. 564

[96] p. 565

Burch, J.D. Craib, K.J.P. Choi, B.C.K. Miller, A.B. Risch, H.A & Howe, G.R 1987, 'An exploratory case-control study of brain tumours in adults', J Natl Cancer Inst, vol. 78, pp.601-609. RMA ID 9548 & 1664

180. The purpose of this study was to generate hypotheses relating to a variety of environmental exposures as possible etiologic factors for brain tumours in adults.

181. This was a case-control study of 215 cases diagnosed in Southern Ontario between 1979 and 1981, with individually matched hospital controls[97].

- 215 cases – All individuals who were aged between 25 and 80 with brain tumours diagnosed during the period of January 1, 1977 to December 31, 1981, and were residents of metropolitan Toronto and the rest of southern Ontario were eligible to be cases (provided they were still in the area at the time of the study 1979-1982).

- 215 controls – Hospital based controls were selected from individuals who were patients admitted to any hospital in the study area and who had a condition other than cancer of any site. Each control was matched to each case based on sex, area of residence, marital status, year of birth (within 5 years), date of diagnosis (within 1 year) for live cases and date of death (within 1 year) for dead cases.

182. Methods:

> All cases, controls and their proxies were interviewed at home by a specially trained interviewer. No indication was given to the respondent during the interview that the primary focus of the study was cancer. The questionnaire included questions on occupational, residential, and medical histories, smoking, and certain dietary variables. [98]

183. For alcohol consumption and consumption of other beverages, the authors measured risk based on 'ever versus never' consumption.[99] They found only wine but not beer or spirits, had an increased RR.

184. They also measured three types of alcohol based on three degrees of exposure. The authors found a significant dose-response relationship with increasing wine consumption (*P-trend*=.006).[100] In contrast, there was no dose-response relationship with beer, and spirits showed a non-significant inverse association.

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97 p. 602

98 p. 602

99 p. 605, Table 7

100 p. 605, Table 8

185. Results for the relation between brain tumours and water supply, family history of cancer, smoking, head injuries, occupational history (rubber industry, plastics production, household products manufacturing, packaging industry, farming, propellants, refrigeration industry), birth order, use of hair dyes or hair sprays, medications, dietary variables are not relevant for the scope of this review. Of note however, the authors found that cigarette smoking and the use of hair dyes/hair sprays to be positively associated with adult brain tumours.

186. The authors considered the weaknesses of their study included:

- Use of proxy respondents may have less reliable data than the subjects
- Recall bias as some cases were diagnosed a few years before the interview
- Missing data for some subjects.

187. The authors in summary stated that:

> … despite some of the methodological problems inherent in a study of brain tumours in adults, the present study has served to identify several hypotheses that, if causally associated with tumours of the brain, could be responsible for a sizable portion of cases seen in Canada and other similar population and that merit further investigation in other detailed studies.[101]

Council's Comments

188. The Council noted that this case control study of malignant brain tumors explored their potential association with many factors, raising the potential problem of chance findings.

189. The apparent positive association between wine drinking and cancer needed to be balanced against the trend towards the negative relationships found for beer and spirits drinking. The authors found no association with either beer or spirits, but did find an association with wine consumption. Balancing the trend towards the negative relationships for beer and spirits, the wine specificity **does not support** an effect of alcohol.

190. Council further noted that alcohol studies are difficult to interpret, for example, heavy drinkers are more likely to have unhealthy lifestyles and this leaves the results open to the possibility of confounding by other lifestyle habits.

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[101] p. 607

191. Council considered the study **does not support** the relevant association with alcohol consumption.

Hochberg, F.Toniolo, P. & Cole, P 1990, 'Nonoccupational risk indicators of glioblastoma in adults', Journal of Neuro-Oncology, vol. 8, pp. 55-60. RMA ID 14158

192. The purpose of this case-control study was to evaluate the nonoccupational risk factors of glioblastoma.

193. There were 160 cases with glioblastoma, grade 3 or 4 astrocytoma or anaplastic astrocytoma, and 128 healthy controls identified from hospitals in Boston, Providence and Baltimore between 1977 and 1981. Controls were obtained from the cases' friends, not blood relatives.

194. The authors used a questionnaire to assess the relationship between brain tumour and the risk factors.

195. The authors' findings were that there was no association of glioblastoma with consumption of **beer** (RR 0.7, 95%CI 0.4-1.1).

196. The authors considered that a strength of their study included the use of friends as controls for matching the current socioeconomic status of cases.

197. The authors considered study weaknesses to be:

- Low level of case participation
- Fewer controls

198. The authors in conclusion stated that they:

> …found no association with life-style characteristics such as … consumption of alcohol…and glioblastoma[102].

Council's Comments

199. Council noted that the findings of this study show an inverse (protective) association between beer consumption and glioma of borderline statistical significance.

200. Council considered the study **does not support** the relevant association with alcohol consumption.

[102] p. 59

Hurley, S.F. McNeil, J.J. Donman, G.A. Forbes, A. Salzberg, M. & Giles, G.G 1996, 'Tobacco smoking and alcohol consumption as risk factors for glioma: a case-control study in Melbourne, Australia', J Epidemiol Community Health, vol. 50, no. 4, pp. 442-446. RMA ID 14033

201. The purpose of this population-based case-control study was to investigate the association between tobacco smoking and alcohol consumption and the risk of adult glioma, in Melbourne, Australia.

202. There were 416 cases and 422 controls. Cases were defines as people with histologically confirmed primary glioma, diagnosed between July 1987 and December 1991, who were aged 20-70 year at diagnosis. Controls were randomly selected from the Victorian electoral roll.

203. The authors used a questionnaire (administered by a research nurse) to assess the relationship between brain tumour and smoking history and alcohol consumption.

204. Ever consumption was defined as drinking an alcoholic beverage at least once a month for a year or more. Average daily consumption was calculated over the period they reported drinking, and classified into three tertiles, and by the type of alcoholic beverage.[103]

205. The authors' findings for alcohol consumption and primary glioma were that:

- there was no association of glioma and ever drinking alcohol for all subjects (RR 0.96, 95%CI 0.67-1.37)
- men who have ever drunk alcohol had a non-significant increased risk (RR 1.40, 95%CI 0.81-2.43), while women had a non-significant decreased risk.
- there was no significant difference in risk for different levels of alcohol consumption. [104]

206. The authors considered the weaknesses of their study included:

- possibility of recall bias
- use of proxy respondents for patients who had died

207. The authors in summary stated that their study:

[103] p. 443

[104] p. 445 - Table 3

> …does not support the associations between alcohol consumption and the risk of glioma.[105]

Council's Comments

208. The Council considered this a good study that attempted to minimise biases. The authors found little evidence that alcohol had any relationship with brain tumours.

209. This case-control study showed no association with ever-consumption of alcohol, and no dose-response. The study was limited by potential recall bias and surrogate reporters of consumption for a number of cases.

210. Council considered the study **leaves open** the relevant association with alcohol consumption.

Lee, M. Wrensch, M. & Miike, R 1997, 'Dietary and tobacco risk factors for adult onset glioma in the San Francisco Bay area (California, USA)', Cancer Causes and Control, vol.8, pp.13-24. RMA ID 14066

211. The purpose of this case-control study was to evaluate dietary intake (including alcohol) and tobacco as potential risk factors for adult glioma.

212. Eligible cases were all histologically confirmed incidence cases of glioma in adults at least 20 years of age diagnosed in the San Francisco Bay area between 1 August 1991 and 31 March 1994.

213. The authors compared the dietary and tobacco use histories of 434 adults newly diagnosed with glioma in the San Francisco Bay area between 1991 and 1994, with population-based frequency-matched controls for age, gender and ethnicity through random-digit dialling.

214. All cases (or their proxies) and controls received a 79-item food-frequency questionnaire about the recollection of usual food consumption habits during the year before diagnosis for cases and for the previous year for controls.

215. Results were compared within gender using generalized linear models to adjust for age, family income and education.

216. The authors completed interviews 494 of 604 eligible cases (82%). Proxy interviews were done for 46% of the cases due to cases' death or disability.

217. For the controls, 462 interviews of 732 eligible controls were completed (63%).

218. The authors' findings with respect to alcohol were:

[105] p. 446

- For both men and women, cases had higher intakes of beers and other alcohol than controls.

- The mean levels of beer and alcohol consumption were higher for cases than controls, but median levels of consumption were lower for cases compared with controls.

- No significant trends were found among men or women for increased or decreased consumption of beer or other alcohol for cases in comparison with controls.[106]

Council's Comments

219. This case-control study provided no consistent associations between consumption of beer or alcohol and glioma. Low response rates among cases due to death (high use surrogates), low response rate in controls and alcohol measured only for the year pre-diagnosis are major limitations of the study.

220. The study highlighted the inherent difficulties in identifying causation, but failed to identify any relationship with alcohol consumption.

221. Council considered the study **does not support** the relevant association with alcohol consumption.

Ruder, A.M. Waters, M.A. Carreon, T. Butler, M.A. Davis-King, K.E. Calvert, G.M et al 2006, 'The Upper Midwest Health Study: a case-control study of primary intracranial gliomas in farm and rural residents', Journal of Agricultural Safety and Health, vol. 12, no. 4, pp. 255-274. RMA ID 45783

222. The purpose of this population-based, case-control study was to evaluate the association between gliomas and rural and farm exposures among adults from Iowa, Michigan, Minnesota and Wisconsin.

223. 798 of 872 eligible cases consented to participate. The cases were residents in non-metropolitan counties of Iowa, Michigan, Minnesota and Wisconsin aged 18-80 years with histologically confirmed primary intracranial gliomas diagnosed from 1 January 1995 to 31 January 1997.

224. 1175 of 1669 controls consented to participate. Controls were selected from residents who lived in those eligible counties on 1 January 1995.

225. Cases and controls were interviewed in person or by phone by a trained interviewer with a standardized questionnaire. Proxies for 360 cases and 34 controls were interviewed.

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[106] pp. 16-18 and Table 2

226. For the relation between ever drinking alcohol and glioma occurrence, the authors found that alcohol had a significantly decreased risk of glioma (OR 0.73, 95%CI 0.59-0.92), regardless of whether or not proxy interviews were included in the analysis.[107]

227. The authors considered the strengths of their study included:

- largest case-control study of glioma focusing on non-metropolitan populations at the time of publication
- large number of histologically confirmed gliomas and the use of population-based controls
- successful collection of biological specimens from a majority of participants.

228. The authors considered the weaknesses of their study included:

- high proportion (>40%) of proxy interviews for case participants
- recall bias for occupational exposures could not be assessed.

Council's Comments

229. The Council considered that this paper suggests alcohol is protective against brain cancer, as the authors found a significant decreased risk of glioma in the alcohol drinkers.

230. Assessment of the association of alcohol with glioma was a secondary aim of this study that was primarily assessing association with farming-related exposures. Alcohol exposure was assessed only as ever-never and not by dose or duration. Nonetheless an inverse relation with glioma was found, including when proxy interviewers' responses were excluded.

231. The Council considered the study **points against** the relevant association with alcohol consumption.

Zampieri, R. Meneghini, F. Grigoletto, F. Gerosa, M. Lieata, C. Casentini, L et al 1994, 'Risk factors for cerebral glioma in adults: a case-control study in an Italian population', Journal of Neuro-Oncology, vol. 19, pp. 61-67. RMA ID 9464

232. The purpose of this case-control study was to evaluate the risk factors for brain tumours from four neurosurgical departments in an Italian population.

[107] Table 4

233. The authors identified 195 cases between 1986 and 1988. Cases were of the age range 18-70 years with histologically confirmed diagnosis of brain cancer.

234. Controls were selected from patients admitted to the same hospital in which the case had been recruited, and matched to each case for age, sex, date of hospitalization and place of residence.

235. Next-of-kin interviews were used for both cases and controls to collect information on exposure to risk factors. The questionnaire was about risk factors and demographic details.

236. The authors' findings were:

- None of the risk factors considered in this study (alcohol, smoking, blood group, birth group, education level, occupation, head trauma, diagnostic radiations, CNS tumours in any first-, or second-degree relative) proved statistically associated with cerebral glioma.[108]

- For the risk factor relevant for this review:

  - Alcohol=OR 0.7, (95%CI 0.4-1.3).

237. The authors considered the strengths of their study included:

- Using next-of-kin interviews to collect information as many cerebral glioma patients have mental impairment.

238. The authors considered the weaknesses of their study included:

- Recall bias

- Difficult to quantify exposure to radiations

- The frequency of occurrence was small and this could lead to unstable odd ratio estimates.

239. The authors in conclusion stated:

> … this study yielded no clear and meaningful association for the various risk factors investigated.[109]

[108] p. 63 and Table 3

[109] p. 65

Council's Comments

240. There was a non-significant inverse association found between alcohol consumption and glioma. This was a hospital-based case-control study and proxy respondents were used for all subjects thus there is the potential for some recall bias and confounding of the results.

241. Council considered the study **leaves open** the relevant association with alcohol consumption.

Cross-sectional studies

Williams, R.R. & Horm, J.W 1977, 'Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: Interview study from the Third National Cancer Survey', J Natl Cancer Inst, vol. 58, pp.525-547. RMA ID 3613

242. The purpose of this population-based cross-sectional study was to evaluate specific sites of cancer for associations with exposure to tobacco, alcohol, socioeconomic status.

243. The authors obtained personal interviews for 7,518 incident cases of invasive cancer from the population-based Third National Cancer Survey (TNCS).

244. Lifetime alcohol history and tobacco history were quantified and standardised.

245. The authors used 'intercancer comparison' of one cancer site with controls from other sites. Cancer sites which are known to be strongly associated with tobacco and alcohol were compared individually to all remaining 'non-related' sites and control. Then each site of the non-related set was compared with all other non-related sites combined.

246. For the alcohol consumption analysis, a specific type of alcohol eg. Wine, was compared only with non-drinkers.

247. The results were stratified by five-year age groups and race, marital status, and geographic location.

248. The authors' findings for alcohol use:

- there was no association between brain/CNS cancer and alcohol
- the consumption of wine, beer, hard liquor and all combined showed positive associations with cancer of the oral cavity, larynx, oesophagus, colon, rectum, breast and thyroid gland.[110]

[110] p. 529, Table 3, 6A

249. The authors considered a strength of their study was the accurate information obtained from medical records for the diagnosis and classification of cancer with 95% of those interviewed having a histology report.

250. The authors considered the weaknesses of their study included:

- geographic location was biased by non-response
- intercancer comparison approach may lead to possible misinterpretations
- some of the remaining cancer sites included as controls were associated with the exposure variables and hence they could have biased the control group enough to prevent the detection of weak associations
- recall bias for the lifetime history of exposure variables.
- tobacco, alcohol and SES could possibly act as confounding variables
- the large number of multiple comparisons performed can lead to over-interpretation of statistical significance.

251. The authors in conclusion stated:

> The numerous findings presented …should provide stimulus for further detailed analysis and interpretation of the TNCS data as well as some insight into the kinds of hypotheses that should be tested in future epidemiologic studies.[111]

Council's Comments

252. The Council noted that the cancers studied are of the nervous system collectively and not specifically malignant neoplasm of the brain. Thus it is not possible to interpret these data with regard to malignant neoplasm of the brain alone, even though it is noted that that there was no association of alcohol with nervous system cancer overall.

253. Council considered the study **does not support** the relevant association with alcohol consumption.

[111] p. 546

Exposure to non-ionising electromagnetic radiation emitted from radio equipment (as used in aircraft) or radar equipment.

Meta-analysis

Ballard, T., Lagorio, S., De Angelis, G. & Verdecchia, A., 2000, 'Cancer incidence and mortality among flight personnel: a meta-analysis,' Aviat Space Environ Med., vol. 71, no. 3, pp. 216-24. RMA ID 34866

254. The purpose of this meta-analysis was to evaluate the relation between exposure to cosmic radiation, electromagnetic fields from cockpit instruments, other volatile and chemical agents, and cancer in flight personnel.

255. Methods:

- The authors performed a literature search for published and unpublished cohort studies of flight personnel from 1986-1998.
- They initially identified 10 studies (six published flight personnel-specific cohort studies, one study of US Air Force pilots, 1 proportionate mortality study of pilots taken from a US occupational mortality surveillance system and two additional flight personnel cohort studies in the process of publication at the time).
- Out of the 10 studies identified, six were included in the combined analysis. The relative risks of six studies were combined using standard meta-analytic methods.

256. The authors' findings for combined RRs, adjusted for socioeconomic status[112] were:

Male pilots:

- Non-statistically significant increased risk of mortality from brain cancer [RR 1. 45 , 95%CI 0.75 -2.80],
- Non-statistically significant increased incidence of brain cancer [RR 1.74, 95%CI [0.87-3.30].

For female flight attendants:

- Non-statistically significant increased risk of incidence of all cancers [RR 1.29, 95%CI 0.98-1.70][113].

[112] pp. 218-220, Table 3

257. The authors considered the weaknesses of their study[114] included:

- Due to few studies in each category, the resulting combined relative risk estimates cannot be interpreted as summary measures of effect across studies.
- Bias in the combined estimates of effect for several cancers may have occurred due to missing data.
- Inability to control for confounding factors other than SES such as diet, tobacco, alcohol use, reproductive factors and family history of certain cancers.
- Detection bias due to more frequent medical check-ups by flight personnel who have higher income levels and may have more access to health care than the general population.
- The data used in this 'meta-analysis came from comparisons of flight personnel with standard populations, and did not take into account specific occupational hazards.

258. The authors in conclusion stated that:

> A meta-analysis of six cohort studies of flight personnel for a series of causes of death or cancer sites demonstrated small, elevated risks for tumours of the prostate and brain among male pilots, for tumours of the breast cancer among female flight attendants, and for malignant melanoma in both groups. [115]

Council's Comments

259. Council noted that the major finding of this meta-analysis were non-significant increases in the point estimates for the relative risk for both incidence and mortality from brain cancer in pilots.

260. However, the Council also noted that the authors were unable to control for confounding lifestyle factors such as diet, tobacco, alcohol use, reproductive factors, and family history of certain cancers. Nor were they able to disentangle the various exposures for flight personnel such as cosmic radiation, electromagnetic fields from cockpit instruments, and other volatile and chemical agents.

261. The Council further noted that this is a major review. The pooled analysis in relation to brain cancer included data from studies that are already in the

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113 This sub-analysis in female pilots was not adjusted for SES

114 pp. 221-223

115 p. 220

pool by Irvine et al 1992[116], Band, et al 1996,[117] and Salisbury et al 1991,[118] each of which found elevated but not-statistically significant, estimates for brain cancer in pilots. The Council considered that each of those studies leaves open the relevant association and therefore has not discussed each in detail in these reasons. As this is a more recent meta-analysis combining the data from these and other studies, the Council considered this study to be more comprehensive and thus carries a greater weight than each of the studies carries individually.

262. Council considered the study **leaves open** the relevant association with non-ionising electromagnetic radiation as emitted by radar or radio equipment.

Barron, C.I & Baraff, A.A 1958, 'Medical considerations of exposure to microwaves (radar)', JAMA, vol. 168, no. 9, pp. 1194-1199. RMA ID 25480

263. The three objectives of this study were:

- To detect any cumulative biological effects of long-time exposure to microwaves of varying frequency and power output in persons who had taken minimal precautions.
- To observe possible effects on persons working for short periods of time with or near extremely high-powered airborne radar with pulsed wave emissions.
- To establish correlation between objective findings and units of exposure expressed in time-power density factors with the highly idealized objective of establishing safe maximum exposure standards.[119]

264. This was an observational study over four years with 225 radar-exposed employees and 88 non-exposed control subjects in 1954.

265. The data was collected a part of a medical surveillance program of 335 employees working with or exposed to microwaves in an airframe manufacturer, Lockheed Aircraft Corporation, in 1954. Examinations were performed at intervals of 6, 12, and 24 months.

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116 Irvine, D. & Davies, D.M. 1992, 'The mortality of British Airways pilots, 1966-1989: a proportional mortality study', *Aviat Space Environ Med*, vol. 63, pp.276-279. RMA ID 26124

117 Band, et al 1996, Cohort study of Air Canada pilots: mortality, cancer incidence, leukemia risk,' Am J Epidemiol., vol. 143, no. 2, pp.137-43. RMA ID 12371

118 Salisbury, D.A., Band, P.R., Threlfall, W.J., Gallagher, R.P., 1991, 'Mortality among British Columbia pilots,' Aviat Space Environ Med, vol.62:351-352. RMA ID 14719

119 p. 1195

266. The authors' findings for the effects of long periods of exposure were:

> No person in this study had sustained any acute or chronic injury secondary to radar exposure. [120]

267. The authors' findings for the safe maximum exposure standards were:

> …this objective could not be achieved in our study. We uncovered no pathology caused by either single or repeated exposure, and consequently we cannot speak authoritatively of so-called hazardous exposure conditions.[121]

268. The authors in summary stated that:

> In our study we have failed to detect an acute, transient, or cumulative physiological or pathological changes in subjects working with and frequently exposed to high-power radar transmitters…The examinations have failed to detect any significant changes in the physical inventories of the subjects. The incidence of death and chronic disease, sick leave, and subjective complaints was comparable in both groups…On the basis of these studies there appears to be no justification for public concern about the effects of greatly attenuated microwave energy in the environment.[122]

Council's Comments

269. The Council noted that this was quite an old paper, only pertinent to short-term follow-up of exposure, with review of exposed individuals only to 24 months after exposure.

270. This is a relevant negative paper because the study found no increase in chronic disease in the exposed subjects compared to the unexposed. The absence of any findings of malignant neoplasm of the brain indicates no association between radar and malignant neoplasm of the brain.

271. The Council considered the study **does not support** the relevant association with non-ionising electromagnetic radiation as emitted by radar equipment.

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120 p. 1195

121 p. 1197

122 p. 1199

Cohort Studies

Grayson, J.K. & Lyons, T.J 1996, 'Cancer incidence in United States Air Force Aircrew, 1975-1989', Aviation Science and Environmental Medicine, vol. 67, no. 2, pp.101-104. RMA ID 14408

272. The purpose of this study was to measure the association between flying status and incident cancers detected while officers were employed by the US Air Force.

273. The authors used cohort analyses of incident cancers among all Air Force officers on active duty during the study interval, January 1, 1975 and December 31, 1989. Flying and demographic information were ascertained from personnel records.

274. Cohort definition:

> All male Air Force officers who had completed at least one full year of Air Force service between January 1, 1975 and December 31, 1989.[123]

275. The cohort was then sub-divided into 'aircrew' (any officer who had flown professionally) and 'other officers' (no record that they had ever flown professionally).

276. Cases were defined as:

> Air Force officers who were newly diagnosed with primary malignancies while on active duty during the study period.[124]

277. Cases were identified by screening hospital discharge records for any officer diagnosed with an incident cancer. Repeat diagnoses for the same type of cancer were not counted.

278. The authors' findings were:[125]

- There were 59,940 individuals in the aircrew sub-cohort that contributed 532,980 person-years, and 167,263 other officers that contributed 1,084,370 person-years during the study period.
- In comparison to the external SEER standard population, the overall age-adjusted standardized incidence ratio (SIR) for cancer among Air Force aircrew group was significantly elevated (SIR=1.19, 99%CI 1.03-1.36).

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123 p. 102

124 p. 102

125 pp. 102-103 and Table 2

- In comparison to the SEER standard population, there was lower, incidence of brain cancer in the aircrew sub-cohort, but the difference was not significant (SIR 0.71, 99%CI 0.30-1.40).

- Relative to non-flying officers, Air Force aircrew experienced a significantly increased age-adjusted risk of cancer for all sites (RR 1.31, 99%CI 1.11-1.54).

- For cancer of the brain and nervous system, there was an increased, but non-significant risk association with the aircrew sub-cohort relative to non-flying officers (RR 1.20, 99%CI 0.52-2.78).

279. The authors considered the strengths of their study included:

    - Using an internal comparison ie. other officers in the Air Force who do not have a record of flying professionally, helped account for sources of confounding and threats to internal validity such as selection bias

    - Lower risk of information bias due to using an internal comparison with similar methods in obtaining and recording cases, and diagnostic effort.

280. The authors did not report any weaknesses for their study.

281. The authors in conclusion stated that they:

> The results of this investigation indicate that Air Force aircrew are not at excess risk for cancers of the colon and rectum, skin, brain or lymphatic systems in comparison to non-flying Air Force officers. Statistically significant excess risks were detected for all cancers combined…[126]

Council's Comments

282. The Council noted that this paper shows no statistically significant difference in brain cancer incidence in USAF aircrew compared with a non-flying cohort.

283. More importantly, the comparison between the aircrew group showed no increase (and a non-significant reduction) in incidence of brain cancer compared to that of the standard population.

284. The Council considered the study **points against** the relevant association with non-ionising electromagnetic radiation as emitted by radar or radio equipment.

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[126] p. 104

Groves, F.D. Page, W.F. Gridley, G. Lisimaque, L. Stewart, P.A. Tarone, R.E. et al 2002, 'Cancer in Korean war Navy technicians: Mortality survey after 40 years', Am J Epidemiol, vol. 155, no. 9, pp. 810-818. RMA ID 25344

285. This was a retrospective cohort study of 40,581 US Navy veterans of the Korean War that evaluates the mortality effects of high-intensity radar over a follow-up period from 1950 to 1997.

286. Methods:

- Authors identified 40,581 out of 40,890 Navy personal with high potential for radar exposure from Navy records that served during the Korean War 1950-1954.

- Naval personnel were classified by occupation and radar exposure potential: Low radar exposure potential (Radar operator, radio operator, aviation electrician's mate) and High radar exposure potential (Aviation electronics technician, fire control technician).[127]

287. The authors' findings for standardized mortality ratios for whole cohort:

- A total of 8,393 deaths were identified by the end of follow-up with a cumulative crude mortality rate of 20.7% after about 40 years. The overall standardized mortality ratio (SMR) for the cohort was 0.74 (95%CI 0.73-0.76), which was significantly less than the US white male death rate.

- SMRs for all diseases in the cohort (SMR 0.72, 95%CI 0.70-0.74), specifically all malignant neoplasms (SMR 0.81, 95%CI 0.78-0.85), were significantly less than the US white male death rate.

- High-exposure occupations had significantly lower total SMR than low-exposure occupations (SMR 0.69 vs. 0.80).

- High-exposure occupations were not associated with an increased risk of brain cancer or testicular cancer. [128]

288. The authors' findings for relative risk of death for men with high-exposure occupations vs low-exposure occupations:

- Deaths from all diseases, specifically all malignant neoplasms and brain cancer were significantly less common in the high-exposure group than in the low-exposure group.

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[127] P. 812, Table 2

[128] p. 814 and table 3

289. Authors' findings for occupation-specific risks:

> Overall mortality and, in particular, total disease mortality were significantly decreased among electronics technicians (RR=0.77, 95%CI 0.73-0.81) and aviation electronics technicians (RR0.79, 95%CI 0.73-0.87).[129]
>
> No significant excesses were seen for any job category for lymphoid malignancies, brain cancer, or testicular cancer.[130]

290. The authors considered the strengths of their study included:

- Size of the study
- Long duration of follow-up.

291. The authors considered the weaknesses of their study included:

- Lack of dosimetry for microwave exposures and other occupational and environmental chemical exposures
- Misclassification of exposures due to reliance on job titles
- Absence of exposure information after naval duty
- Lack of date of birth and year of graduation for many subjects
- Absence of Social Security number for almost half the cohort.

292. The authors in conclusion stated that:

> For occupations with high potential for radar exposure, no significant excesses were found for all malignant neoplasms combined, lymphoid malignancies, brain cancer or testicular cancer… Overall, it appears that radar exposure had very little effect on mortality in this cohort of US Navy veterans.[131]

Council's Comments

293. The Council noted that this article, which examined radar exposure in a military cohort, found reduced standardised mortality ratios (SMR) for the high-exposed occupations, and no association with brain cancer.

294. The Council considered that if the electromagnetic fields were to have had an impact on these veterans, the results would be expected to show that

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129 p. 813, Table 5

130 p. 815

131 p. 818

SMR would correlate positively with exposure. In fact, the data showed the reverse: the group with the high exposure had the lowest SMR, suggesting a trend towards a protective effect.

295. The Council considered the study **does not support** the relevant association non-ionising electromagnetic radiation as emitted by radar or radio equipment.

Szmigielski, S., 2006, 'Cancer morbidity in subjects occupationally exposed to high frequency (radiofrequency and microwave) electromagnetic radiation,' The Science of the Total Environment, vol. 180, pp. 9-17. RMA ID 10413

296. The purpose of this study was to evaluate cancer morbidity in a group of military personnel in Poland in the 20-59 years age group who were occupationally exposed to pulse modulated radiofrequency/microwave (RF/MW) radiation during 1971 to 1985.

297. The whole study population was military career personnel in Poland during a 15-year period (1971 to 1985).

298. Subjects exposed occupationally to RF/MW radiation were selected from this study population on the basis of their service records and documented exposures (on average approximately 3700 military personnel (2.98%) were considered exposed to RF/MW radiation.

299. All subjects (exposed and non-exposed to RF/MW) were divided into 4 age groups (20-29, 30-29, 40-49, 50-59).

300. The 'observed' rate of morbidity was defined as the number of newly diagnosed cases of neoplasm in the RF/MW-exposed group (per 100,000 subjects annually).

301. The 'expected' rate of morbidity was defined as the incidence of neoplasms for the whole population, including the RF/MW-exposed personnel (per 100,000 subjects).

302. Incidence of neoplasm (12 types) was calculated for every year and during the whole period of analysis (1971-1985).

303. The authors' findings were:

- The incidence of all neoplasms was significantly greater in the RF/MW exposed group in comparison to the unexposed group (OER 2.07, 95%CI 1.12-3.58, $p<0.05$)
- The incidence of brain tumours was also significantly higher in the exposed group (OER 1.91, 95%CI 1.08-3.47, $p<0.05$).

- The incidence for haematopoetic system and lymphatic organs, skin, oesophageal and stomach, and colorectal cancers was also significantly higher in the exposed group. [132]

304. The authors considered the strengths of their study included:

- The RF/MW-exposed subjects had considerably uniform exposure conditions with 80% of the investigated personnel being exposed to RF/MW fields of 0.1-2 W/cm^2 and 15% to mean power densities of 2-6 W/m^2.

305. The authors considered the weaknesses of their study included:

- The incidence of brain and skin cancer was relatively low -2-4 cases over 15 years.[133]

- Diverse exposure conditions among electric and electronic workers analysed retrospectively may result in dilution of the morbidity effects.

- The exposure conditions of the investigated personnel were almost limited to the pulse-modulated high frequency EM fields (150- to 3500 MHz RF/MW radiation).

306. The authors in conclusion stated:

> …the high incidence of certain forms of neoplasm in personnel exposed to pulse-modulated RF/MW radiation clearly shows a need for urgent identification of causal factors present in the occupational environment.[134]

Council's Comments

307. Council noted that pulse-modulated radio frequency is a form of radar.

308. The Council had some misgivings about the methodologies used by this study group. The numbers of cases involved were too small to give a strong conclusion. 3700 individuals in the study were exposed, and there were only four cases of nervous system tumours identified.

309. Furthermore, the Council noted that the type of tumour beyond being of the nervous system, including brain tumours, was not described in the study.

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132 Table 1

133 For brain and nervous system cancers this was calculated as 4.36 per 100,000 person years., see p.15 and Table 1

134 p. 16

310. Council considered the study **leaves open** the relevant association with non-ionising electromagnetic radiation as emitted by radar or radio equipment.

Morgan, R.W., Kelsh, M.A., Zhao, K., Exuzides, K.A., Heringer, S. & Negrete, W., 2000, 'Radiofrequency exposure and mortality from cancer of the brain and lymphatic/hematopoietic systems,' Epidemiology, vol.11, no. 2, pp. 118-127. RMA ID 24970

311. The purpose of this cohort mortality study of Motorola employees was to investigate the relation between radiofrequency (RF) exposures and brain cancer and all lymphoma and leukaemias.

312. The occupational cohort consisted of 195,775 U.S. Motorola employees who were employed for at least 6 months with at least one day during that time being between January 1, 1976 and December 31, 1996. The study population was followed from 1976 to 1996.[135]

313. The authors used the job titles of the subjects to classify them into high, moderate, low, and background RF exposure groups.

314. The authors' findings were:

- There was a pronounced healthy worker effect in the total cohort (all-cause SMR 0.66, 95%CI 0.64-0.67)
- For brain cancers, there was no risk associated with RF exposure (SMR 0.53, 95%CI 0.21-1.09)
- There was no increased risk of cancer associated with increased exposure duration or latency. [136]

315. The authors considered the strengths of their study included:

- Large cohort with employees who have received higher RF exposures than the general public.

316. The authors considered the weaknesses of their study included:

- Relying on estimate of relative exposure rather than personal exposure
- Use of the job exposure matrix and potential misclassification bias
- Unknown confounding factors

[135] p. 119

[136] pp. 122 – 123, Figure 1, Figure 2, Table 4

– Although the cohort was large, statistical power was limited by the relatively young age, the small proportion of the cohort that had died the rarity of the cancers and the small percentage of the cohort who had RF exposure.

317. The authors in conclusion stated:

> The lack of elevated mortality risk for brain cancers and all lymphatic/hematopoietic cancers combined suggests that occupational RF exposure, at the frequencies and field levels experienced within this cohort, are not associated with an increased risk of these diseases.[137]

Council's Comments

318. The Council noted that the SMR for brain cancers in this study was halved in the radiofrequency-exposed workers. Furthermore, the Council noted that the type of tumour beyond being of the nervous system, including brain tumours, was not described in the study.

319. The Council noted that the results lacked statistical significance, and that a healthy worker effect may have affected the results. Unhealthy people often are not employed and thus miss being counted in the study. The Council noted however that, the point estimate for brain cancer mortality was greatly reduced.

320. Council considered the study **leaves open** the relevant association with non-ionising electromagnetic radiation as emitted by radar and radio equipment.

Pukkala, E., Aspholm, R., Auvinen, A., Eliasch, H., Gundestrup, M., Haldorsen, T., et al., 2003, 'Cancer incidence among 10,211 airline pilots: a Nordic study,' Aviation, Space, and Environmental Medicine, vol. 74, no. 7, pp. 699-706. RMA ID 29797

321. The purpose of this study was to describe the cancer incidence among commercial airline pilots from all five Nordic countries (Denmark, Finland, Iceland, Norway, Sweden).

322. The authors noted that as well as cosmic radiation, flight personnel may also be exposed to electromagnetic fields from cockpit instruments, jet fuel, and substances emanating from materials used in aircraft construction.[138]

323. The authors identified a cohort of 10,051 male and 160 female airline pilots from various registries, and followed them up for cancer incidence through

[137] p.124

[138] p.699

record linkage with the national countrywide cancer registries that exist in all Nordic countries.

324. Follow-up for cancer for each subject started at the date of first employment, at immigration, or on the date of the beginning of cancer registration whichever was latest, and ended at emigration, at death or on the date that cancer registration was complete. The mean length of follow-up was 17 years.

325. The authors' findings were:

- No significant excess incidence of cancer in this cohort of pilots. 466 cases of cancer were observed in men (SIR 1.02, 95%CI 0.93-1.12). In women, only 2 cancers were observed and the expected is 1.8.

- Skin cancer was the only cancer with statistically significant increases in SIRs including melanoma of the head and neck (SIR 2.49), trunk (2.33), limbs (2.29), and non-melanoma skin cancer (excluding basal cell carcinoma) (2.08). They also found that the SIR for skin cancers increased with the time since first employment.

    1. Pilots who had flown for at least 5000 block hours showed an increased incidence of skin melanoma

    2. There was no excess incidence of brain/CNS cancer in this cohort (n=18, SIR 0.84, 95%CI 0.50-1.33). There was a slight, but not significant, increase in brain/cancer in pilots with more than 20 years since first employment (n=11, SIR 1.09, 95%CI 0.56-1.90).[139]

326. The authors considered the strengths of their study included:

- Large cohort size

- Access of carefully registered incidence data

- Calculations used are specifically valid for Norwegian SAS airline pilots.

- Complete population registration systems in all Nordic countries allowed for complete follow-up for deaths and emigration for the period of this study.

- Cancer registration systems are virtually complete with precise computerized record linkage procedures.

327. The authors considered the weaknesses of their study included:

[139] Table 2

- Some incomplete documentation in the very oldest flight data, which are a minor part of the exposure data

- May have diluted the dose-response trends by classifying the flight hours into the category of lowest potential radiation and fixed the exposure to the latest potential calendar time.

328. The authors in summary stated:

> Out study did not show any excess of tumours of the brain or nervous system, nor any trend with increasing numbers of hours spent in the electromagnetic fields exposure in the cockpit of various aircraft.[140]

The present study calls for a need of detailed studies focusing on possible work-related factors involved in the evidently increased skin cancer risk…[141]

Council's Comments

329. Council considered this to be a useful large study of over 10,000 pilots. However that the authors were not able to identify the particular exposures which ranged from cosmic radiation, to electromagnetic fields from cockpit instruments, and various chemical exposures.

330. The major finding of relevance to this review is the absence of an increased incidence of malignant neoplasm of the brain in pilots (SIR of 0.86).

331. Council considered the study **does not support** the relevant association with non-ionising electromagnetic radiation as emitted by radar or radio equipment.

Case-Control Studies

Berg, G., Spallek, J., Schüz, J., Schlehofer, B., Böhler, E., Schlaefer, K. et al., 2006, 'Occupational exposure to radio frequency/microwave radiation and the risk of brain tumours: Interphone Study Group, Germany', Am J Epidemiol, vol. 164, 6, 538-48. RMA ID 45665

332. The purpose of this study was to evaluate the role of occupational radio frequency/microwave electromagnetic fields (RF/MW-EMF) exposure in the risk of glioma and meningioma.

333. This was a population-based, case-control study including 381 meningioma cases, 366 glioma cases, and 1,494 controls aged 30-69 years, performed in three German regions in 2000-2003.

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140 p. 705

141 p. 705

334. Cases were eligible if their tumour was diagnosed between October 1, 2000 and October 31, 2003. Cases were all patients with histologically confirmed diagnoses of primary glioma or meningioma (benign or malignant), and selected from four neurosurgical clinics located in Bielefeld, Heidelberg/Mannheim and Mainz.

335. Controls were drawn from the compulsory population registries in the three regions and matched to cases by sex, age, and centre. Two corresponding controls were match to each case with 732 matched controls for 366 glioma cases and 762 controls for the 381 meningioma cases.

336. A detailed questionnaire on occupational activities related to RF/MW-EMF and the whole range of EMF, including static fields and very low frequency EMF, as well as ionizing radiation, was collected in a computer-assisted personal interview. Trained interviewers, with the same interviewer questioning the case and matched controls, conducted these interviews.

337. All occupational activities were classified with regard to possible exposure to RF/MW-EMF as 'no RF/MW-EMF' exposure, 'not probable,' 'probable' and 'high' exposure.

- The outcome of 'high' exposure was defined as an occupational exposure that surely existed continuously during the mentioned working hours and sometimes exceeded 0.08 W/kg (which corresponds to the exposure limits of RF/MW-EMF for the general population).

- Occupational activities were classified as 'probable' exposure if the exposure existed and was probably present continuously during the mentioned working hours.

- Activities were grouped as 'not probable' when the activity mentioned was related to RF/MW-EMF but it was presumed that the person was not exposed to RF/MW-EMF.

338. The different activities were grouped together for each person and duration of exposure of each category was calculated: no high exposure (including no exposure, not probable, and probable), less than 10 years of high exposure, and 10 or more years of high exposure.

339. Multiple conditional logistic regressions were performed and stratified for the three regions and for sex.

340. The authors' findings for the association of RF/MW-EMF exposure with glioma were:

> RF/MW-EMF exposure was not associated with occurrence of glioma. For glioma, the adjusted odds ratio was 1.04 (95%CI 0.68-1.61).

> When…duration of RF/MW-EMF exposure and focused solely on high exposure, the odds ratios for gliomas increased slightly. For persons who worked less than 10 years, the adjusted odds ratio for high exposure compared with not high exposure was 1.11 (95%CI 0.48-2.56); for persons who worked 10 years or more, the corresponding odds ratio was 1.39 (95%CI 0.67-2.88). [142]

341. The authors considered the strength/s of their study included:

- assessment of occupational exposure was based on individual activities during employment instead of job titles…[which] enabled [the authors] to consider individual exposure to RF/MW-EMF and the use of shielding systems.

- The category of high-exposure activities derived from the comprehensive questionnaire was established to consider the specific exposure situation during an activity. This method was used to allow a more sensitive exposure estimation of the real situation and a more specific exclusion of a non-exposure situation during a possible-exposed occupation.

- The number of cases included in this case-control study is the highest of all published case-control studies investigating occupational RF/MW-EMF exposure

342. The authors considered the weaknesses of their study included:

- recall bias may have been present, particularly because of the extensive questionnaire used

- selection bias: The response rate differed between cases (83.8%) and controls (62.4%).

- the number of people with high exposure among cases and controls identified is still small (22 glioma cases and 11 meningioma cases).

343. The authors in conclusion stated that:

> We did not find a significant association between occupational exposure to RF/MW-EMF and brain tumours, but odds ratios for both glioma and meningioma were slightly increased for long-duration and high exposure.[143]

Council's Comments

344. The Council concluded that, even for high risk of exposure and prolonged duration of exposure, there was a wide range of confidence interval that straddled 1.0, and as such no clear conclusion of impact could be identified.

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142 p. 543 and Table 4

143 p. 546

345. Council considered the study **leaves open** the relevant association with non-ionising electromagnetic radiation as emitted by radar or radio equipment.

Grayson, J.K., & Lyons, T.J., 1996, 'Brain cancer, flying, and socioeconomic status: a nested case-control study of USAF Aircrew,' *Aviation Science and Environmental Medicine*, vol. 67, no. 12, pp. 1152-1154. RMA ID 14304

346. The purpose of this nested case-control study was to investigate the association between brain cancer risk of male United States Air Force (USAF) aircrew and non-flying Air Force personnel, and to ascertain the influence of socioeconomic status (SES) on USAF brain cancer risk between 1970 and1989.

347. This case-control study was nested within a cohort composed of all males in the USAF who had completed at least one full year of service between January 1, 1970 and December 31, 1989.

348. Cases were identified by screening computerized hospital discharge records for all primary malignant brain cancer diagnoses among individuals who were on active duty during the study period.

349. Controls were randomly selected in a 4:1 ratio (4 controls to 1 case) from all individuals in the cohort who exactly matched each case on year of birth and race, and who were present in the USAF cohort at the time of diagnosis.

350. Complete occupational histories for all subjects were obtained through USAF personnel records. The histories of the control group was censored at the index case's diagnosis date to ensure case and control person-time coincided.

351. The authors defined career aircrew members as those who retained a flying Air Force Specialty Code (AFSC) for more than 50% of the USAF careers. All others were classified as non-aircrew.

352. Military rank at the time of index case diagnosis was included as a substitute for SES, and it was stratified into 6 categories

353. The study population of about 880,000 USAF individuals contributed to 11,174,248 person-years to the cohort between 1970 and 1970. From this cohort, 230 cases of brain cancer and 920 matched controls were selected for the nested case-control study.

354. The authors' findings were:

- Individuals with career aviation exposure had statistically significantly increased odds of brain cancer in comparison to the non-aircrew group (OR 1.77, 95%CI 1.17-2.68), after controlling for age and race.[144]

- When the authors controlled for age, race and military ranking, the risk of brain cancer in career Air Force aviators (compared with non-aircrew members) was reduced to OR 1.22, (95%CI 0.76-1.95) showing that much of the apparent Air Force career aircrew brain cancer risk was attributable to the confounding effect of senior military rank.[145]

355. The authors considered the weaknesses of their study included:

- Misclassification bias – Authors arbitrarily defined career aircrew member as subjects who retained a flying AFSC for more than 50% of their USAF careers because detailed individual flying histories were not available

- No analysis of brain cancer risk by flying hours.

356. The authors in conclusion stated that they:

> Our data suggest that career USAF aircrew had only an extremely weak, statistically non-significant risk of developing brain cancers when compared to their non-flying counterparts after accounting for the confounding effects of socioeconomic status as measured by senior military rank.[146]

357. Senior USAF officers above the rank of captain had the highest brain cancer risks in this investigation.[147]

Council's Comments

358. Council noted that this paper examines brain cancer incidence in USAF aircrew (compared with non-flying USAF control group). Incidence adjusted for Social Economic Status (SES) estimated by service rank, and age showed an elevated but not statistically significant increase in flying personnel (OR 1.22).

359. The Council noted that the authors suggested that any apparent excess in brain cancer risk in USAF flying personnel is attributable to factors other than flying (eg, age, SES).

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144 p. 1153 and Table 2

145 p. 1153 and Table 2

146 p. 1153

147 p. 1154

360. Council considered this study does not support the relevant association with non-ionising electromagnetic radiation as emitted by radar or radio equipment.

Reviews

Elwood, J.M., 2003, 'Epidemiological studies of radio frequency exposures and human cancer,' *Bioelectromagnetics*, suppl 6, pp. S63-S73. RMA ID 30503

361. The purpose of this review was to evaluate whether the available epidemiological studies show that exposure to radio frequencies causes cancers in humans.

362. This was review of published studies from 1988 to November 2002. The authors excluded case reports, studies with no comparison group, and studies based only on largely routinely collected data sets.

363. The paper is based on two earlier studies (Elwood, 1999 and Australian Radiation Protection and Nuclear Safety Agency, 2002) and focuses more on studies after 1999, with only a brief summary of studies up to 1999.

364. The authors reviewed and summarised the findings of two studies on the relationship between cancer and radio and television transmitters.

- Cooper et al., 2001[148] found there were no significant declines in risk with distance for adults, but there were increased risks for several types of leukemia for the whole area.

- Michelozzi et al., 2002[149] showed there was a statistically significant decline in leukemia mortality with increasing distance from the transmitters, for men, but no association for women, and a non-significant decrease in risk for both sexes combined

365. The authors reviewed three occupational studies where employees were exposed to radio frequencies

- Morgan et al., 2000[150] did not find a significantly increased risk of death associated with US Motorola employees

- Groves et al., 2002[151] found that 'radar exposure had very little effect on mortality in this cohort of US Navy veterans.'

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148 Cooper, D. et al. 2001. Re: 'Cancer incidence near radio and television transmitters in Great Britain I. Sutton Coldfield transmitter II. All high power transmitters.' Am J Epidemiol 153: 202-204.

149 Michelozzi, P. et al, 2002, 'Adult and childhood leukemia near a high-power radio station in Rome, Italy.' Am J Epidemiol 155: 1096-1103.

150 Morgan, R.W. et al. 2000, 'Radiofrequency exposure and mortality from cancer of the brain and lymphatic/hematopoietic systems,' Epidemiology, 11:118-127.

- De Roos et al., 2001[152] evaluated parental exposures to radio frequencies in relation to neuroblastoma in offspring, and found no clear association.

366. The authors also reviewed eight studies of cancer in association with the use of cellular telephones, finding no association with any kind of head cancer.

367. In conclusion, they stated that:

> The epidemiological results fall short of the strength and consistency of evidence, which is required to come to a conclusion that RF emissions are a cause of human cancer.[153]

Council's Comments

368. The Council noted that this was a good review article, although not a systematic review.

369. The Council further noted that the authors argue that the results fell short of consistency among the various articles they reviewed.

370. Council considered the study **leaves open** the relevant association with non-ionising electromagnetic radiation as emitted by radar and radio equipment.

Fisher, J.L. Schwartzbaum, J.A., Wrensch, M. & Wiemels, J.L., 2007, 'Epidemiology of brain tumours,' *Neurologic Clinics*, vol. 25, no. 4, pp. 867-890. RMA ID 49055

371. The purpose of this article is to review the incidence, risk factors and prognostic factors of brain tumours.

372. The authors summarize the incidence and survival probability of brain tumours using information from the Central Brain Tumour Registry of the United States and the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute.

373. The authors' findings for risk factors associated with primary brain tumours:

a) Reproductive and menstrual factors:

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151 Groves, F.D. et al., 2002, 'Cancer in Korean war navy technicians: Mortality survey after 40 years,' Am J Epidemiol 155: 810-818.

152 De Roos, A.J., et al., 2001, 'Parental occupational exposures to electromagnetic fields and radiation and the incidence of neuroblastoma in offspring,' Epidemiology, 12:508-517.

153 p. S72

> Women have a lower glioma risk (incidence rate of 5.35 in females vs 7.67 in males)… Meningioma is approximately twice as common in women as in men (incidence rate 6.01 vs 2.75).[154]

b) Environmental and behavioural risk factors:

- Ionizing radiation

  > Only one such factor is associated consistently with brain tumour risk – exposure to therapeutic doses of ionizing radiation… There are homogenous and strong results suggesting associations between ionizing radiation and brain tumour risk.[155]

- Cellular telephone use - Further studies are needed as studies are inconsistent.

- The authors found inconclusive, minimal or no evidence for the association between brain tumours and other environmental and behavioural risk factors such as alcohol consumption, tobacco consumption, and exposure to electromagnetic fields.

- The authors also noted that there has been 'no comprehensive review of occupational factors associated with brain tumour risk since 1986'[156]

c) Genetic factors

374. The authors found that familial history and rare mutations of penetrant genes are associated risk factors for brain tumours.

375. Brain tumours seemed to have increase in incidence over the past 30 years, but the rise probably results mostly from use of new neuroimaging techniques.[157]

Council's Comments

376. The review article found inconclusive, minimal or no evidence of a link between exposure to electromagnetic fields and brain tumours in the scientific literature it reviewed.

377. The authors explain that the apparent (recent) increase in prevalence of gliomas is due to improved diagnostic techniques.

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154 p. 875 and Table 1

155 p. 877

156 p. 878

157 p. 884

378. The authors specifically note that the relationship between ionizing radiation and malignant neoplasm of the brain relates to 'therapeutic' levels of exposure, which are multiples of thousands greater than background exposures. As such, no relationship with environmental/occupational exposure was identified.

379. The Council considered the study **leaves open** the relevant association with non-ionising electromagnetic radiation as emitted by radar or radio equipment.

Jauchem, J.R., 1998, 'Health effects of microwave exposures: a review of the recent (1995-1998) literature,' Journal of Microwave Power & Electromagnetic Energy, vol. 33, no. 4, pp. 263-274. RMA ID 15634

380. The purpose of this paper was to review the literature of the health effects of microwaves and other radiofrequency (RF) radiation from the time period 1995 to 1998.

381. The authors explored the areas of the relation between microwaves and cancer and health effects. There was little focus on the association between microwaves and RF radiation and brain cancer specifically.

382. The authors' reviewed two studies for the association of brain tumours and microwaves/RF radiation were:

- Beall et al, 1996[158] found that there was a slightly higher odds ratio among workers involved in the development of video display terminals.
- Grayson, 1996[159] found a significant excess of brain tumours in military personnel who worked with radar (OR 1.39, 95%CI 1.01-1.90).

383. The authors reviewed other studies that looked at the association between all cancers[160] and microwave/RF radiation:

- Lagorio et al., 1997[161] found among a cohort of plastic-ware workers who were potentially exposed to RF radiation exhibited a higher standardized mortality rate from all cancers.
- Finkelstein, 1998[162] found that among police officers there were lower cancer rates than the general population for 13 of 15 specific cancers.

158 Beall, C. et al., 1996, Brain tumours among electronics industry workers, Epidemiology, vol. 7: 125-130.

159 Grayson, JK. 1996. Radiation exposure, socioeconomic status, and brain tumour risk in the US Air Force: a nested case-control study. Am J Epidemiol. 143: 480-486.

160 When the authors refer to 'All cancers' I have assumed that that will include brain cancer.

161 Lagorio, S. et al. 1997. Mortality of plastic-ware workers exposed to radiofrequencies. Bioelectromagnetics. 18: 418-421.

The only two that had increased incidence rates were testicular cancer and melanoma skin cancer.

384. The authors evaluated cellular telephones and the health effects, not brain tumours specifically:

- Rothman et al., 1996[163] found that in a large cohort of 250,000 portable and mobile phone users, there were no difference in age-specific mortality rates between the two types of telephones. They also noted that the data would be too early to reflect the development of cancers.

385. The authors in summary stated:

> On the basis of studies reported in the past several years… one can conclude that the evidence for any proven health effects of low-level microwave exposure is minimal to non-existent.[164]

Council's Comments

386. The Council noted that the reviewed study by Grayson (1996) argues that increased risk is related to (senior) officer status as the effect was no longer significant when adjusted for this (see para 272). Council further noted that there was no identifiable relationship with exposure to radio wave or ionising radiation exposure.

387. The study by Grayson is discussed elsewhere in these Reasons and therefore its data has already been taken into account by the Council and cannot be considered as separate data.

388. The Council noted that there is a difference in terms of exposure between sitting near a device and having it against one's ear (as with a radio in the same cockpit or holding a phone against one's ear) (the inverse square law - see footnote 11).

389. The Council considered the study **leaves open** the relevant association with radiofrequency EMR exposure.

Michaelson, S.M., 1982, 'Health implications of exposure to radiofrequency/ microwave energies,' British Journal of Industrial Medicine, vol. 39, pp. 105-119. RMA ID 5224

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162 Finkelstein, MM. 1998. Cancer incidence among Ontario police officers. Am J Ind Med. 34: 157-162.

163 Rothman, KJ. et al. 1996. Overall mortality of cellular telephone customers. Epidemiology 7: 303-305.

164 p. 270

390. The purpose of this review was to analyse publications about the biological effects of exposure to microwave or radiofrequency (MW/RF) energies.

391. The authors discussed that microwave (300MHz – 300GHz) or radiofrequency (300kHz-300MHz) energies may cause functional, biological or structural alterations as a result of energy absorption and increased thermal effects.

392. The first part of this article discussed the experimental observations from animal experiments and cell cultures, then clinical studies looking at the health effects of MW/RF exposure.[165]

393. For cancer (overall, not brain cancer specifically), the authors reviewed four studies and found that they did not show an excess of any form of cancer to 'date' (ie. 1982) that could be associated with MW/RF exposure (Silverman, 1979[166]; Silverman, 1980[167]; Ruggera, 1980[168]; Barron and Baraff, 1958[169]).

394. The authors in conclusion stated:

> Well-designed and appropriately controlled epidemiological and clinical investigations of groups of workers and others exposed to microwaves should be fostered…Although there is no direct evidence that microwaves are carcinogenic, more intensive and extended morbidity monitoring to identify malignancies would be appropriate.[170]

Council's Comments

395. The Council noted that the microwave effects studied in this paper were not relevant to thermal effects, and noted that the inverse square law means that radiation received depends on proximity and field strength, see footnote 10.

396. The Council considered the study **leaves open** the relevant association with MW/RF exposure.

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165 pp. 106-113

166 Silverman C. 1979. Epidemiologic approach to the study of microwave effects. Bull NY Acad Med 55:1166-1181

167 Silverman C. 1980. Epidemiologic studies of microwave effects. Proceedings of the Institute of Electrical and Electronic Engineers 68:78-84

168 Ruggera PS. 1980. Measurements of emission levels during microwave and shortwave diathermy treatments. Rockville, MD: Bureau of Radiological health. (HHS Publication (FDA) 80-8119)

169 Barron CI, Baraff AA. 1958. Medical considerations of exposure to microwaves (radar). JAMA 168:1194-1199.

170 p. 116

Valberg, PA, 1997, 'Radio frequency radiation (RFR): the nature of exposure and carcinogenic potential,' Cancer Causes and Control, vol. 8, pp. 323-332. RMA ID 23977

397. The purpose of this paper was to review the epidemiologic evidence on the relation between radio-frequency radiation (RFR) and cancer. The author reviewed studies about occupational exposure to RFR and brain cancer and commented that for many studies, any relative risk identified cannot be associated with any one aspect of the exposure/occupational environment.

- Thomas, TL et al., 1987[171] in a study of US males with electrical and electronics jobs found an elevated risk of brain tumours among men with occupational exposure to RFR for more than 5 years, while men who have RFR exposure in jobs not involving electronic and electrical equipment did not have an excess of brain tumour risk. In addition, assemblers who held electronics jobs but were presumably not exposed to RFR had an excess brain tumour risk.

- A WHO review[172] found that the epidemiologic studies of occupations did not provide clear evidence of detrimental health effects in humans from RF exposure.

- Rothman KJ et al., 1996[173] a review that examined leukemia and brain cancer outcomes in association with RF and EMF, found that the results were inconsistent and that links between the occupations studied and the actual exposure was weak.

398. The author reviewed studies about non-occupational exposure to RFR and brain cancer:

- Selvin, S et al,[174] found that there was no association between the distance from a microwave tower and the incidence of childhood leukemia, brain cancer, Hodgkin's and non-Hodgkin's lymphoma.

- Linet, MS and Devesa, SS, 1991[175] and Brown, PN et al., 1989[176] found no association between RFR and cancer.

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171 Thomas TL et al., 1987, Brain tumour mortality risk among men with electrical and electronics jobs: a case-control study. JNCI 79:233-8.

172 WHO. 1993. Environmental Health Criters 137: Electromagnetic fields (300 Hz to 300 GHz). Geneva, Switzerland: WHO: 1-290.

173 Rothman KJ et al. 1996. Assessment of cellular telephone and other radio frequency exposure for epidemiologic research. Epidemiology 7:291-8.

174 Selvin S et al, 1992, 'Distance and risk measures for the analysis of spatial data: a study of childhood cancers'. Soc Sci Med 34: 769-77.

175 Linet, M. S. & Devesa, S. S. 1991, 'Descriptive epidemiology of childhood leukemia', *Br J Cancer*, vol. 63, pp. 424-9.

176 Brown, P. N. et al, 1989, 'Incidence of childhood cancer in Denmark 1943-1984', *Int J Epidemiol,* vol. 18, pp. 546-55.

– Rothman et al., 1996[177] found that there was a slightly lower mortality rate for portable cellular-telephone users.

399. The author also reviewed the mechanism whereby EMR might cause a thermal effect and noted that the mechanism by which a 'hot spot'[178] could be created was not possible at a cellular level for this type of electromagnetic radiation.[179]

400. The author in conclusion stated:

> At the present time, cancer risks from RFR exposure would seem to be small and hypothetical.[180]

Council's Comments

401. The Council noted that the author reviewed the available literature of the day, and found that the epidemiological evidence supporting the concept of carcinogenicity from radiofrequency radiation was lacking, nor was a plausible mechanism found.

402. The Council considered the study **leaves open** the relevant association with RFR exposure.

SUMMARY OF THE COUNCIL'S CONSIDERATION OF THE SOUND MEDICAL SCIENTIFIC EVIDENCE

403. The first critical question in the second step of the Council's review was whether there is sound medical-scientific evidence that indicates ('points to', as opposed to merely 'leaves open') that a contended factor could provide a link or element in a reasonable hypothesis connecting malignant neoplasm of the brain or death from malignant neoplasm of the brain to relevant service. Only if the Council was satisfied of a reasonable hypothesis, did the Council go on to consider the balance of probabilities.

404. The Council, having closely analysed all the information in the pool, placed particular weight on the articles discussed in detail above, which it considered most salient to the questions. In its consideration of the sound medical scientific evidence, the Council looked for evidence of an association between malignant neoplasm of the brain and the contended factor. As noted

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177 Rothman, K. J. et al. 1996, 'Overall mortality of cellular telephone customers', *Epidemiology* vol. 7, pp. 303-305.

178 A 'hot spot' is a volume (of tissue in this instance) receiving an increased radiation dose due to co-inciding of waves of electromagnetic radiation, and thus increased effect would be anticipated.

179 p. 327

180 p. 331

above, malignant neoplasm of the brain as defined in the Statement of Principles, includes gliomas but not benign meningiomas or other benign central nervous system tumours. Thus, the Council paid careful attention to identifying studies that analysed this type of cancer.

Exposure to heat beyond fever temperature and Melatonin depletion due to sleep deprivation.

405. As set out at [123] to [128] above, the Council found no sound medical scientific information available to the RMA that could indicate a relevant association.

Alcohol

406. The Council noted that some studies dealing with alcohol did not clearly identify malignant brain tumours in their analysis, as distinct from benign brain and nervous system tumours. In addition, the Council recognised that several of the papers reviewed explored a number of lifestyle factors, of which alcohol was only one, raising the potential for chance findings. Other papers may not have adequately adjusted for possible confounding by a range of known or unknown factors.

407. The Council was not satisfied that the statistically significant dose-response relationship found by Burch et al 1987 in respect of increasing wine consumption was indicative of a true association in respect of alcohol. The Council considered that the statistical relationship with wine needed to be balanced against the trend towards negative statistical associations with beer and spirits, resulting in no overall significant association with alcohol.

408. The Council, conscious that the reasonable hypothesis test is a test of possibility and an unusually light burden, carefully considered the only remaining article in the available information reporting a positive statistical association between alcohol and brain cancer (Robinette et al 1979). The Council was not satisfied that the association found by Robinette to arise from 5 cases of brain cancer (of which only three were glioma) in more than 4,400 admissions for alcoholism followed for 29 years, points to a relevant association.

409. Having found no sound medical scientific evidence indicating the relevant association, the Council's conclusion is reinforced by the papers by Hochberg and Ruder, which found an inverse association between the consumption of alcohol and MNB, perhaps indicative that alcohol is protective against MNB. The Council noted Hochberg's findings of a decreased RR of glioblastoma incidence of borderline statistical significance while Ruder's findings of statistically significant decreased risk of glioma in 'ever drinkers' vs 'never drinkers' pointed against a relevant association.

410. The Council was therefore not satisfied that there was sound medical-scientific evidence available to the RMA sufficient to justify the inclusion of a factor or factors for alcohol consumption. As the Council found the sound medical-scientific evidence insufficient to justify amendment on the reasonable hypothesis test, it did not go on to consider the balance of probabilities.

Exposure to non-ionising electromagnetic radiation emitted from radio equipment (as used in aircraft)

411. The Council agreed with the Commissions' submission that the available epidemiological studies for these exposures had a number of methodological shortcomings and results which were inconclusive.

412. The Council carefully reviewed the studies by Ballard Gundestrup and Pukkala all of which directly concerned cancer incidence in pilots and/or aircrew. None of these papers specifically addressed the contended factors in respect to radio frequency radiation.

413. The most persuasive of these papers was the meta-analysis by Ballard et al 2000. This paper noted an increased pooled point estimate for the relative risk for brain tumours in flight personnel. In common with most of the flight personnel studies reviewed, the authors were unable to control for a range of other lifestyle factors and occupational exposures, raising questions of confounding in the conclusions about pilots. The authors reported no attempt to disentangle the effects of the contended radio frequency factor from many of other factors that the pilots were exposed to, including cosmic radiation.

414. The Council considered that findings by Band, Irvine and Salisbury which were suggestive of a link between brain cancer and flying and included in Ballard's meta-analysis, relied on a small number of cases and lacked statistical significance, leaving open the question of a relevant association with malignant neoplasm of the brain.

415. The Council conclusions on the absence of sound medical scientific evidence indicating a relevant association were strengthened by the paper by Grayson 1996, which showed no increase in incidence of brain cancer for aircrew when compared with the standard population.

416. The Council also closely analysed the seven studies that looked specifically at exposure to radiofrequency. None of these studies provided evidence pointing to the contended association.

417. The study by Szmigielski was the only paper to present findings of an increased incidence of brain tumours in exposed workers. However, as noted in the summary above, the authors did not identify the type of brain tumour.

The Council also considered that this paper had a number of methodological weaknesses and for these reasons it left open the question of the relevant association.

418. Neither the Berg nor Michaelson papers found a significant association between occupational exposure to RF/MW-EMF and brain tumours. Council considered Elwood's review study to be inconclusive and noted that the results fell short of consistency among the papers reviewed.

419. Groves' large retrospective study of US navy technicians exposed to high-intensity radar, found reduced SMR for exposed workers, and no significant association with brain cancer. Morgan's study of occupational exposure found the SMR for brain cancers was halved in the radiofrequency-exposed workers. The Council considered that this paper and the paper by Groves pointed against the relevant association.

420. The Council considered that the review paper by Valberg which concluded that cancer risks from RFR exposure appeared to be "small and hypothetical", confirmed the absence of sound medical scientific evidence supporting a relevant association.

421. The Council was therefore satisfied that the sound medical-scientific evidence available to the RMA is insufficient to justify the inclusion of a factor or factors for non-Ionising electromagnetic radiation emitted from radio equipment (as used In aircraft) or radar equipment. As the Council found the sound medical-scientific evidence insufficient to justify amendment to the reasonable hypothesis Statement of Principles, it did not go on to consider the balance of probabilities Statement of Principles.

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE A FACTOR(S) FOR THE FIVE CONTENDED EXPOSURES

422. For the reasons discussed in detail above, the Council concluded that the sound medical-scientific evidence available to (before) the RMA at the relevant times was insufficient to justify the inclusion of a factor or factors in the Statements of Principles concerning malignant neoplasm of the brain for any of:

- Exposure to heat beyond fever temperature
- Melatonin depletion due to sleep deprivation
- Alcohol consumption
- Exposure to non-ionising electromagnetic radiation emitted from radio equipment (as used in aircraft)
- Exposure to non-ionising electromagnetic radiation emitted from radar equipment.

DECISION

423. The Council made the declarations summarised in **paragraphs 1 and 2** above.

COUNCIL'S ANALYSIS OF THE NEW INFORMATION

424. The status of the information discussed below is 'new information', that is, it is information that was not available to (not before) the RMA. Accordingly, it the Council did not take it into account for the purposes of the review.

425. Rather, the Council has considered the new information to determine whether, in the Council's view, it warrants the Council making any directions or recommendations to the RMA.

426. In the Council's view any such direction or recommendation should only be made by the Council if it formed the view that the new information:

- comprised sound medical-scientific evidence as defined in section 5AB(2) of the VEA being information which:
- epidemiologists would consider appropriate to take into account; and
- in the Council's view, 'touches on' (is relevant to) any contended factor and has been evaluated by the Council according to epidemiological criteria, including the Bradford Hill criteria; and

- could potentially satisfy the reasonable hypothesis and/or balance of probabilities tests (as appropriate; see paragraphs [108.1] and [108.2] above for the relevant associations).

427. The Council applied these criteria to the 'new information' in Appendix C (ie information that was not available to (not before) the RMA at the relevant times) to which it was referred by the Applicant and the Commissions with respect to the contended factors.

428. The Council considered only two studies provided by the Commissions and the Applicant; Benson et al 2008 and Baglietto et al 2010 fell within that criteria. The Council was independently cognisant of, and included in its consideration of new information, a third and subsequent paper, Galeone et al 2012 which the Council considered met the criteria at paragraph [426] above.

429. The Council considered this new information potentially referrable to the contended alcohol factor.

Benson, V.S., Pirie, K., Green, J., Casabonne, D., Beral, V., 2008, 'Lifestyle factors and primary glioma and meningioma tumours in the Million Women Study cohort,' *Br J Cancer,* vol. 99, pp. 185-190.

430. The purpose of this large prospective cohort study was to examine the effect of anthropometric and lifestyle factors on the risk of developing glioma or meningioma tumours.

431. From May 1996 to March 2001, 1.3 million middle-aged women were recruited into the Million Women Study cohort and asked to complete a questionnaire about socio-demographic factors, reproductive and lifestyle factors.

432. Participants were followed prospectively for cancer incidence from date of recruitment until the date of registration with the tumour of interest, date of death or end of follow-up, whichever was the earliest.

433. The end of follow-up for cancer incidence 31 December 2005 for all registries except 4 registries where follow-up was to 31 December 2004, one was until 30 June 2005 and one was until 31 December 1999. Follow-up was complete for over 99% of the cohort population.

434. Cases were participants who developed any central nervous system tumour, glioma, or meningioma in the follow-up period. Women who were diagnosed with any malignant tumour before recruitment were excluded from the analysis.

435. The authors' findings were:[181]

- Of the 1,249,670 women aged between 50 and 65 years, 1563 incident primary central nervous system tumours were diagnosed after an average 6.2 years of follow-up.

- Alcohol intake was not associated with the incidence CNS tumours, glioma or meningioma (all CNS tumours RR 0.95, 95%CI 0.84-1.08; glioma RR 0.87, 95%CI 0.71-1.06; meningioma RR 1.13, 95%CI 0.88-1.44).

- relative risk for all CNS tumours, glioma and meningioma increased with increasing height, as well as an increased risk for all CNS tumours and meningioma with increasing weight and strenuous exercise.

- smoking status, socioeconomic level, oral contraceptive use other reproductive factors were not associated with the incidence of CNS tumours, glioma or meningioma.

436. The authors considered the weaknesses of their study included:

- exposure data is self-reported.

- majority of the women in the study were moderate drinkers (<1U per day), so this study cannot examine the effects of heavy drinking as that group only represented 5% of the population.

437. The authors in conclusion stated:

> Our findings indicate that increasing height and increasing BMI increase the incidence of all central nervous system tumours, and of both glioma and meningioma tumours.[182]

Council's Comments

438. The Council considered the study does not support the relevant association with alcohol consumption.

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181 pp. 186-188, Table 2

182 p. 189

Baglietto, L., Giles, G.G., English, D.R., Karahalios, A., Hopper, J.L & Severi, G., 2010, 'Alcohol consumption and risk of glioblastoma; evidence from the Melbourne Collaborative Cohort Study,' Int J Cancer, vol. 128, pp. 1929-1934.

439. The purpose of this prospective cohort study was to examine the association between alcohol consumption and the risk of glioblastoma.

440. The authors analysed the data from 39,766 participants of the Melbourne Collaborative Cohort Study (MCCS). The MCCS was a prospective cohort study of 41,514 people living in the Melbourne metropolitan area and aged between 27 and 81 years of age. Participants were recruited between 1990 and 1994 via the electoral rolls and advertisements, and followed until the end of 2008.

441. All participants were asked to complete a questionnaire about demographic details, specific alcohol consumption and dietary habits. It should be noted that the authors defined lifelong abstainers as subjects who never consumed at least 12 alcoholic drinks in a year.

442. Cases were participants with a primary diagnosis of glioblastoma during follow-up between baseline interview and 31 December 2008, and these were determined though the population-based Victorian Cancer Registry.

443. The authors categorized total alcohol consumption into five categories: non-drinkers (0 g/day), 1-19 g/day, 20-39 g/day, 40-59 g/day and 60 g/day or more.

444. Follow-up began at baseline and continued until diagnosis of glioblastoma, other brain/CNS tumours, death, left Australia or 31 December 2008, whichever came first. Less that 1% of participants were loss to follow-up

445. The authors' findings were[183]:

- 67 incident cases of histopathologically confirmed invasive glioblastoma over an average 15 years of follow-up between baseline attendance and 31 December 2008
- Incidence of glioblastoma in this cohort was similar to the general population of Melbourne, Australia, with age standardized incidence ratios of 1.19 (95%CI 0.88-1.62) for males and 0.98 (95%CI 0.67-1.43) for females
- 'Alcohol was positively associated with the risk of glioblastoma. The estimated hazards ratios for glioblastoma for each additional 10 g/day

[183] pp. 1930 -1932, Table 2

of alcohol consumption was 1.16 (95%CI, 1.05-1.29; p-value for linear trend= 0.007).'[184]

- Participants who drink more than 40 g/day of alcohol had a three-fold higher risk of glioblastoma compared to non-drinkers (HR 3.07, 95%CI 1.26-7.47)

- When stratified by sex or amount smoked, there was no difference in the association between alcohol consumption and risk of glioblastoma.

- All types of alcoholic beverages were associated with increased risk of glioblastoma, but not significantly so. For wine, the HR for each additional 10 g/day was 1.17 (95%CI 0.98-1.41) and for beer the HR was 1.23 (95%CI 0.98-1.54).

446. The authors considered the strengths of their study included:

- prospective cohort design

- almost complete follow-up of participants

- detailed measurements of alcoholic beverage consumption

447. The authors considered the weaknesses of their study included:

- relatively small number of cases and single measure of alcohol consumption from baseline, which average alcohol consumption during the current decade of age was recorded

- too few cases to repeat the analyses by censoring after 10 years of follow-up

- effect of cumulative exposure to alcohol on the risk of glioblastoma may be different.

- possibility of residual confounding due to risk factors for glioblastoma such as family history

448. The authors in conclusion stated:

> …alcohol consumption increased the risk of glioblastoma consistent with a dose-response relationship. The increase in relative risk for each additional 10 g/day was 16%; people drinking 40 g/day or more had up to three-fold higher risk relative to non-drinkers.[185]

[184] p. 1931

[185] p. 1933

Council's Comments

449. The Council noted that with every additional 10g of alcohol there was an apparent increased association between brain cancer and alcohol consumption.

450. However, the Council noted the more recent meta-analysis, which specifically addressed studies of alcohol and brain tumours.

Meta-analysis

Galeone C, Malerba S, Rota M, Bagnardi V, Negri E, Scotti L, Bellocco R, Corrao G, Boffetta P, La Vecchia C, Pelucchi C., 2012, 'A meta-analysis of alcohol consumption and the risk of brain tumours.', *Ann Oncol*, vol. 24, no. 2, pp. 514-23.

451. This paper summarises the findings of a meta-analysis of pooled data from several studies that investigated the association between alcohol consumption and risk of brain cancer.

452. The authors noted that as well as being an established risk for other types of cancer, alcohol is capable of crossing the blood–brain barrier and is therefore a possible risk factor for brain cancer.

453. They conducted a systematic review of epidemiological data from 19 studies, (13 case–control and six cohort studies) and data from 12 studies were included in a meta-analysis.

454. The systematic review included over 4200 cancer cases providing risk estimates for total alcohol or specific alcoholic beverage. The authors concluded that alcohol consumption does not appear to be associated with adult brain cancer. The authors cautioned however, that there was a degree of heterogeneity across studies, study design and gender, and that limited data are available for heavy alcohol consumption.

455. The meta-analysis for gliomas and meningiomas showed similar results and did not support any association with alcohol consumption for either subtype.

456. The largest number of studies on a specific alcoholic beverage was available for beer (n = 9). Until the late 1980s to early 1990s beer was a dietary source of nitrosamines, which have been suspected to increase brain cancer risk. The meta-analysis did not support a role for beer drinking in adult brain cancer.

There was no evidence indicating higher risks in early studies, i.e. before the decline in nitrosamine contents in beer, as the summary RR of brain cancer for beer drinking among four studies published up to 1990 was 0.79 (95% CI 0.55–1.13, though more

recent studies include consumption in the past as well). Thus, our findings give little support to the N-nitroso hypothesis.[186]

The authors found no association with wine consumption, but did find a 20% increase in risk for spirits consumption. The results in relation to spirits consumption was reasonably homogeneous across the available studies but the authors considers that the association was, '…modest and was based on limited data. Further confounding is possible … (and in) … the absence of associations with other beverages containing ethanol, these findings should be considered as merely indicative.'

457. There were few studies on high alcohol consumption; two finding an increased risk for heavy drinkers, two finding no association and:

> …overall, a moderate, non-significant increase in risk emerged, mainly based on findings from cohort studies.[187]

458. The authors concluded from their systematic review of epidemiological data, that:

> …alcohol consumption does not appear to be associated with adult brain cancer.'[188]

Council's Comments

459. The Council considered it important that when the data from all relevant studies were pooled, the risk of glioma for alcohol drinkers versus non-drinkers was slightly reduced (RR 0.93). The relative risk of all adult brain cancers for those who had <2 drinks per day, versus non-drinkers, was null (1.01).

460. Council considered the study **leaves open** the relevant association with alcohol consumption.

461. The Council noted that the study incorporated data from both the Baglietto and Benson papers referred to above, as well as other studies on the subject. The Council considered therefore that it has a greater relative epidemiological weight than the individual data of those and other earlier papers.

THE COUNCIL'S CONCLUSIONS ON THE NEW INFORMATION

462. In this Council's view, Baglietto's findings of an apparent association, were against the findings of equally valid studies (as included in Galeone's meta-analysis). The Council has not investigated other current relevant literature,

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186 p. 521

187 p. 521

188 p. 151

and therefore refers these three papers to the RMA for its consideration within the context of the full body of literature on this topic.

EVIDENCE BEFORE THE COUNCIL

463. Second preliminary list of the proposed pool of information, as advised to the Applicant and the Commissions by letters dated 16 July 2012 (see [46]) is listed in **Appendix A**.

This list also identifies the information upon which the Council understands the Applicant and the Commissions relied (being information which the RMA advised was available to (before) the RMA at the relevant times and which the RMA sent to the Council in accordance with section 196K of the VEA).

464. Information forwarded to the Council under section 196K of the VEA referable to the Council's review of Statements of Malignant Neoplasm of the Brain Nos. 58 and 59 of 2008 as amended by Amendment Statements of Principles Nos. 37 and 38 of 2011, is listed in **Appendix B**.

465. The information to which the Applicant, the Commissions and the Council referred (being information which the RMA advised was new information, that is, information which was not available to (not before) the RMA at the relevant times, and so was not considered by the Council in reaching its review decision) is listed in **Appendix C**.