Specialist Medical Review Council

Reasons for Decisions

Section 196W
Veterans' Entitlements Act 1986

Re: Statements of Principles Nos. 13 & 14 of 2009
In Respect of Macular Degeneration
Matter No. 2009/16
Request for Review Declaration No.16

SUMMATION

1. In relation to the Repatriation Medical Authority (the RMA) Statement of Principles No. 13 of 2009 in respect of macular degeneration and death from macular degeneration, made under subsection 196B (2) of the *Veterans' Entitlements Act 1986* (the VEA), the Specialist Medical Review Council (the Council) under subsection 196W of the VEA:

DECLARES that it is of the view that there is sound medical-scientific evidence on which the RMA could have relied to amend the Statement of Principles to include the factors set out below; and

DIRECTS the RMA to amend Statement of Principles No. 13 of 2009 by including the following factor in respect of ***passive smoking***:

– **For late macular degeneration only:**
being in an atmosphere with a visible tobacco smoke haze in an enclosed space for at least 10 000 hours within the 20 years before the clinical onset of late macular degeneration, and where the person was a non-smoker during the entire period of the exposure.

2. In relation to the RMA Statement of Principles No. 14 of 2009 in respect of macular degeneration and death from macular degeneration, made under subsection 196B (3) of the VEA, the Council under subsection 196W of the VEA:

DECLARES that it is of the view that the sound medical-scientific evidence available to the RMA is insufficient to justify an amendment to include a factor for exposure to passive smoking or any other factor.

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. If the Council 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.

4. When a review is undertaken the Council is constituted by three to five Councillors selected by 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.

5. Dr David Newman was the Presiding Councillor for this review. 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 head of the Aviation Medicine Unit in the Department of Epidemiology and Preventive Medicine at Monash University.

6. The other members of the Council were:

(i) Professor Robyn McDermott

Professor McDermott is a clinical epidemiologist and a National Health and Medical Research Council practitioner fellow at the University of South Australia. She specialises in chronic disease epidemiology and is also the foundation director of the state-wide data linkage unit, SA-NT DataLink.

(ii) Professor Paul Mitchell

Professor Mitchell is a leading retinal ophthalmologist and an international speaker on macular degeneration. Professor Mitchell was the principal investigator of the Blue Mountain Eye Study. Professor Mitchell is a member of the discipline of ophthalmology at the University of Sydney, Director of the Eye Clinic at Westmead Hospital and a world expert in the epidemiology of macular degeneration.

(iii) Associate Professor Justin O'Day

Professor O'Day is an ophthalmologist and has worked throughout Australia (including in rural Victoria), London, Southern Sudan and as a World Health Organisation consultant.

THE LEGISLATION

7. 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)[1].

8. 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. [2]

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

2 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.

9. 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:

- Statement of Principles No. 13 of 2009, in respect of macular degeneration and death from macular degeneration, being a Statement of Principles determined by the RMA under section 196B(2)[3] of the VEA ('the **reasonable hypothesis** test') and

– Statement of Principles No. 14 of 2009, in respect of macular degeneration and death from macular degeneration, being a Statement of Principles determined by the RMA under section 196B(3)[4] of the VEA ('the **balance of probabilities** test').

10. 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. 13 and 14 of 2009, exposure to passive smoking.

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[3] 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

(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.

[4] 196B(3) provides;

If the Authority is of the view that on the sound medical-scientific evidence available it is more probable than not that a particular kind of injury, disease or death can be related to:

(a) eligible war service (other than operational service) rendered by veterans; or

(b) defence service (other than hazardous service and British nuclear test defence service) rendered by members of the Forces; or

(ba) peacetime service rendered by members;

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

(c) the factors that must exist; and

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

before it can be said that, on the balance of probabilities, an injury, disease or death of that kind is connected with the circumstances of that service.

11. 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]

12. 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

Application for review by the Council

13. On 24 April 2009, the RMA under subsections 196B(2) and (3) of the VEA determined Statements of Principles Nos. 13 and 14 of 2009, in respect of macular degeneration. The Statements of Principles took effect from 6 May 2009.

14. On 30 April 2009 the Statements of Principles were registered on the Federal Register of Legislative Instruments.

15. On 12 May 2009 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.

16. An Application for Review of Statements of Principles Nos. 13 and 14 of 2009 was received by the Council on 7 July 2009. The Application contended that the Statements of Principles should include a factor or factors concerning exposure to passive smoking.

17. 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 macular degeneration and invited eligible persons or organisations so authorised to make submissions to the Council. [6] The Council gazetted two 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

18. By letter dated 21 September 2009 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.

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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.

6 Gazette Notice No. 35 of 9 September 2009 p. 2358.

7 Gazette Notices No. 2 of 20 January 2010 and No. SG231 of 30 December 2010.

19. 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 participants in the review via confidential password. The information which was available to (before) the RMA at the relevant times was posted on FILEForce on 8 October 2009.

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

20. In separate letters, dated 15 June 2011, to each of the Applicant and the Commissions, the Council in summary:

- advised of the Council's preliminary decisions on the 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 preliminary decisions by close of business on 18 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.

21. No comments were received.

22. The Council held a meeting on 9 August 2011 to consider all the written submissions and complementary oral submissions.

Proposed Scope of Review

23. The Council's preliminary decision on the scope of the review, as advised to the Applicant and Commissions on 15 June 2011, was as follows:

> Without limiting the scope of the Council's review of some or the whole of the contents of Statements of Principles No. 13 and 14 of 2009, in respect of Macular Degeneration … the Council 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 by the possible inclusion of 'passive smoking' as a factor for clinical:
>
> (a) onset; and/or
>
> (b) worsening
>
> of macular degeneration.

Proposed Pool of Information

24. 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 determined the original Statements of Principles in respect of macular degeneration 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 which was available in April 2009 when the RMA determined the Statements of Principles under review. 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 macular degeneration which was in the possession of the RMA at the time it (the RMA) made the decision that triggered the Council's review.

25. The chronology of the RMA sending the information to the Council is detailed in [18]. As mentioned above, all the information which was available to the RMA at the relevant times was made available to the Applicant and the Commissions for the purposes of the review.

26. In determining its preliminary view on the proposed pool of information the Council applied the methodology it had advised the Applicant and Commissions on 15 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 which:
  (1) epidemiologists would consider appropriate to take into account; and
  (2) in the Council's view 'touches on' (is relevant to) passive smoking; and
- which has been evaluated by the Council according to epidemiological criteria, including the Bradford Hill criteria.[8]

27. Information which 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'.

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

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[8] 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.

APPLICANT'S SUBMISSIONS

29. The Applicant made:

- two written submissions (the first submitted with his Application dated 3 July 2009 and the second dated 17 February 2011), and
- an oral submission complementing his written submissions on 9 August 2011

all of which were taken into account by the Council. [9]

30. In his Application to the Council of 3 July 2009, the Applicant stated that his grounds for review were as follows:

> … the applicant who requested [an investigation by the RMA] … spent a high percentage of his off duty time in the smoke contaminated Officers' Mess i.e. the source of his contention re Passive Smoking.
>
> He was a non-smoker and like many other non-smoking veterans he was subjected to passive smoking not only on service but also post service in all walks of life such as office/factory, on various types of transport in fact where ever smoking was partaken.
>
> Irrespective of rank a veteran in a confined space would inhale cigarette smoke laden air every time he/she breathes which on average is every second i.e. 60 per minute, whereas the confirmed smoker if smoking say 20 per day over 12 hours is inhaling a lesser quantity of smoke at a much slower rate depending how quickly the cigarette was smoked.
>
> In a densely crowded smoke filled mess hall non-smoking veterans, are in such an environment as if he or she were actually holding the cigarette...

31. In his written submission dated 17 February 2011, which was received by the Council on or about 23 February 2011, the Applicant contended that:

> …the non-smoking veteran has been overlooked at the expense of the smoking veteran.
>
> … A disease or any medical condition suffered is not due to the physical mechanics of smoking it is due to the mechanics of breathing ie exposure from the actual products of smoking; smoke and the many ingredients it contains.
>
> …in a crowded situation, it doesn't matter who is actually smoking the cigarette every veteran present is breathing in contaminated air at a general rate of 60 breaths per minute and subsequently is open to harmful effects. On service the veterans both smoker and non-smoker were in many crowded situation[s] such as mess rooms, recreation halls, troopship/trains to name a few and post service in all walks of life until bans started of recent times…
>
> The labelling of two distinct types i.e. active and passive smoking is wrong. In a smoke contaminated environment, both are subjected to the same detrimental contaminated air…

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[9] 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.

32. The Applicant submitted that according to his 'rough calculations':

> A person breathing is taking in something like 60 breaths a minute, which in an hour is 3,600 breaths. Now, if he's in a smoke contaminated area, he's doing a lot of contaminated breathing. [10]

33. The Applicant submitted that veterans in earlier conflicts, such as World War II, were exposed to extremely high levels of environmental tobacco smoke within confined spaces. He asked the Council to consider that these levels of exposures might have been much higher than those to which non-veterans are ordinarily exposed.

34. The Applicant submitted, in his written submission of 17 February 2011, that from his research there had not been any:

> 'in depth' investigational studies… regarding the relationship between macular degeneration and passive smoking…

35. However, he submitted that environmental or passive smoking is of major concern worldwide. He submitted that this was evidenced by Government legislation which bans smoking from many public areas.

36. In his oral submission complementing his written submissions, the Applicant contended that his research had shown that:

> there has [not] been much worldwide study [but] there's a large group of people …who are concerned with … 'passive smoking'. [11]

37. In his written submission of 17 February 2011, the Applicant referred the Council to the following two documents (listed in Appendix D):

- An abstract of a review by Lois et al (2009). While the Lois et al abstract as cited by the applicant was not in the information available to the RMA at the relevant times (and so could not be taken into account in the review), the Lois et al review itself was included in the information that was before the RMA at the relevant times. The review was taken into account by the Council and is discussed below.
- A medical news article by Barclay (2008), which is a summary of a study by Klein et al (2008). While the news article was not in the information available to the RMA at the relevant times (and so could not be taken into account in the review), the Klein study itself was included in the information that was available to the RMA at the relevant times. The study was taken into account by the Council and is discussed below.

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10 See at page 7 of the transcript of oral submissions.

11 See at page 6 of the transcript of oral submissions.

Applicant did not comment on the Proposed Scope of the Review and Proposed Pool of Information decisions

38. The Applicant made no comment on the Council's proposed scope of review and proposed pool of information decisions, other than to refer to the new information noted above.

SUBMISSIONS BY THE COMMISSIONS

39. The Commissions made a written submission dated January 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 9 August 2011. [12]

40. The Commissions noted that active smoking is an existing factor in both the reasonable hypothesis and balance of probabilities Statements of Principles, and submitted that the RMA had extensive evidence available to it at the relevant times supporting the relevant association between active smoking and macular degeneration.[13]

41. The Commissions submitted that there was limited evidence on passive smoking and macular degeneration in the information available to the RMA at the relevant times. [14]

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12 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 E.

13 See at [34] and [48] of the Commissions' written submission.

14 See at [23] of the Commissions' written submission.

42. Of the information that was available to the RMA at the relevant times, the Commissions submitted that the following studies touched on the matters within the scope of review:

- **Klein et al (2008)**, [15] of which the Commissions submitted:[16]
  Exposure to ETS [17] was not associated with the prevalence, 5-year incidence or progression of AMD [18] in men or women. No data were provided. The five-year incidence of both exudative AMD [19] and pure geographic atrophy [20] was too low to examine the association between exposure to ETS and those endpoints. [21]
- **Klein et al (1993**), of which the Commissions submitted:[22]
  Current exposure to passive smoking was not associated with early ARM, [23] exudative AMD nor geographic atrophy. Data were not provided.
- **Khan et al (2006)**, in respect of which the Commissions submitted: [24]
  In non-smokers [25] passive smoking exposure was associated with an increased risk for AMD with an odds ratio (OR) of 1.87 (95% confidence interval [CI], 1.03-3.40) in all non-smoking cases (n=158).
- **Smith et al (1996)** in respect of which the Commissions submitted: [26]
  the study found passive smokers [27] were at increased risk for "late AMD", but the results did not reach statistical significance. For males and females combined, the

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15 The representative of the Commissions noted in his complementary oral submissions that these two reports, of which Klein was the lead author, were of the Beaver Dam study.

16 See at [26] of the Commissions' written submission.

17 Environmental tobacco smoke.

18 Age-related macular degeneration.

19 A form of late age related maculopathy, see Klein et al at page 190.

20 Another form of late age related maculopathy, ibid.

21 In his oral submission complementing the Commissions' written submission, the Commissions' representative submitted that the Klein 2008 study was:
the best starting point … prospectively gathered data, prospectively followed - prospective follow-up and the passive smoking exposure assessment in that was probably the best that was available in that they took account of workplace, social and home exposure, whereas the other studies tended to just look at exposure in the home.
So this would be the best study to look at the association if it was long enough and had enough cases, which it doesn't on either account really. .. (Transcript of oral hearing at page 13).

22 See at [28] of the Commissions' written submission.

23 Age-related maculopathy. The Councillors considered that the classifications previously applied on the basis of the original Beaver Dam study - of age-related macular degeneration, which was late stage and maculopathy which included early stage - should be ignored, in favour of categorising the whole disease as early or late stage age-related macular degeneration (AMD), see [62].

24 See at [30] of the Commissions' submission.

25 The Commissions noted that a passive smoker was defined in the Khan et al study as a never smoker living in the same house as a smoker for at least five years.

26 See at [32] of the Commissions' written submission.

27 Which the Commissions noted were defined in the Smith article as a never smoker whose spouse was a smoker.

odds ratio for any late AMD for passive smoking vs. non-passive smoking (in never smokers) was 1.42 (95% CI, 0.62 to 3.26).

43. The Commissions submitted that the Khan and Smith studies provided data on passive smoking and found an elevated risk for late AMD. However, the Commissions submitted that the results reached statistical significance only in the Khan study and only for late AMD combined.[28]

44. The Commissions submitted that the studies demonstrated that :

An association between passive smoking and early ARM was not found in any study [29]

and so submitted there was no relevant association between passive smoking and early age-related maculopathy. [30]

45. The Commissions further submitted that:

the strength of the possible association between passive smoking and late AMD would appear to be limited at best.[31]

46. However, the Commissions submitted that the lack of statistically significant associations for passive smoking and late AMD:

may be attributable to the limited power of the studies to detect such associations, due to small case numbers. The Kahn (sic) et al case-control study, that did find the only significant association, was multi-fold larger than the two cross sectional-studies, in terms of case numbers of late AMD.[32]

47. The Commissions acknowledged that an association between passive smoking and late AMD was biologically plausible:

Active smoking is an established risk factor for late AMD and passive smoking has been causally implicated in other diseases for which active smoking is a risk factor, so it is biologically plausible that passive smoking could cause late AMD. [33]

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28 See at [44] of the Commissions' written submission.

29 See at [45] of the Commissions' written submission and at [30] of the transcript of the oral hearing.

30 The Commissions' representative in his oral submission complementing the Commissions' written submission summarised the evidence which he contended supported the Commissions' submission that there was no relevant association with early onset macular degeneration as follows:

> …for early disease we've got no association in the Blue Mountain study, no association in the Beaver Dam study, an indication – in the cross-sectional Beaver Dam study – an indication of no association in the prospective data, because they looked at disease overall, about 90 per cent were early, so that's an indication of no association there. And the Kahn (sic) study didn't report, so we've got no positive evidence there, so …. for the Commission that's a fairly easy question, there's no basis for putting in a passive smoking factor for early disease ([30] of page 16 of the transcript of the oral hearing).

31 See at [47] of the Commissions' written submission.

32 See at [46] of the Commissions' written submission.

33 See at [48] of the Commissions' written submission.

48. The Commissions concluded their written submission by submitting that:[34]

* the Council should carefully consider whether the limited available evidence is sufficient to raise a reasonable hypothesis to indicate that late AMD can be caused by passive smoking; [35]

* the available evidence does not establish on the balance of probabilities that late AMD can be caused by passive smoking; and

* the available evidence indicates that there is no association between passive smoking and early ARM and is insufficient to establish this at the balance of probabilities standard of proof.

… If a clinical onset factor for passive smoking was to be included then the Commission[s] would see it as appropriate to also include a clinical worsening factor.

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

49. The Commissions sought no amendment to the Council's proposed scope of review, but there was discussion in the Commissions' written submission, [36] and with the Council at the hearing of oral submissions, about differing terminology used when describing the disease vis a vis the definition of the disease in the Statements of Principles. [37] Many papers refer to the condition as age-related maculopathy and others as age-related macular degeneration. These terms are equivalent and are two of the many terms used for the same condition. The Statements of Principles relates to late macular degeneration and the Council in these Reasons similarly refers to late macular degeneration.

50. The Commissions did not propose any alteration to the Council's proposed decision on the pool of information.

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34 See at [49] of the Commissions' written submission.

35 The Commission's representative in his oral submission complementing the Commissions' written submission submitted that the evidence:

> falls short of the balance of probabilities standard but it's quite interesting at the reasonable hypothesis test as to whether that is enough or not.
>
> Now, the Commission doesn't actually want to offer a conclusion about that, that's my specific instructions from the Commission, so I'm not going to … offer a particular view about whether there should be a factor in the reasonable hypothesis SOP for passive smoking for late stage disease. But I would say that it's pretty close to the mark and it's certainly worthy of close consideration (see [10] of the transcript of the oral hearing at page 17).

36 See at [18] - [22].

37 See at pages 11 - 13 of the transcript of the oral hearing.

REASONS FOR THE COUNCIL'S DECISION

The Council's Task

51. 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 [8] 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.

52. The second step required the Council to determine whether the sound medical-scientific evidence in the pool of information:

52.1. 'points to' (as opposed to merely 'leaves open') [38] the relevant possibility whether exposure to passive smoking (if found to exist in a particular case) could provide a link or element in a reasonable hypothesis connecting macular degeneration or death from macular degeneration to relevant [39] service.[40] 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.' [41]

52.2. concerning passive smoking (if found to exist in a particular case) could provide a relevant connection between macular degeneration or death from macular degeneration and relevant [42] service according to a standard of satisfaction 'on the balance of probabilities', or as being more probable than not.

53. In these Reasons the association for both the **reasonable hypothesis** test (at [52.1] and the **balance of probabilities** test at [52.2]) are respectively referred to as the 'relevant association'.

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

39 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.

40 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].

41 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].

42 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.

54. It was with these tests firmly at the forefront of its collective mind 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.

55. In forming its judgement on whether the sound medical-scientific evidence 'pointed to' (as opposed to merely 'leaving open') the relevant association, the Council was conscious that the reasonable hypothesis test is ‘a test of possibility’ [43] and ‘an unusually light burden.’ [44] If the reasonable hypothesis test was found not to be satisfied, the balance of probabilities test necessarily could not be met.

Scope of Review

56. The Council's final view on the scope of the review was that it should comprise the scope which the Council had identified on a preliminary basis in respect of exposure to passive smoking (see [20]).

Pool of Information

57. 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 preliminary basis as listed in Appendix A.

58. In reaching this 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.

59. 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 D). As mentioned above, 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.

THE COUNCIL'S ANALYSIS OF THE INFORMATION BEFORE THE RMA

Preliminary comment on age-related macular degeneration

60. Set out below are some general and introductory comments on age-related macular degeneration and the Council's analysis of the information in the pool.

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

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

61. Statements of Principles Nos. 13 and 14 of 2009 define macular degeneration, also known as age-related macular degeneration as meaning:

> degenerative changes involving the macula of the eye, either involving soft drusen or pigmentary abnormalities (early age-related macular degeneration) or geographic atrophy or choroidal neovascularisation (late age-related macular degeneration). This definition excludes toxic maculopathy.

62. The Council noted that age-related macular degeneration may involve early or late stage disease. Clinicians now see this as a continuation of the same disease process rather than as two separate categories of disease. [45] However, most epidemiological studies distinguish in their analyses between the stages and between sub-types of the disease. In these Reasons, the Council refers to age-related macular degeneration (AMD). The Council distinguishes between early and late stage disease, but does not distinguish (unless otherwise stated) between different sub-types of the disease.

DOES THE SOUND MEDICAL-SCIENTIFIC EVIDENCE 'POINT TO' OR 'LEAVE OPEN' THE RELEVANT ASSOCIATION

63. As mentioned above, having settled the pool of information, the second question for the Council to consider was whether the sound medical-scientific evidence in the pool of information 'points to' a contended factor in the scope of the review as a link or element in a reasonable hypothesis connecting macular degeneration to relevant service (see [52.1] and footnotes), and if so, whether the relevant association exists on the balance of probabilities (see [52.2] and footnotes).

64. As mentioned above, 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.

65. 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. The Council agreed with the submissions of the Applicant and the Commissions that the information touching on passive smoking is limited.

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[45] As stated above, previous classifications described early stage age-related macular degeneration as age-related maculopathy, see [49].

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

THE REVIEW COUNCIL'S ANALYSIS OF THE INFORMATION IT CONSIDERED MOST IMPORTANT AS BEING POTENTIALLY REFERABLE TO THE CONTENDED FACTOR

Original Studies

Klein, R, Klein, BEK, Linton, KLP & DeMets, DL 1993, 'The Beaver Dam Eye Study: The Relation of Age-related Maculopathy to Smoking', *Am J Epidemiol,* 137(2), pp. 190-200. (RMA ID 06408)

67. The authors conducted a cross-sectional analysis of data from the Beaver Dam population study, with retrospective exposure assessment of AMD outcomes. The potential association was analysed in 4771 participants aged 43-84 years. Data were collected by questionnaire and fundus photography and a standardised grading system for lesions was applied. [46]

68. The authors defined a subject as a passive smoker if he or she was either a never smoker [47] or an ex-smoker, [48] living in a household with a current smoker.[49] 362 females and 335 males were classified as passive smokers.

69. The authors found no association between cigarette smoking (active or passive) and early AMD.[50] They also found that current exposure to passive smoking was not associated with late stage AMD. [51]

Council's comments

70. The Council considered this to be an important and well-conducted study, while noting the limitations that occur in all cross-sectional studies, including that the assessment of exposure levels can be subject to error and possible recall bias. The Council noted that this study did not find any association between passive smoking and AMD. Measurement of the exposure to passive smoking was not quantified and data were not provided.

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46 See at page 191.

47 Defined as someone who had smoked less than 100 cigarettes in his or her lifetime (see at page 192).

48 Defined as someone who had smoked more than 100 cigarettes in his or her lifetime, but who had stopped smoking before the examination, ibid.

49 Defined as someone who had not stopped smoking, ibid.

50 See at page 195.

51 See at page 196.

71. The Council noted, however, that a methodological limitation of this study was that it grouped ex-smokers together with non-smokers in the passive smoking analysis. The Council considered that this may have limited the ability of the study to detect a difference between the exposed and non-exposed groups.[52]

72. The Council considered that this study did not support the relevant association.

Klein, R, Knudtson, MD, Cruickshanks, KJ & Klein, BEK 2008, 'Further Observations on the Association Between Smoking and the Long-term Incidence and Progression of Age-related Macular Degeneration. The Beaver Dam Eye Study', *Arch Ophthalmol,* 126(1): 115-21. (RMA ID 49688)

73. The authors conducted a follow-up analysis of the Beaver Dam cohort, to analyse potential associations between a number of factors and outcomes of AMD incidence and progression. They examined exposure to environmental tobacco smoke (ETS) over the final five year interval of the study. ETS exposure was first measured in 2480 subjects at the ten year follow-up and outcomes were measured five years later for the surviving 2119 subjects. Data for ETS exposure were gathered by combining information from reported home, social and workplace exposures among non-smoking participants. Past smokers and never smokers were categorised as passive smokers if exposed.[53]

74. High ETS exposure was categorised as:

- more than four hours of workplace exposure daily;
- living with a smoker; or
- social exposure on a daily basis.

75. Moderate exposure corresponded to one to four hours per day in the workplace or socially several times per week. [54]

76. Analyses were adjusted for age, sex and baseline diagnosis and took into account the effects of the level of alcohol consumption, vitamin use and systolic blood pressure on the results.

77. For current smokers compared to never smokers, the incidence of early AMD and AMD progression were significantly elevated at 15 years. [55] Age at quitting was related to progression, but no relationship was displayed with past smoking, or intensity of smoking in relation to the progression of AMD. [56]

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52 See at pages 192-193.

53 See at page 116.

54 See at page 116.

55 See at page 120.

56 See at pages 117 and 118.

78. There was an association between active smoking and late AMD. The authors suggested a number of reasons why a strong association between smoking and late AMD was not found. In particular, the authors noted the limitations arising from participants' smoking status being assessed only at baseline. Many participants who may otherwise have been at risk for AMD would have quit smoking by age 65. [57] This left too few smokers in the study to determine whether there were any differences between smokers and non-smokers and the development of late AMD.

79. Whilst the authors stated that exposure to ETS was not associated with the prevalence, incidence or progression of AMD over the five year period, they did not provide any data in relation to the analysis of ETS. [58]

Council's comments

80. The Council noted that this study was the follow-up of the Beaver Dam study, but with analysis of prospective data.

81. The Council noted that this was the first major study which attempted to quantify occupational exposure to passive smoking, although it did this on an average daily basis and did not report total exposure duration. A limitation was that, as the study was conducted with older participants, much of the estimation of workplace exposure was dependent on the memory of the participants or their spouses.

82. This was also one of the few studies which attempted to control for other factors which potentially could have confounded the analyses, such as alcohol, nutrition and cardiovascular indicators. However, the Council considered that it was subject to the limitation that many subjects may have died from other causes before it could be determined whether they had developed AMD.

83. As with the earlier Beaver Dam study, past smokers were included with non-smokers in the analysis of passive smoking. The Council considered that this method of classifying exposure to passive smoking may have limited the ability of the study to detect differences between the exposed and non-exposed groups. The findings of this follow-up study did not support the relevant association. However, the Council also noted that no detailed statistical analysis of the findings in relation to ETS was provided and the Council considered this to be a major limitation of this study.

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57 See at page 120.

58 See at pages 118 and 120.

Smith, W, Mitchell, P & Leeder, SR 1996, 'Smoking and Age-Related Maculopathy: The Blue Mountains Eye Study', *Arch Ophthalmol,* Vol 114 pp. 1518-1523. (RMA ID 13646)

84. This representative cross-sectional Australian study, known as the Blue Mountains Eye Study, was of 3654 subjects older than 49 years. The aim of the study was to assess any association between AMD and passive smoking. The authors measured AMD using standardised clinical assessment measures. Smoking history was ascertained using interviewer assisted questionnaire.

85. Passive smokers were defined as subjects who had never smoked, but whose spouse was a smoker. [59]

86. Current smoking was found to be significantly associated with both late and early AMD after adjusting for age and sex. [60] The odds ratio for the association between current smoking (versus never smoking) and late AMD was high (OR 4.46, 95% CI 2.20-9.03), but for early stage AMD was of a lower magnitude with an OR of 1.89 (95% CI 1.25-2.84). Past (ever versus never) smoking was also found to be significantly associated with late AMD at a lower magnitude (OR 1.83, 95%CI 1.07-3.13), though not with early AMD which had an OR of 1.03 (95% CI 1.93-1.14). The authors found little convincing evidence of a dose response relationship.

87. There were 30 cases of late AMD among passive smokers. The authors found a moderate but non-significant increase in the risk of late AMD (OR 1.42, 95% CI 0.62-3.26) for passive smokers, who had never themselves smoked, but who lived with a smoking spouse. [61] No association was found between passive smoking and early AMD (OR1.00, 95% CI 0.63-1.59). [62]

88. The authors posited that the lack of statistical significance may reflect the low statistical power of the study.

Council's comments

89. The Council considered this study was important, in particular because:

- it examined a large sample of adults who were highly representative of the Australian population at the time;
- of its methodological quality; and
- it attempted to explore any relationship with other (dietary) exposures, although none were found.

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59 See at page 1519.

60 See at page 1520.

61 See at page 1520.

62 See Table 3 at page 1521.

90. However, the Council considered the study was subject to the limitations of cross-sectional analyses, in particular, the difficulty in accurately measuring the level of exposure retrospectively. At the time this study was conducted, few studies recognised the importance of gathering quantitative data on exposure to environmental smoke, or lacked the resources to do so.

91. The study differed in its exposure classification from the Klein et al study. In this study, only never-smokers were included in the passive smoking group, whereas in the Klein study, ex-smokers were also included. The Council considered that a particular strength of this paper was that only never smokers were included in the passive smoking analysis. This strengthened the ability of the analysis to detect an association if one were present. In contrast, the two Klein papers may not have found an association because they included ex-smokers as passive smokers, which could have confounded the ability to detect an effect of passive smoking.

92. The study's findings suggested a positive association between passive smoking and late AMD; and the Council agreed that the lack of statistical significance may have been due to the low case numbers.

93. The Council considered that the findings from this study point to the relevant association. In the Council's view, the findings did not satisfy the balance of probabilities test.

Khan, JC, Thurlby, DA, Shahid, H, Clayton, DG, Yates JRW, et al 2006, 'Smoking and age related macular degeneration: the number of pack years of cigarette smoking is a major determinant of risk for both geographic atrophy and choroidal neovascularisation', *Br J Ophthalmol*, Vol. 90, pp. 75-80. (RMA ID 37432)

94. In this UK case control study, the authors examined confirmed late stage AMD in one or both eyes of participants, all of whom were white and aged over 50 years. Controls were recruited from spouses of the cases and accepted even if they had early stage AMD. Passive smokers were defined as never smokers who had lived in the same house with a smoker for at least five years. [63] Results were adjusted for age and sex.

95. Passive smokers were found to have an almost doubled risk of all AMD (OR 1.87, 95% CI 1.03-3.40), [64] compared to non-smokers without passive smoke exposure. For sub-types of AMD an increased relative odds was shown which did not reach statistical significance, possibly due to smaller numbers of available cases for analysis.

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63 See at page 76.

64 See at page 75.

96. In former smokers, the authors found that risk decreased as time since quitting increased. The risk for those who had not smoked for over 20 years was comparable to that of non-smokers. [65]

Council's comments

97. The Council noted the methodological shortcomings of case control studies generally, including retrospective recall of exposures. The Council considered that this study suffered from an inadequate level of measurement, as the authors did not take into account different workplace exposures. However, the Council did acknowledge that this type of study has some positive features. It allows for a greater number of cases to be identified (435 in this study) whereas prospective studies require a very large number of participants and tend to identify fewer cases. In this study 158 cases were examined with data on passive smoking, as only non-smokers were included in that analysis.[66]

98. The Council considered that a positive feature of this study was that the authors attempted to quantify the level of exposure to passive smoking by classifying it as *'at least five years'* of living with a smoker, although because the study was conducted with older participants, the Council considered it was likely that the exposure could have continued for much longer than five years.

99. The Council considered that an important limitation of this study was that the controls used were spouses of participants (although controls were not necessarily matched with their own spouse). The Council considered that this weakened the study, which would have been stronger had controls been matched from a randomly sampled population of healthy persons. The Council also considered that including as controls some persons with early stage eye disease was a methodological weakness, although it was more likely to have biased the results against detecting an association, so did not weaken the conclusions.

100. A further weakness was that the study only adjusted for age and gender, and made no attempt to adjust for other potential confounders such as family history and diet.

101. The Council nevertheless considered that the overall findings of the study were not invalidated by the methodological weaknesses. The study remained, in the Council's view, a persuasive study in favour of the relevant association. The Council considered important the study's finding that subjects who stopped smoking more than 20 years ago had no greater risk of developing AMD than non-smokers.

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65 See at page 78.

66 See at page 76.

102. The Council considered that despite the methodological limitations of this study, the findings 'point to' the relevant association. In the Council's view the study did not satisfy the balance of probabilities test.

Chakravarthy, U, Augood, C, Bentham, GC, de Jong, PTVM, et al 2007, 'Cigarette Smoking and Age-Related Macular Degeneration in the EUREYE Study', *Ophthalmology*, 114(6), pp. 1157-1163. (RMA ID 44748)

103. This study examined the association between smoking and AMD in a representative sample of 4750 participants aged over 65 years. Data were gathered from seven centres across Europe (the EUREYE study).

104. Participants were categorised as never smokers, ex-smokers (further sub-categorised by years since quitting smoking) and current smokers.[67] Age, gender, diabetes, socioeconomic status and history of cardiovascular disease were all identified as potentially confounding. [68]

105. The strongest association found was for current smokers (OR 2.91, 95% CI 1.66-5.08).[69] All ex-smokers had an elevated risk of AMD (OR 1.69, 95% CI 1.10-2.59).[70] However, no association was observed in those who had quit smoking more than 20 years previously. Their odds of developing the disease were similar to those of never smokers. [71]

106. The authors contended that their study provided additional evidence for the association between active smoking and AMD. They noted that the small number of cases in individual studies (for example, the Beaver Dam study and the Blue Mountains study) provided limited statistical power to detect an association. [72]

Council's comments

107. The Council noted that this study did not consider passive smoking. However, it considered it was nevertheless relevant to the scope of review, because it supported the findings in Khan et al that any association between active smoking and AMD ceased 20 years after quitting smoking.

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67 See at page 1158.

68 See at page 1158.

69 See at page 1159 and Table 1.

70 Ibid.

71 Ibid.

72 See at pages 1161 - 2.

Delcourt, C, Diaz, J-L, Ponton-Sanchezl, A & Papoz, L 1998, for The POLA Study Group, 'Smoking and Age-Related Macular Degeneration. The POLA study', *Archives of Ophthalmology*, Vol. 116, pp. 1031-1035. (RMA ID 20953)

108. The authors of this prospective French population based study examined 2196 representative participants aged 60 years or older.

109. The authors found a dose-dependant gradient between smoking and AMD in the number of pack-years. Risk increased with increasing levels of exposure. For smokers of 40 pack-years, the risk reached 5.2 times that of never smokers.

110. After age and sex adjustment, current smokers had 3.6 times the risk of AMD, which remained with borderline statistical significance after adjusting for diabetes and cardiovascular indications (OR 3.5, 95% CI 1.0-12.2). Former smokers had 3.2 times the risk of never smokers, which remained significant (OR 2.8, 95% CI 1.1-6.9) after adjusting for the same potential confounding factors. [73]

111. The authors found that as the years since cessation increased, the risk of AMD decreased. Participants who had quit smoking less than 20 years ago had a similar risk profile as current smokers. However, those participants who had quit smoking more than 20 years ago did not have a significantly different risk profile than that of never smokers. [74]

112. The authors pointed out that the participants who had ceased smoking for more than 20 years had a shorter duration of smoking and suggested that this may explain the reduction in risk. [75]

113. The study did not consider passive smoking.

Council's comments

114. The Council considered that this study supported the conclusions in Khan et al and the EUREYE study that the association of AMD from active smoking disappears 20 years after smoking cessation. This study was one of four studies that found there is no association between active smoking and AMD 20 years after quitting smoking.

115. While the study did not examine any association with passive smoking, it assisted the Council to determine the recency limits of the exposure of active smoking, which plausibly and by analogy, must also indicate the maximum duration of any passive smoking recency.

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73 See at page 1033.

74 See at page 1034.

75 See at page 1034.

Pooled studies

Smith, W, Assink, J, Klein, R, Mitchell, P, Klaver, CCW, Klein, BEK, Hofman, A, Jensen, S, Wang, JJ & de Jong, PTVM 2001, 'Risk Factors for Age-related Macular Degeneration. Pooled Findings from Three Continents', *Ophthalmology*, Vol. 108: 697-704. (RMA ID 27058)

116. This study pooled the findings from three large population studies - the Beaver Dam Eye Study, the Rotterdam Study and the Blue Mountains Eye Study - comprising a total of 14 752 participants all with objectively confirmed AMD diagnoses from gradable photographs.

117. The authors noted that, apart from age, tobacco smoking constituted the only clear association with AMD at all sites and pooled over all sites. [76]

118. The authors noted the strengths of the study were its large sample size, the relatively similar photographic documentation of the disease and consistency of grading; although it was noted that the photographic technique and grading could still contain inconsistencies between populations. [77] It was noted that exposure measurements could be different at each site and that there were potential differences in interviewer administered questionnaires. [78]

119. When pooled, active smoking was found to be strongly associated with all AMD, as well as with its two main sub-types. Current smokers had a statistically significant three-fold risk of AMD (3.12, 95% CI 2.10 - 4.64). [79] For ex-smokers, the associations were not statistically significant, but size and direction of the odds ratios consistently favoured an association (OR 1.36, 95% CI 0.97-1.90).[80]

120. Any potential association between exposure to passive smoking and AMD was not reported.

Council's comments

121. The Council noted that the Rotterdam Study was not available to the RMA at the relevant times, but the pooled analysis (which was available to the RMA at the relevant times) included data from that study.

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76 See at page 700.

77 See at page 700.

78 See at page 700.

79 See Table 3 at page 701 and at page 702.

80 See Table 3 at page 701.

122. The Council considered that pooling the data overcame the limited power of individual studies to detect associations for sub-types of AMD and was the best way to overcome the methodological shortcomings of smaller individual studies. The pooling confirmed the strong association between active smoking and AMD. While the study did not address passive smoking, the Council considered that the findings about active smoking contributed to the body of evidence and by inference, pointed to the relevant association.

123. The Council considered that the findings did not satisfy the balance of probabilities test.

Meta-analysis

Cong, R et al 2008, 'Smoking and the Risk of Age-related Macular degeneration: A Meta-Analysis', *Ann Epidemiol*, 18: 647-56. (RMA ID 50074)

124. This review of quality studies examined the association between smoking and AMD. The reviewers meta-analysed the results of the five cohort and eight case controls studies which met their defined inclusion criteria.

125. Consistent with other reviews, the pooled results demonstrated strong and statistically significant associations between smoking and AMD.

126. Current and 'ever' smoking history all increased the risk of AMD with a dose response.

127. Several biological mechanisms were suggested. [81]

128. The strongest associations were for current smoking, whereas past smoking did not quite reach statistical significance in the prospective studies. The findings of studies, including the EUREYE study, that the association ceased 20 years after quitting smoking were noted and the authors suggested that the reason may be that current smokers have a longer exposure time than past smokers.[82] The study did not report any analysis of any potential association with passive smoking.

Council's comments

129. Although this study did not directly address the question of passive smoking, the Council considered the paper to be useful because of its methodology. Meta-analysis is considered by epidemiologists to be a high level of evidence, providing that the study is well conducted. This study supported the findings of the previous pooled study by Smith et al where the association was found between active smoking and AMD. It added weight to the reasonableness of the relevant association.

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81 See at pages 649 - 652.

82 See at page 654.

Review Studies

Lois, N, Abdelkader, E, Reglitz, K, Garden, C & Ayres, JG 2008, 'Environmental tobacco smoke (ETS) exposure and eye disease', *Br J Ophthalmol*, 92(10): 1304-10. (RMA ID 49834)

130. This review focused on the scientific evidence of any association between exposure to ETS and certain eye diseases, including AMD. Only three analytical studies were found to have considered any association between passive smoking and AMD, the original studies of all of which have been analysed above:

- **Klein *et al* (1993)** of the Beaver Dam Eye Study, which did not find an association between passive smoking and AMD;
- **Khan *et al* (2006**) who did find a statistically significant increased risk of late AMD; and
- **Smith *et al* (1996)** the Blue Mountains Eye Study, which was unable to detect a statistically significant increased risk, but found that the size and direction of the effect were suggestive of a positive association.

131. The authors noted that Klein et al (1993) found no association between passive smoking and any type of AMD. However, the reviewers considered it a limitation that in this study ex-smokers living in a household with a current smoker were considered to be passive smokers, suggesting that this may have drawn the results toward the null. [83]

132. The reviewers noted the contrast with the Klein et al (1993) findings, in the:

132.1. Blue Mountains Eye Study, which found a statistically non-significant association between exposure to passive smoking and AMD; and

132.2. Khan et al, which found that exposure to passive smoking had a statistically significant association with AMD. [84]

133. The reviewers noted the different definitions of passive smoking in these studies.

134. The authors also reviewed potential biological mechanisms which might explain the relevant association.

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83 See at page 6.

84 See at page 6.

135. They explained that smoking may cause oxidative damage to the retina and may activate the release of inflammatory mediators, reduce choroidal blood flow, reduce absorption of key antioxidants such as lutein and may lead to interactions with a variant of the complement factor H gene, Y402H, in some people. [85]

136. Additionally, "sidestream" smoke from the tip of a burning cigarette, which is thought to be approximately 80% of ETS exposure, has been shown to be particularly toxic and may induce inflammation and tumour development. [86] Tobacco smoke contains over 4000 substances, of which around 150 have clear data on toxicity. [Those most likely to cause irritation include acrolein, formaldehyde and other aldehydes and solvents such as styrene and phenol. Additionally, smoke particles themselves can be irritants.][87]

137. Experimental studies identified by the authors showed that mice exposed to passive smoking had increased levels in their blood of vascular endothelial growth factor, which the authors considered may induce the growth of small blood vessels in the eye, as occurs in neovascular macular degeneration.[88]

Council's comments

138. The Council in its review placed most weight upon the data in original studies, although it noted that review studies can provide a useful summary.

139. The Council noted that the reviewers suggested several mechanisms by which active smoking could be associated with AMD.

140. The Council considered that the reviewers made a strong case that the relevant association is biologically plausible.

141. However, biological plausibility of itself is not sufficient (biological plausibility is only one of the Bradford Hill criteria which applies at Step 1 in determining the pool of information). The Council must determine whether the sound medical-scientific evidence in the pool points to the relevant association, and if so, whether it satisfies the balance of probabilities test.

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85 See at page 7.

86 See at pages 3 - 4.

87 See at page 4.

88 See at page 7.

Thornton, J, Edwards, R, Mitchell, P, Harrison, RA, Buchan, I & Kelly, SP 2005, 'Smoking and age-related macular degeneration: a review of association', *Eye*, Vol. 19, pp. 935-944. (RMA ID 42214)

142. The authors conducted a systematic review of the evidence of association of active smoking to AMD. They included cross-sectional, case control and prospective cohort studies published in English.

143. The reviewers noted that the Beaver Dam Eye study, which found a strong association between active smoking and AMD at baseline, found the association was weaker at the five and ten year follow-up. [89]

144. This review noted that strong and consistent evidence existed for an association between active smoking and AMD, with evidence of dose-response and temporality. However, the authors noted the potential for exposure misclassification, noting that a study which did not account for a change in a partner's smoking status from baseline may bias the results towards the null. [90]

145. In relation to passive smoking, the authors noted the sparse evidence available, but commented on the tendency in more recent studies to use assessments of multiple exposures, for example in the workplace and the home. [91]

Council's comments

146. The Council noted the reviewers' comments, but relied on its own analysis of the original studies.

THE COUNCIL'S CONCLUSIONS ON THE SOUND MEDICAL-SCIENTIFIC EVIDENCE

147. The Council agreed with the Commissions' submission that for active smoking the information available to the RMA at the relevant times:

- 'pointed to' the relevant association; [92] and
- provided a relevant connection on the balance of probabilities. [93]

148. The Council noted the studies which found no association with active smoking 20 years after cessation (the EUREYE study, the POLA study, Khan et al and Delcourt et al).

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89 See at page 937.

90 See at page 942.

91 See at page 941.

92 See [52.1].

93 See [52.2].

149. The Council noted that several key studies had addressed the association between active smoking and AMD. However, of these, only Klein et al (1993, 2008), Khan et al (2006) and Smith et al (1996) had reported on passive smoking. Only Khan et al had found a positive association that was statistically significant. Smith et al had found a statistically non-significant association. Klein et al had found no association.

150. Of the reviews and meta-analyses, only Lois et al (2008) and Thornton et al (2005) mentioned passive smoking and considered further research was required.

151. The Council considered that all the studies in the information were underpowered so far as considering any potential association with passive smoking was concerned. The positive association found by Khan et al was weaker than that found for active smoking, but results between studies showed some consistency, particularly with respect to the equivalence of risk between former smokers and never smokers 20 years after former smokers quit smoking.

152. The Council considered that the studies suffered from limitations concerning:

- exposure measurement (which is limited by the questions asked of the participants)
- case definition
- insufficient adjustment for changes in exposure status
- insufficient adjustment for confounding factors, such as nutrition, and
- retrospective recall of smoking history.

153. Survival biases in the follow up Klein et al study (2008) may have also biased against a stronger association and numbers of cases were sometimes too small to detect a statistically significant association.

154. The Council considered that an association with passive smoking was biologically plausible and noted that possible biological mechanisms had been suggested by a number of authors: see, for example, Lois et al (2008). However, as mentioned above, biological plausibility is not sufficient.

155. An issue which exercised the Council was the need for exposure to passive smoking to be recent and continuing. While the Council accepted that active smoking was addictive, passive smoking is not.

156. The Council noted the studies which found no association with active smoking 20 years after cessation. As it must be assumed that passive smoking is not as deleterious as active smoking, an analogy with active smoking (i.e. that any association ceases after 20 years from the most recent exposure) would be generous.

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE A FACTOR(S) FOR PASSIVE SMOKING

157. The Council, having closely analysed all the information in the pool, placed particular weight on the articles discussed in detail above. The critical question for the Council was whether the sound medical-scientific evidence 'points to', as opposed to merely 'leaves open' the possibility of the 'relevant association'. [94]

158. The Council noted that the average age of onset of late AMD is generally from the seventh to ninth decades of life. The disease is common in older persons and is known to be associated with ageing. However, there are exceptions and rare cases may present with a much earlier onset of the disease. Consideration of the length of time between exposure to passive smoking and disease onset is therefore important. The contribution of lifestyle factors is difficult to determine.

159. The Council recognised the strength of the evidence of the association with active smoking. However, the Council considered that there was limited evidence in the information available to the RMA which 'touched on' any association with passive smoking.

160. The Council also noted that there was very limited sound medical-scientific evidence supporting an association between the early stages of the disease and past smoking; which suggested to the Council that the continuation of smoking, right up to the development of late stage disease, i.e. current or very recent smoking, is important.

161. The Council noted that the study by Khan et al was the only one in the pool of information which found a statistically significant positive association with passive smoking. For the reasons discussed above, the Council considered that study was affected by methodological shortcomings. However, the Council was not in a position to dismiss the findings as invalid.

162. The Council also noted the Applicant's submission that Australian service personnel in the past have often been exposed to extreme levels of environmental tobacco smoke in confined spaces. [95]

163. Notwithstanding the limitations of the Khan et al paper, and the limited sound medical-scientific evidence generally on passive smoking, the Council was very cognisant of the low threshold of the reasonable hypothesis test. Given the positive data from the Khan et al paper and the supportive, but not statistically significant, findings from the Blue Mountains Eye Study, the Council considered that the sound medical-scientific evidence that was available to the RMA at the relevant times 'pointed to' the relevant association for late AMD.

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94 See full Federal Court decision at [49] per Branson J and [52] of these Reasons.

95 Although the Council remained cognisant that it is constrained to conduct its review by reference to the information which was available to the RMA at the relevant times.

164. Accordingly, the Council decided that there was sufficient information on which the RMA could have relied to amend Statement of Principles No. 13 of 2009 by including a passive smoking factor for clinical onset.

165. The Council considered that there was insufficient sound medical-scientific evidence which touched on any potential association between passive smoking and clinical worsening of AMD. The Council also noted that as AMD is a disease of advanced age, the possibility of an association between passive smoking and clinical worsening is not persuasive. The Council decided that the sound medical-scientific evidence available to the RMA at the relevant times was insufficient to justify an amendment to Statement of Principles No. 13 of 2009 by the inclusion of a clinical worsening factor.

166. The Council considered that the sound medical-scientific evidence concerning passive smoking did not provide a relevant connection on the balance of probabilities. The sound medical-scientific evidence fell short of supporting an association on the balance of probabilities due to methodological limitations, lack of statistical significance and the paucity of studies addressing passive smoking and AMD. Accordingly, the Council decided that the information available to the RMA at the relevant times was insufficient to justify an amendment to Statement of Principles No. 14 of 2009.

Consideration of new factor

167. In formulating a factor for clinical onset in the reasonable hypothesis Statement of Principles, the Council noted the EUREYE study, which found a strong association between active smoking and late AMD where the smoking had occurred for a period of over six years. It considered that this duration of exposure was somewhat consistent with the Khan et al case control study, which found an association for passive smoking where the exposure occurred for at least five years.

168. By letters dated 10 January 2012, the Council provided the Applicant and the Commissions with an opportunity to comment, by 17 February 2012, on the wording of a proposed new factor in respect of passive smoking in Statement of Principles No. 13 of 2009. The proposed new factor was:

> For late macular degeneration only:
>
> being in an atmosphere with a visible tobacco smoke haze in an enclosed space for at least 10 000 hours within the 20 years before the clinical onset of late macular degeneration, and where the person was a non-smoker during the entire period of the exposure.

169. The Commissions made no comment on the wording of the proposed new factor. The Applicant contended that the wording of the proposed new factor was:

> too restrictive, in fact in its present form with the words 'within the 20 years' it doesn't cover WW2 veterans. … I consider that the wording for this factor should be as follows,
>
> > For Age Related or late macular degeneration ONLY:
> >
> > being in an atmosphere with a visible tobacco smoke haze in an enclosed space for 10 000 hours before the clinical onset of late macular degeneration and where the person was a non-smoker during the entire period of the exposure.

170. The Applicant contended that the proposed new factor should not contain a requirement that the exposure to passive smoking must have occurred within 20 years before the clinical onset of late macular degeneration.

171. The Council took the Applicant's comments into account. However, the Council noted the EUREYE study, Khan et al and the POLA study, all of which found that there was no association with active smoking 20 years after the cessation of smoking.

172. In other words, these studies found that the prevalence of late macular degeneration was not increased in persons whose exposure to smoking had ceased 20 years before, compared to persons who had not been exposed.

173. As stated above (see [156]), as it must be assumed that passive smoking is not as deleterious as active smoking, the Council was of the view that the requirement that the exposure to passive smoking must occur within 20 years prior to the clinical onset of late macular degeneration was supported by the sound medical-scientific evidence available to the RMA at the relevant times.

174. On the basis of these studies, the Council considered that a minimum of five years' exposure to passive smoking by a person who was a non-smoker at the time of the exposure, is required, where exposure must occur continuously or discontinuously within the 20 years before clinical onset.

DECISION

175. The Council made the declarations summarised in **paragraphs 1 and 2** above.

EVIDENCE BEFORE THE COUNCIL

176. The information considered by the Council (being the information that 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) is listed in **Appendix B**.

177. As mentioned above, 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) is listed in **Appendices C and E** respectively.

178. The information to which the Applicant 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 D**.

Articles cited in the Council's analysis

Information before the RMA:

Appendices

Appendix A	Preliminary list of the proposed pool of information, as advised to the Applicant and Commissions by letters dated 15 June 2011 (see [28] of the Reasons).
Appendix B	Information forwarded to the Council under section 196K of the VEA referable to the Council's review of Statements of Principles Nos. 13 and 14 of 2009
Appendix C	Information upon which the Applicant 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).
Appendix D	Material that the RMA advised was not available to (not before) the RMA (which the Applicant contended was in existence at the relevant times, and so could have been accessed by the RMA).
Appendix E	Information upon which 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).

APPENDIX A

Preliminary and final list of the pool of information, as advised to the Applicant and Commissions by letters dated 15 June 2011 (see [28] and [57] of the Reasons).

RMA ID	DESCRIPTION
6408	Klein, R, Klein, BEK, Linton, KLP & DeMets, DL 1993, 'The Beaver Dam eye study: The relation of age-related maculopathy to smoking' A*m J Epidemiol*, vol. 137, no. 2, pp. 190-200.
6410	Klein, R, Klein, BE & Linton, KL 1992, 'Prevalence of age-related maculopathy. The Beaver Dam Eye study', *Ophthalmology*, vol. 99, no. 6, pp. 933-943.
6411	Mitchell, RA 1993, 'Prevalence of age related macular degeneration in persons aged 50 years and over resident in Australia', *J Epidemiol Community Health*, vol. 47, pp. 42-45.
6414	The Eye Disease Case-Control Study Group 1992, 'Risk factors for neovascular age-related macular degeneration', *Arch Ophthalmol*, vol.110, pp.1701-1708.
7980	Seddon, JM, Willett, WC, Speizer, FE & Hankinson, SE 1996, 'A prospective study of cigarette smoking and age-related macular degeneration in women', *JAMA,* 276(14) pp 1141-46.
7981	Christen, WG, Glynn, RJ, Manson, JE, Ajani, UA & Buring, JE 1996, 'A prospective study of cigarette smoking and risk of age-related macular degeneration in men', *JAMA*, vol. 276, no. 14, pp. 1147-1151.
7982	Klein, R & Klein, BEK 1996, '[Comment] Smoke gets in your eyes too', *JAMA,* vol. 276, no.14, pp.1178-79.
9102	Smith, W, Mitchell, P & Leeder, SR 1996, 'Smoking and age-related maculopathy: the Blue Mountains eye study', *Arch Ophthalmol*, vol. 114, pp. 1518-1523.
13630	Egan, KM & Seddon, JM 1994, 'Age-Related Macular Degeneration: Epidemiology'. In Albert, DM & Jakobiec, FA (Eds). *Principles & Practice of Ophthalmology*, 1st Edition, Vol. 1, Chapter 109, pp. 1266-1274. Philadelphia, PA, W.B. Saunders Company.
13631	Klein, R & Klein, BEK 1996, '[Comment] Smoke Gets in Your Eyes Too', *JAMA,* vol. 276, no. 14, pp 1178-1179.
13632	Christen, WG, Glynn, RJ, Manson, JE, Ajani, U & Buring, JE 1996, 'A Prospective Study of Cigarette Smoking and Risk of Age-Related Macular Degeneration in Men', *JAMA*, vol. 276, no. 14, pp. 1147-1151.
13633	Seddon, JM, Willett, WC, Speizer, FE & Hankinson, SE 1996, 'A Prospective Study of Cigarette Smoking and Age-Related Macular Degeneration in Women', *JAMA*, vol. 276, no. 14, pp. 1141-1146.
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13642	Klein, R, Klein, BEK, Jensen, SC & Meuer, SM 1997, 'The Five-year Incidence and Progression of Age-related Maculopathy. The Beaver Dam Eye Study', *Ophthalmology,* vol.104, no.1, pp. 7-21.

13643	Cruickshanks, KJ, Hamman, RF, Klein, R, Nondahl, DM & Shetterly, SM 1997, 'The Prevalence of Age-Related Maculopathy by Geographic Region and Ethnicity. The Colorado-Wisconsin Study of Age-Related Maculopathy', *Arch Ophthalmol*, vol. 115, pp. 242-250.
13644	Klaver, CCW, Assink, JJM, Vingerling, JR, Hofman, A & de Jong, PTVM 1997, 'Smoking Is Also Associated With Age-Related Macular Degneration in Persons Aged 85 Years and Older: The Rotterdam Study.' *Arch Ophthalmol*, vol. 115, p. 945.
13646	Smith, W, Mitchell, P & Leeder, SR 1996, 'Smoking and Age-Related Maculopathy. The Blue Mountain Eye Study', *Arch Ophthalmol*, vol. 114, pp. 1518-1523.
13647	Vingerling, JR, Hofman, A, Grobbee, DE & de Jong, PTVM 1996, 'Age-Related Macular Degeneration and Smoking', *Arch Ophthalmol*, vol. 114, pp. 1193-1196.
13702	Hirvela, H, Luukinen, H, Laara, E & Laatikainen, L 1996, 'Risk Factors of Age-related Maculopathy in a Population 70 Years of Age or Older', *Ophthalmology*, vol. 103, no. 6, pp. 871-877.
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13705	Bressler, NM & Bressler, SB 1995, 'Preventative Ophthalmolgoy. Age-related Macular Degeneration', *Ophthalmology*, vol. 102, no. 8, pp. 1206-1211.
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13820	Vingerling, JR, Klaver, CCW, Hofman, A & de Jong, PTVM 1995, 'Epidemiology of Age-related Maculopathy', *Epidemiologic Reviews*, vol. 17, no. 2, pp. 347-360.
13864	Klein, R, Klein, BEK & Moss, SE 1998, 'Relation of Smoking to the Incidence of Age-related Maculopathy', *American Journal of Epidemiology*, vol. 147, no. 2, pp. 103-110.
14633	Delcourt, C & Papoz, L 1998, 'Smoking and age-related macular degeneration', *Arch Opthalmol*, vol. 116, no. 8, pp. 1031-1035.
20943	Seddon, JM 2000, 'Epidemiology of age-related macular degeneration', in Albert, DM & Jakobiec, FA (Eds). *Principles & Practice of Ophthalmology*, 2nd edn, vol. 1, Chapter 47, pp. 521-531, Philadelphia, PA, W.B. Saunders Company.
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20952	Friedman, E 2000, 'The role of the atherosclerotic process in the pathogenesis of age-related macular degeneration', *American Journal of Ophthalmology*, vol. 130, no. 5, pp. 658-663.

20953	Delcourt, C, Diaz, J-L, Ponton-Sanchez, A & Papoz, L 1998, 'Smoking and age-related macular degeneration. The POLA study', *Archives of Ophthalmology*, vol. 116, pp. 1031-1035.
20954	Chaine, G, Hullo, A, Sahel, J, Soubrane, G, Espinasse-Berrod, M, Schutz, D, Bourguignon, C, Harpey, C, Brault, Y, Coste, M, Moccatti, D & Bourgeois, H 1998, 'Case-control study of the risk factors for age related macular degeneration', *British Journal of Ophthalmology*, vol. 82, pp. 996-1002.
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28320	Snow, KK & Seddon, JM 1999, 'Do age-related macular degeneration and cardiovascular disease share common antecedents'. *Opthalmic Epidemiology*, vol. 6, no. 2, pp. 125-43.
31991	Klein, R, Peto, T, Bird A & Vannewkirk, MR 2004,'The epidemiology of age-related macular degeneration', *Am J Ophthalmology*, vol.137, pp.486-495.
31993	Miyazaki, M, Nakamura, H, Kubo, M, Kiyohara, Y, Oshima, Y, Ishibashi, T & Nose, Y 2003, 'Risk factors for age related maculopathy in a Japanese population: the Hisayama study', *Br J Ophthalmology*, vol. 87, pp.469-472.
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36167	West, ES & Schein, OD 2005, 'Sunlight and age-related macular degeneration', *International Ophthalmology Clinics*, vol. 45, no. 1, pp. 41-7.
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37696	DeAngelis, MM, Lane, AM, Shah, CP, Ott, J, Dryja, TP & Miller, JW 2004, 'Extremely discordant sib-pair study design to determine risk factors for neovascular age-related macular degeneration', *Arch Ophthalmology*, vol. 122, no. 4, pp. 575-80.
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APPENDIX B

Information forwarded to the Council by the RMA under section 196K of the VEA referable to the Council's review of Statements of Principles Nos. 13 and 14 of 2009

APPENDIX B

Australian Government
Repatriation Medical Authority

MACULAR DEGENERATION

RMA ID Number	Reference List for Investigation #225-4 as at 08 April 2008 **[as amended 23 October 2009]**

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Appendix C

Information upon which the Council understands the Applicant 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). (see para 37 of the reasons)

RMA ID	DESCRIPTION
49688	Klein, R, Knudtson, MD, Cruickshanks, KJ & Klein, BEK 2008, 'Further observations on the association between smoking and the long-term incidence and progression of age-related macular degeneration. The Beaver Dam Eye Study', *Arch Ophthalmol,* vol. 126, no. 1, pp. 115-21.
49834	Lois, N, Abdelkader, E, Reglitz, K, Garden, C & Ayres, J 2008, 'Environmental tobacco smoke (ETS) exposure and eye disease', *Br J Ophthalmol*, vol. 92, no. 10, pp.1304-10.

Appendix D

Information that the RMA advised was not available to (not before) the RMA (which the Applicant contended was in existence at the relevant times, and so could have been accessed by the RMA).

RMA ID	DESCRIPTION
	Barclay, L 2008, 'Current Smoking related to Age-related Macular Degeneraton', *CME,* 16 January 2008.
	Handcock, C 2011, 'Environmental tobacco smoke exposure and eye disease. An Abstract of "Lois, N, Abdelkader, E, Reglitz, K, Garden, C & Ayres, J 2008, 'Environmental tobacco smoke (ETS) exposure and eye disease', *Br J Ophthalmol,* vol. 92, no. 10, pp. 1304-10"', written submission to the Specialist Medical Review Council, dated 17 February 2011.

Appendix E

Information upon which 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).

RMA ID	DESCRIPTION
6408	Klein, R, Klein, BEK, Linton, KLP & DeMets, DL 1993, 'The Beaver Dam eye study: The relation of age-related maculopathy to smoking', *Am J Epidemiol*, vol.137, no.2, pp. 190-200.
9102 & 13646	Smith, W, Mitchell, P & Leeder, SR 1996', Smoking and Age-Related 13646 Maculopathy. The Blue Mountain Eye Study', *Arch Ophthalmol*. Vol. 114, pp. 1518-1523.
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49834	Lois, N, Abdelkader, E, Reglitz, K, Garden, C & Ayres, J 2008, 'Environmental tobacco smoke (ETS) exposure and eye disease', *Br J Ophthalmol*, vol. 92, no. 10, pp. 1304-10.
50074	Cong, R, Zhou, B, Sun, Q, Gu, H, Tang, N & Wang, B 2008, 'Smoking and the risk of age-related macular degeneration: a meta-analysis', *Ann Epidemiol*, vol. 18, pp. 647-56.
42214	Thornton, J, Edwards, R, Mitchell, P, Harrison, RA, Buchan, I & Kelly, SP 2005, 'Smoking and age-related macular degeneration: a review of association', *Eye*, vol.19, pp. 935-944.
27058	Tomany, SC, Wang, JJ, van Leeuwen, R, Klein, R, Mitchell, P, Vingerling, JR, Klein, BEK, Smith, W & de Jong, PTVM 2004, 'Risk factors for incident agerelated macular degeneration', *Ophthalmology*, vol. 111, pp. 1280-7.
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