Specialist Medical Review Council

Declaration and Reasons for Decisions

Section 196W
Veterans' Entitlements Act 1986

Re: Statements of Principles Nos. 50 and 51 of 2017 concerning rheumatoid arthritis

Request for Review Declaration No. 35

1. In relation to the RMA Statements of Principles **Nos. 50 and 51 of 2017 concerning rheumatoid arthritis** made under subsections 196B of the *Veterans' Entitlements Act 1986* (the VEA), the Council under subsection 196W(5) of the VEA:

   DECLARES that there is **insufficient** sound medical-scientific evidence on which the RMA could have relied to amend the Statements of Principles to include factor(s) for:

   - exposure to mineral oils containing PCBs or acute PCB exposure.

INDEX of CONTENTS

REASONS FOR DECISIONS

Introduction

2. The Specialist Medical Review Council (the Council) is an independent statutory body established by the VEA. In general terms, upon receipt of a valid application the Council is to review as relevant:

   - the contents of Statement/s of Principles in respect of a particular kind of injury, disease or death; or
   - a decision of the RMA not to determine, not to amend, Statement/s of Principles in respect of a particular kind of injury, disease or death.

3. In conducting a review, the Council must review all of the information (and only that information) that was available to the RMA when it made the decision under review. This is information which was actually used by the RMA as opposed to information which was generally available but not accessed by the RMA. A list of the information that was available to the RMA is listed in **B1 of Appendix B**.

4. Fundamental to Statements of Principles, and so to a Council review, is the concept of sound medical-scientific evidence (SMSE), as that term is defined in section 5AB(2) of the VEA[1].

5. The SMSE relevant to this application (the relevant SMSE) is listed in listed in the **reference list at the end of this document**.

6. The information to which the Applicant referred, being information which the RMA advised was new information, that is, information which was not available to

---

[1] The SMSE is a subset of the available information. It comprises those articles which the Council considers:

a) are relevant to the matters within the proposed scope of review, and

b) satisfy the definition in the VEA of 'sound medical-scientific evidence'.

Sound medical-scientific evidence is defined in section 5AB(2) of the VEA as follows:

"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 kind of injury, disease or death may be caused – meets the applicable criteria for assessing causation currently applied in the field of epidemiology.

The later requirement is held to mean 'appropriate to be taken into account by epidemiologists'.

the RMA at the relevant times, and so was not considered by the Council in reaching its review decision is listed in **B2 of Appendix B**.

7. **Appendix A** sets out further details regarding the composition of the Council for this review and the legislation relating to the making of Statements of Principles.

Scope of the Review

8. The SMRC received an application seeking review of the decision made by the RMA in November 2017 following its decision not to amendment to Statements of Principles Instrument Nos. 50 & 51 of 2017 as already determined in respect to rheumatoid arthritis.

9. The Applicant contended that there was SMSE on which the RMA could have relied to amend SoPs Nos 50 and 51 in respect to rheumatoid arthritis, and to include factors for:

- mineral oils containing PCBs or acute PCB exposure.

10. The Council, when reviewing the SMSE, must determine whether or not there is SMSE on which the RMA could have relied to determine a Statement of Principles under subsection 196B(2), or a Statement of Principles under subsection 196B(3), in respect of that kind of injury, disease or death.

11. The Council, when reviewing the SMSE, must determine whether or not there is SMSE which indicates a reasonable hypothesis connecting the particular injury, disease or death to the relevant service.

12. In a reasonable hypothesis, the evidence 'points to' as opposed to merely 'leaves open' a link between injury, disease or death and the relevant service. In a reasonable hypothesis, the link is not 'obviously fanciful, impossible, incredible or not tenable or too remote or too tenuous.'[2]

13. If the Council is of the opinion that a reasonable hypothesis has been raised, the Council proceeds also to determine whether a connection exists to relevant service on the balance of probabilities,[3] i.e. whether the connection is more probable than not.

---

2 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].

3 Relevant service in balance of probabilities statements of principles refers to non-operational service having regard to the various definitions applying to types of 'service' as defined in the VEA and the MRCA.

14. In these Reasons the association for both the reasonable hypothesis test and the balance of probabilities test are respectively referred to as the 'relevant association'.

15. The Council exercises its scientific judgement in weighing the evidence about the relevant association.

Council's decision on the scope of review

16. The Council wrote to both the Applicant and the Commissions advising its decision on the proposed scope of the review and inviting comment. No comments were received on the proposed scope of the review and therefore the Council decided that, consistent with its role, it will have particular regard to whether there was sound medical-scientific evidence (SMSE) on which the Repatriation Medical Authority (RMA) could have relied to amend SoPs 50 and 51 of 2017 in the following ways:

   - the possible inclusion of a factor or factors, or possible amendment of factors, in Statement of Principles Nos. 50 and 51 of 2017, as contended, for exposure to mineral oils containing PCBs or acute PCB exposure.

Submissions

17. The Council took into account all submissions made to it.

Applicant

18. The Applicant made an oral submission to the SMRC on 9 August 2018.

19. The Applicant submitted that there is sufficient SMSE supporting the contention to include factors for PCBs and rheumatoid Arthritis.

20. In his oral submission to the SMRC the Applicant outlined his military service as a radar specialist and provided details of his medical history since being exposed to transformer oil.

21. The Applicant contended that when heated, PCB based transformer oils form chlorinated dioxins and chlorinated dibenzofurans. In support of his contentions that chlorinated dioxins and chlorinated dibenzofurans are implicated in the onset of Rheumatoid Arthritis, the Applicant referred the Council to papers on the exposure of humans to furans in two incidents of rice oil contamination by PCBs contaminated with PCDFs, in Japan (Yusho) and Taiwan (Yucheng).

22. The Applicant referred the Council to a number of papers previously available to the RMA and some new papers and drew Council's attention in particular to a paper by Akahane et al, 2017, Long-Term Health Effects of PCBs and Related Compounds: A Comparative Analysis of Patients Suffering from Yusho and the General Population.

Commissions

23. The Repatriation Commission and the Military Rehabilitation and Compensation Commission (the Commissions) made a written submission to the Council received in February 2018.

24. In their submission the Commissions contended that the sound medical-scientific evidence that was available to the RMA was insufficient to warrant the inclusion of any factors concerning PCB exposure, whether acute or chronic, in the reasonable hypothesis SOP for rheumatoid arthritis, Instrument 50 of 2017.

25. Dr Jon Kelley made an oral submission for the Repatriation Commission and the Military Rehabilitation and Compensation Commission (the Commissions) on 9 August 2018. Dr Kelly advised the Council that the Commissions agree with the conclusions made by the RMA, that the available evidence is insufficient to support the inclusion of a factor in the SoPs for PCBs. Dr Kelley did not make specific contentions about the medical science in his submission.

26. At the oral hearing held on 9 August 2018, Dr Kelley noted that the Applicant has indicated a concern with transformer oils, and advised the Council that he had made an error in the Commissions submission at paragraph 45. Dr Kelley clarified, that while transformer oil can be a type of mineral oil, and there are mineral oil-based transformer oils that contain or become contaminated with PCBs, the Applicant's exposure was to an Askarel transformer oil which contains PCBs but is not a mineral oil.

Council's decisions on the relevant SMSE

27. The Council considered that the SMSE to be assessed in the review should comprise information:
    - that was available to 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:
        a. epidemiologists would consider appropriate to take into account; and
        b. in the Council's view 'touches on' (is relevant to) matters within the scope of review.

28. The Council's final decision on the SMSE for the review was that it should comprise the information listed in the reference list at the end of this document.

29. Information which the RMA advised was not available to it 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'.

Council's Evaluation of the SMSE

30. When evaluating the SMSE, the Council focussed on information relevant to the scope of the review and the information listed reference list at the end of this document.

31. In forming its decisions on the SMSE, the Council brings to bear its scientific expertise and judgement. The Bradford Hill criteria of causation[41] and other tools or criteria appropriate to be taken into account by epidemiologists were applied to the articles as it considered appropriate.

32. The Council also considered any methodological limitations or flaws (including such things as statistical power, control of confounders, bias, exposure assessment methods etc.) in the various articles.

33. For ease of reference, the Bradford Hill criteria (noting that these are not exhaustive) are:
    - strength of association
    - consistency across investigation
    - specificity of the association

- temporal relationship of the association
- biological gradient
- biological plausibility
- coherence
- experiment
- analogy

34. The Council notes that these criteria are not necessary conditions of a cause and effect relationship. They act to provide some circumstantial evidence of such a relationship.

35. The Council considers that while animal studies may sometimes support the biological plausibility of an association, the results from animal studies may not be generalisable to humans. At best these might be used as initial research to generate hypotheses, which may indicate a need for further studies on human subjects or to demonstrate possible biological mechanisms. For this reason, the Council focussed on studies that involved human subjects rather than animals for this review.

36. In discussing the factors in each section of these reasons, the Council arranged the papers in order of study type, from the highest quality to the lowest quality (meta-analyses and systematic reviews; cohort and case-control studies; cross-sectional studies; and case reports and case series. General (non-systematic) reviews of high quality were also included to provide an overview of the evidence and highlight important issues relevant to the review.

37. While the Council considered, it did not focus its evaluation on those articles that:

    - were reviews of available information that the Council has evaluated in these reasons for decisions;
    - did not provide data that the Council could draw conclusions about rheumatoid arthritis.

Council's Conclusions on the Relevant SMSE

38. In reaching a decision about the existence or otherwise of a reasonable hypothesis the Council must consider and evaluate all of the SMSE. In the situation where there is a single piece of evidence, such as a single study or paper, in support of a reasonable hypothesis, on its own that may be enough to support the hypothesis. However, this information should be considered with other SMSE in identifying

whether the SMSE indicates the relation to the medical condition. It is therefore important that the Council considers all information in context.

39. From the information that was available to the RMA at the relevant time, the Council considered all studies important to the scope of this review. In considering the matters within the scope of the review, the Council closely analysed these studies, both individually and collectively, taking into consideration both quantitative and qualitative evidence in its evaluations.

Rheumatoid arthritis

40. In the SoPs 50 and 51 of 2017, the RMA defined rheumatoid arthritis as:

a) a symmetric, inflammatory, peripheral polyarthritis persisting for a continuous period of at least six weeks, characterised by inflammatory synovitis; and

b) excludes juvenile rheumatoid arthritis and non-rheumatoid conditions that may have similar clinical features, such as psoriatic arthritis, acute viral polyarthritis, systemic lupus erythematosus and polyarticular gout.

The Council's Conclusions on whether there should be new factor(s)

41. The Council reviewed a number of studies[1-23] which examined the association between PCBs and rheumatoid arthritis. The studies can be broadly split into evidence from exposure to contaminated rice bran cooking oils[1-9], evidence from population based exposure studies[10-14] and industrial cohort studies.[15-23]

Evidence from cohorts exposed to cooking oils contaminated by PCBs (Yusho and Yucheng incidents)

42. A number of studies were available concerning contamination of rice cooking oil with PCBs and other agents in Taiwan ("Yucheng") and in Japan ("Yusho"). The Council considered that most of the studies reviewed[2-6,8-9] did not provide useful information for this review as they did not examine the association between PCBs and rheumatoid arthritis. Two studies which did provide some information on the association between arthritis and PCBs were Guo et al (1999)[1] and Kanagawa et al (2008)[7] and these studies are reviewed in detail below.

43. Guo et al (1999)[1] conducted a matched retrospective case-control study on the Taiwan (Yucheng) cohort who had ingested rice cooking oil contaminated with

PCBs and polychlorinated dibenzofurans (PCDFs) in 1979. Over 2,000 people in Central Taiwan were believed to have been exposed for an average period of eight months to PCBs repeatedly heated and cooled and partially oxidized into PCDFs (primarily 2,3,4,7,8-penta CDF and 1,2,3,4,7,8-hexa CDF) and other polychlorinated multiple ring structures. Symptoms included chloracne, hyperpigmentation, and peripheral neuropathy and the illness is commonly referred to as "Yucheng" (oil disease). Exposure levels in the subjects examined were in the order of 10 to 20 times higher than background PCBs and 100 to 1000 times higher for pentaCDF and hexaCDF.

44. The matched retrospective case-control study was conducted in 1993, 14 years after the exposure. It used the Yucheng registry set up for those exposed and a telephone survey to examine the prevalence of a range of diseases in 795 exposed and 693 controls identified as living closest to the exposed case. Relatively high rates of follow-up were observed for the exposed (79.3%) and control (72.8%) subjects. The study found a positive association between contaminated rice oil and self-reported unspecified arthritis in males with an odds ratio (OR) of 4.1 (95% CI, 1.8 to 11.2) but not in females (OR = 1.3, 95% CI 0.8 to 2.3). Results for rheumatoid arthritis were not separately examined or reported. The Council noted that the ascertainment of arthralgia was based on self-report and was not clinically validated. The Council considered that this is likely to lead to over-reporting of this condition, particularly in the exposed group.

45. Kanagawa et al (2008)[7] investigated the relationships between blood concentrations of 2,3,4,7,8-PeCDF, PCBs and PCQs (polychlorinated quarterphenyls) in patients exposed to a specific batch of rice bran cooking oil which became contaminated in heat exchangers during the production of the oil. Over 1,800 people in western Japan are thought to have been exposed in this event in 1968 with symptoms (forming the diagnostic criteria) similar to the Yucheng incident including, for example, acne-like eruptions, skin pigmentation, general fatigue, eye discharge and dental abnormalities. Similar to Yucheng, the incident is commonly referred to as the Yusho ("oil disease") incident.

46. Although PCBs were initially thought to have been involved in the poisoning, a number of studies have since found the poisoning to be due to polychlorinated quarterphenyls (PCQs) and polychlorinated dibenzofurans (PCDFs) with 2,3,4,7,8-PeCDF identified as contributing two thirds to three-quarters of the total toxicity in Yusho patients.[40]

47. Medical and laboratory data from 501 Yusho patients were analysed across a range of blood PeCDFs, PCBs, and PCQs serum concentrations (172 items) using advanced statistical techniques including principal component and logistic regression analysis. The study found a range of conditions associated with abnormal blood levels in Yusho patients, most of which are considered to be characteristic symptoms of Yusho. In particular, blood concentrations of 2,3,4,7,8-PeCDF and PCQ were significantly related to arthralgia (p=0.001 and p=0.006, respectively). However, there was no statistically significant association found for PCBs and arthralgia (p > 0.10). Similar to the study by Guo et al (1999)[1], a limitation of the study is that arthralgia was assessed by self-report and not clinically validated using a medical examination. There was no mention in the study of rheumatoid arthritis.

Summary of evidence from cohorts exposed to rice cooking oils contaminated by PCBs

48. For the cohort studies examining exposure to rice cooking oils contaminated by PCBs there is some evidence that cooking oil containing a mixture of PCBs, furans and dioxins may cause some arthralgia (in men). However, due to a number of methodological limitations, including small sample sizes, potential bias due to self-reporting of symptoms and poor ascertainment of disease, the evidence is inconsistent and the available studies are limited in quantity or quality. Further, due to similar methodological issues, and an absence of results specifically relating to rheumatoid arthritis or PCBs, the Council considered that there is very limited evidence from these studies of an association between PCBs and rheumatoid arthritis.

Evidence from population based studies

49. The Council reviewed a number of population based exposure studies examining the association between rheumatoid arthritis and PCBs.[10-14] Further details for three of the studies most relevant to this review[10-12] are provided below.

50. Lee et al (2007)[10] examined data from the National Health and Nutrition Examination Survey (NHANES 1999-2002) in the US to investigate cross-sectional associations of serum persistent organic pollutants (POPs) concentrations with the prevalence of self-reported arthritis in the general population. Survey results for a total of 1,721 adults (aged > 20 years) were included as part of the analysis including detailed information for 19 POPs for which at least 60% of study participants had concentrations greater than the limit of detection (LOD). The POPs examined, included: 3 polychlorinated dibenzo-p-dioxins (PCDDs); 3

polychlorinated dibenzo furans (PCDFs); 4 dioxin-like polychlorinated biphenyls (PCBs); 5 nondioxin-like PCBs, and 4 organochlorine (OC) pesticides.

51. The concentration levels of the examined POPs were not reported but were instead categorised into quartiles by cutoff points of 25^{th}, 50^{th}, and 75^{th} values with serum concentrations below the limit of detection (LOD) regarded as the reference group. Assessment of arthritis was based on a participant's past diagnosis by a doctor or health professional. As participants were unaware of their concentrations of POPs prior to conducting the survey the study results were unlikely to have been influenced by a possible self-reporting bias. The authors note that the validity of the subtypes of arthritis based on questionnaire responses has been found to be low.

52. After adjusting for a range of possible confounders, dioxin-like polychlorinated biphenyls (PCBs) and nondioxin-like polychlorinated biphenyls (PCBs) were both found to be positively associated with rheumatoid arthritis in women but not in men. For dioxin-like PCBs, odds ratios for rheumatoid arthritis in women were 1.0, 7.6, 6.1 and 8.5 across quartiles of concentration levels ($p=0.05$ for trend) and similar odds ratios of 1.0, 2.2, 4.4 and 5.4 were found across quartiles of nondioxin-like PCBs concentration levels ($p<0.01$ for trend). In women, rheumatoid arthritis was found to be more strongly associated with PCBs than osteoarthritis. For males, there was no significant association between any POPs and arthritis in general, and results for the subcategory of rheumatoid arthritis were not provided (not statistically significant). There was no significant association with arthritis found for PCDDs and PCDFs in either gender.

53. Compared to other studies in the medical literature on the association between PCBs and RA , some strengths of this study include: the large sample size collected; the adjustment of results for a range of possible confounding variables (e.g age, BMI and smoking); some evidence of dose-response relationships; separation of both the different types of exposures (POPs) and subcategories of arthritis (osteoarthritis and rheumatoid arthritis); and the potential absence of self-reporting bias for the exposure. However, as a cross-sectional study, no temporal relationships could be examined and only background exposure is considered, with actual concentration levels difficult to determine from the information provided. Notwithstanding these issues, the Council considered this study to provide the best evidence to date of any possible association between PCBs and rheumatoid arthritis. Further, the Council noted that the study found no association between any arthritis and PCB levels in males.

54. Lundberg (1994)[11] conducted a population based retrospective cohort study examining the association between rheumatoid arthritis and various occupational exposures. The study population consisted of 375,035 men and 140,139 women who had remained in the same occupation for 10 years between 1960 and 1970 across 13 Swedish counties. The subjects were then followed in relation to their hospital care for rheumatoid arthritis by linkage to the Swedish Hospital Discharge Register for the period 1981 to 1983. Occupational exposures were assessed using a job exposure matrix and a range of exposures were examined including mineral oils (cutting oils) and PCBs. The Council noted that the determination of exposure in this study, and these types of studies, is prone to misclassification and is likely to be quite variable between occupations, making any assessment of actual exposure problematic. On the other hand, the ascertainment of rheumatoid arthritis using hospital records is more certain albeit likely to reflect in this case the more severe cases. The authors reported a relative risk for exposure to PCBs and rheumatoid arthritis (in men) to be 1.1 (95% CI, 0.7 to 1.7) which was not statistically significant. The relative risk of exposure to mineral oils (used during cutting tasks) and rheumatoid arthritis (in men) was also not statistically significant (RR = 1.1 (95% CI, 0.8 to 1.3)). There were no statistically significant results for any exposures for women although numbers were small.

55. A similar occupational based study to that of Lundberg (1994)[11] was conducted by Olsson (2004)[12] in a case-control study. Lifelong occupational history together with exposure experiences were collected through a postal questionnaire which resulted in 293 incident cases of rheumatoid arthritis and 1,346 population based referents. A pooled analysis was also conducted using previously gathered data on 422 prevalent cases and 858 referents. The ascertainment of rheumatoid arthritis was made by a rheumatologist. After adjustment for age and smoking in the pooled analysis there was no statistically significant association between mineral oils and rheumatoid arthritis (OR = 1.2 (95% CI, 0.7 to 2.1). There was no mention of exposure to PCBs in the study. The Council noted that similar misclassification problems to Lundberg (2004) are likely to be prevalent in the assessment of exposure using occupational history as a surrogate for actual exposure.

Evidence from industrial cohort studies

56. The Council reviewed several studies examining the association between various exposures (including PCBs) and a range of health outcomes in cohorts of industrial workers. Most of the studies reviewed[16-18,20-23] did not examine rheumatoid arthritis as an outcome and were not considered by the Council to provide useful information for this review. Two industrial cohort studies which did provide some

information on the association between rheumatoid arthritis and PCBs were Cappelletti (2016)[19] and Illinois Dept (2004)[15].

57. Cappelletti (2016)[19] conducted a retrospective cohort study to examine whether workers of an Electric Arc Furnace (EAF) in Trento, Italy, were at increased risk for a range of health conditions or outcomes, including diabetes, cardiovascular diseases, rheumatoid arthritis and death. A total of 235 workers in the morbidity part of the study were followed for up to 30 years and were mainly exposed to foundry dust containing a number of agents including arsenic, polycyclic aromatic hydrocarbons (PAHs), polychlorinated byphenyls (PCBs) and dioxins. From the 235 workers participating, only three cases of rheumatoid arthritis were identified and when compared to the risk in the local population was found to lead to a significant increase in risk (RR = 6.17 (95% CI, 2.00 to 19.02), p=0.01). The study did not attempt to separate the effects of PCBs from the other agents to which workers were exposed. Due to the small number of rheumatoid arthritis cases identified and the exposure representing a range of agents in addition to PCBs, the Council considered the strength of evidence for an association between PCBs and rheumatoid arthritis from this study to be low.

58. Illinois Dept (2004)[15] conducted a retrospective cohort study of workers from the La Salle Electrical Utilities Company (EUC) which manufactured electrical capacitors at the plant from 1943 to 1981. In the early 1950s, EUC started utilising PCBs and various volatile organic compounds (VOCs) in the manufacturing process. In a cross-sectional examination within the larger cohort of 3,305 workers, a telephone interview was conducted of 596 former employees relating years of working at the plant with health outcomes in the former employees and their children. Ascertainment of rheumatoid arthritis was made using self-report and PCB exposure was assessed by ranking job title and areas a participant worked in the plant from low to high in terms of the likelihood of dermal contact with PCB oil. In a Cox regression analysis, and allowing for years of exposure, the study found no significant association between rheumatoid arthritis and PCBs (HR = 0.72 (95% CI, 0.38 to 1.35)). Similar to other occupational studies reviewed[16-18,20-23], the Council noted concerns with this study in terms of both the reliability of ascertainment of rheumatoid arthritis (self-reported) and poorly defined exposure criteria.

Reviews

59. The Council identified a number of relevant reviews of the medical literature examining the association between PCBs and rheumatoid arthritis[24-37]. A critical

review conducted by Swanson et al (1995)[25], which took into account the strengths and weaknesses of the studies from an epidemiological perspective and included the study by Lee et al (2007)[10], found no evidence of an association between PCBs and rheumatoid arthritis. The Council noted that other reviews since then[24,26-37] have not updated or changed this assessment.

Summary of evidence - overall

60. The Council found that there was insufficient SMSE to support the contention that exposure to PCBs causes rheumatoid arthritis, either because PCBs were only one of the possible agents the participants in the studies were exposed to and/or because the definition of the outcome was not adequate to clearly identify rheumatoid arthritis, as opposed to other types of arthritis or joint pain.

Evidence for a potential mechanism for an association between PCBs and RA through immune dysregulation or impairment

61. The Council also considered evidence for a potential mechanism for an association between PCBs and RA through immune dysregulation or impairment. The Council reviewed a number of studies which examined the association of PCBs with impaired or disturbed immune function arising from the Yusho or Yucheng incident[4,39] and other population[14] or occupational based cohort studies[13] conducted.

62. Kuwatsuka (2014)[39] compared and examined blood levels from 40 Yusho patients and a similar number of age-matched healthy Japanese residents (controls). The authors hypothesised that Yusho patients would show dysregulated T_H17 cell-mediated immune responses. To validate the hypothesis, levels of IL-17 and IL-22 secreted by T_H17 cells, potentially secreted tumor necrosis factor (TNF)- α, and levels of IL-1β and IL-23 were measured and each sample was tested in duplicate.

63. The study found significantly higher levels of serum IL-17, TNFα, IL-1β and IL-23 in Yusho patients compared to controls. In contrast, serum IL-22 levels were significantly lower in Yusho patients than in controls. There was a weak negative correlation between IL-17 levels and PCB levels but no statistically significant correlation was found for the other markers (IL-22, TNFα, IL-1β and IL-23). Overall, the Council found that the results are suggestive of a possible immune dysregulation and mechanistic link to immune mediated inflammation such as rheumatoid arthritis for Yusho patients and a mixture of PCBs, PCDs and PCQs but the findings are limited by the small number of patients examined and inconsistency with the direction of effects seen.

64. Nagayama et al (2001)[4] examined levels of polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzo-furans (PCDFs) and coplanar-PCBs (Co-PCBS) on thyroid hormone and immune systems for 16 Yusho patients at around 30 years after exposure. At the time, the patients' toxic equivalent (TEQ) levels were approximately seven times higher than in healthy Japanese people.

65. Despite the high blood TEQ concentrations, serum levels of thyroid hormones, thyroid stimulating hormones (TSH), immunoglobins (A, G and M), autoantibodies (antinuclear antibody, rheumatoid and lupus erythematosus (LE) factors) and lymphocyte subsets in the blood were not found to be elevated in the Yusho patients. However, the detection rates of rheumatoid factor were found to increase in higher TEQ groups (3.8% in the lowest group, 16.7% in the middle group and 21.1% in the highest group) although they were not significantly different. Separate results based on PCBs were not provided. The authors note that further studies using a larger number of patients are needed to obtain more conclusive findings.

66. Daniel (2001)[13] studied 146 patients who had been occupationally exposed primarily to PCBs for more than six months for evidence of immunological impairments across a range of immune system parameters. The study found only a weak dose response relationship between blood levels of PCBs with cellular immune parameters (in vitro lymphocyte stimulation and the numbers of lymphocyte subpopulations in the blood, as well as titers of different antibody types against immunoglobin parameters). Only a significant negative association of hexachlorocyclohexane-α (HCH-α) with interferon-γ (IFN-γ) was found.

67. The Council also reviewed some studies examining the association of immunoglobin concentrations IgG, IgA and IgM to the development of rheumatoid arthritis where relatively high levels of these immunoglobin concentrations have been observed from the Yusho incident based upon a small number of patients (n=40) examined in Kuwatsuka (2014)[39]. In a case control study (nested within a large cohort) Aho (1997)[14] followed 19,072 Finnish adults who had neither arthritis nor a history at baseline during 1973-79 to the end of 1989. The study found a significant positive association between IgG and rheumatoid factor (RF) positive rheumatoid arthritis. After adjusting for a range of possible confounding variables, the odds ratios of RF positive rheumatoid arthritis in the lowest, mid and highest tertiles of IgG distribution were 1.00, 1.55 (95% CI, 0.81 to 2.97) and 2.22 (95% CI, 1.16 to 4.26). The association persisted throughout the entire observation period but were most distinct when the period of onset to clinical

rheumatoid arthritis was greater than 10 years. A non-linear association was found for IgA and the risk of RF positive rheumatoid arthritis but no significant association was found for IgM. The Council noted that these results may suggest a possible mechanistic link between high IgG levels found in the Yusho patients and the development of rheumatoid arthritis however a specific analysis of that question has not been reported and further research and analyses are needed.

Summary of evidence and conclusion

68. The Council found that there was no consistent SMSE regarding potential mechanisms for PCBs causing rheumatoid and altered immunity leading to rheumatoid arthritis.

Council's analysis of the new information

69. As mentioned above, in conducting a review, the Council is unable to (and so did not) consider information which was not available to (not before) the RMA at the relevant times. However, having formed the view that there was nothing in the pool of information which pointed to the relevant association, and being mindful of the Applicant's comments, the Council considered whether in its view there was a basis for recommending to the RMA that it (the RMA) undertake a new investigation.

70. The Council has neither the capacity nor the jurisdiction to perform an investigative function, including undertaking a comprehensive literature search. However, by reason of the Councillors' specialist expertise in this kind of injury, disease or death, the Council was aware of some new **information (listed at B2 of Appendix B)** which it considered on a preliminary basis.

71. The Council considered the new information to determine whether, in the Council's view, it warranted the Council making any directions or recommendations to the RMA.

72. 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:

- was information epidemiologists would consider appropriate to take into account; and

- in the Council's view, 'touched on' (was relevant to) the contended factor; and could potentially satisfy the reasonable hypothesis and/or balance of probabilities tests (as appropriate; see paragraphs [<>] and [<>] above for the relevant associations).

73. The applicant provided additional papers (listed at B2 of Appendix B). Recognising that this material could not influence the Council's decision because it had not been before the RMA, the Council nevertheless considered this material for completeness.

74. The Council considered that the toxicity studies and hazard guidelines provided by the applicant being based on evidence from studies on effects in response to certain toxins, were not relevant to the review, particularly where they did not refer specifically to the condition of rheumatoid arthritis.

75. The Council further considered that a number of website articles referred by the applicant were not sound medical-scientific evidence in that they were opinion based, were not subject to peer review or, so far as concerning causes of rheumatoid arthritis, did not meet the applicable criteria for assessing causation currently applied in the field of epidemiology.

76. Given that at the Oral Hearing, the applicant drew the Council's attention to the study by Akahane et al (2018)[38] the findings from this study are reviewed in detail below.

77. Akahane et al (2018)[38] conducted a comparative study involving 1,131 patients from the Yusho incident and using the registry established to identify victims they were then matched to a comparison group of participants in the community taking into account age and residential area (n ≈ 1,080). Ascertainment of rheumatoid arthritis was undertaken by self-reporting without clinical validation and assessment of exposure was based on ingestion of rice bran oil contaminated with PCBs and other dioxins and dioxin like compounds. Logistic regression analysis was performed to examine the association between the Yusho patients and various symptoms after adjusting for various potential confounding factors (age, sex, BMI, cigarette smoking, frequency of driving and walking time). The study reported 40 cases of rheumatoid arthritis in the Yusho group compared to 19 cases in the comparison group. After adjustment for the role of possible confounding variables, the study found a significant association between the Yusho patients and rheumatoid arthritis with an odds ratio of 3.29 ((95% CI, 1.59 to 6.81), p=0.001). Significant associations were also found for joint pain (OR =

3.27 (95%CI, 2.56 to 4.18)), back pain (OR = 1.92 (95%CI, 1.57 to 2.36)), and muscle pain (OR = 2.47 (95%CI, 1.87 to 3.27)). The Council had concerns about the absence of a clinical validation of rheumatoid arthritis in Yusho patients in whom an over-reporting bias would be more likely. The Council also noted that the reporting in the community control group appeared lower than would be expected when compared to a similar age group in the Australian population.[42]

78. The Council was not sufficiently persuaded of the matters in [72] to make any recommendations to the RMA concerning undertaking a fresh investigation.

DECISION

79. The Council made the declarations summarised at paragraph 1 above.

REFERENCES

1. Guo YL, Yu ML, Hsu CC, Rogan WJ (1999). Chloracne, goiter, arthritis, and anemia after polychlorinated biphenyl poisoning: 14-year follow-up of the Taiwan Yucheng cohort. Environmental Health Perspectives, 107(9): 715- 719. **RMA ID 18242**

2. Yoshimura T (2003). Yusho in Japan. Ind Health, 41(3): 139-48. **RMA ID 47838**

3. Yoshimura, T. & Hayabuchi, H (1985). Relationship between the amount of rice oil ingested by patients with Yusho and their subjective symptoms, Environ Health Perspect, vol. 59, pp.47-51. **RMA ID 48819**

4. Nagayama J, Tsuji H, Iida T, Hirakawa H, Matsueda T, Ohki M (2001). Effects of contamination level of dioxins and related chemicals on thyroid hormone and immune response systems in patients with "Yusho". Chemosphere, 43: 1005-10. **RMA ID 65354**

5. Tsuji H, Hirahashi T, Ogata H, et al (1999). Serum immunoglobulin concentrations and autoantibodies in patients with Yusho. Fukouka Igaku Zasshi, 90(5): 147-9 [Article in Japanese]. [Abstract] **RMA ID 47834**

6. Tsuji H. (2000). Immune effects of endocrine disrupters. Nihon Rinsho, 58(12): 2533-8. [Article in Japanese]. [Abstract] **RMA ID 80759**

7. Kanagawa Y, Matsumoto S, Koike S (2008). Association of clinical findings in Yusho patients with serum concentrations of polychlorinated biphenyls, polychlorinated quarterphenyls and 2,3,4,7,8-pentachlorodibenzofuran more than 30 years after the poisoning event. Environ Health 7:47. **RMA ID 79237**

8. Masuda Y on behalf of the Study Group for Yusho (2005). Behaviour and toxic effects of PCBs and PCDFs in Yusho patients for 35 years. Journal of Dermatological Science Supplement Volume 1, Issue 1, Pages 511-520 (April 2005). **RMA ID 80657**

9. Kanagawa Y, ImamuraT, on behalf of the Study Group for Yusho (2005). Relationship of clinical symptoms and laboratory findings with blood levels of PCDFs in patients with Yusho. Journal of Dermatological Science Supplement Volume 1, Issue 1, Pages 885-593. **RMA ID 80636**

10. Lee D-H, Steffes M, Jacobs DR Jr (2007). Positive associations of serum concentration of polychlorinated biphenyls or organochlorine pesticides with self-reported arthritis, especially rheumatoid type, in women. Environmental Health Perspectives, 115(6): 883-888**. RMA ID 46247**

11. Lundberg I, Alfredsson L, Plato N, Sverdrup B, et al (1994). Occupation, occupational exposure to chemicals and rheumatological disease. Scand J Rheumatol, 23: 305-310. **RMA ID 5681**

12. Reckner Olsson A, Skogh T & Wingren G (2004). Occupations and exposures in work environment as determinants for rheumatoid arthritis. Occup Environ Med*,* 61: 233-238. **RMA ID 30451**

13. Daniel V, Huber W, Bauer K, et al (2001). Associations of blood levels of PCB, HCHs, and HCB with numbers of lymphocyte subpopulations, in vitro lymphocyte response, plasma cytokine levels, and immunoglobulin autoantibodies. Environ Health Perspect. 109: 173-8. **RMA ID 79244**

14. Aho K, Heliovaara M, Knekt P, et al. (1997). Serum immunoglobins and the risk of rheumatoid arthritis. Ann Rheum Dis, 56(6): 351-6. **RMA ID 47840**

15. Illinois Department of Public Health and the University of Chicago: Final Report. The La Salle electrical utilities company morbidity II study. Obtained from: http://hdl.handle.net/123456789/5549 **RMA ID 47839**

16. Brown D.P. (1987). Mortality of workers exposed to polychlorinated biphenyls-an update. Environ Health, 42: 33-40. **RMA ID 14861**

17. Emmett EA, Maroni M, Schmith JM, et al (1988). Studies of transformer repair workers exposed to PCBs: I. study design, PCB concentrations, questionnaire, and clinical examination results. Am J Ind Med, 13: 415-27**. RMA ID 47832**

18. Gustavsson P, Hogstedt C. (1997). A cohort study of Swedish capacitor manufacturing workers exposed to polychlorinated biphenyls (PCB's). Am J Ind Med, 32(3): 234-9. **RMA ID 40028**

19. Cappelletti R, Ceppi M, Claudatus J, et al (2016). Health status of male steel workers at an electric arc furnace (EAF) in Trentino, Italy. J Occup Med Toxicol, 11: 7. **RMA ID 79240**

20. Kimbrough RD, Doemland ML, Mandel JS (2003). A mortality update of male and female capacitor workers exposed to polychlorinated biphenyls. JOEM, 45(3): 271-82. **RMA ID 38757**

21. Kitamura K, Kikuchi Y, Watanabe S, Waechter G, et al (2000). Health effects of chronic exposure to polychlorinated dibenzo-P-dioxins (PCDD), dibenzofurans (PCDF) and coplanar PCB (Co-PCB) of municipal waste incinerator workers. Journal of Epidemiology, 10(4): 262-70. **RMA ID 48043**

22. Prince MM, Hein MJ, Ruder AM, Waters MA, et al (2006). Update: cohort mortality study of workers highly exposed to polychlorinated biphenyls (PCB's) during the manufacture of electrical capacitors, 1940-1998. Environmental Health, 5: 13. **RMA ID 41895**

23. Ruder AM, Hein MJ, Nilsen N, Waters MA, et al (2006). Mortality among workers exposed to polychlorinated biphenyls (PCB's) in an electrical capacitor manufacturing plant in Indiana: an update. Environmental Health Perspectives, 114(1): 18-23. **RMA ID 41902**

24. Ross G (2004). The public health implications of polychlorinated biphenyls (PCBs) in the environment. Ecotoxicol Environ Saf. Nov;59(3).275-91. **RMA ID 47827**

25. Swanson GM, Ratcliffe HE, Fischer LJ (1995). Human exposure to polychlorinated biphenyls (PCBs): a critical assessment of the evidence for adverse health effects. Regul Toxicol Pharmacol. Feb,21(1):136-50. **RMA ID 47827**

26. American Council on Science and Health (1997). Position paper on the public health concerns about environmental polychlorinated biphenyls (PCBs). Ecotoxicol Environ Saf. Nov,38(2):71-84. **RMA ID 80547**

27. Abella V, Perez T, Scotece M, et al (2016). Pollutants make rheumatic diseases worse: facts on polychlorinated biphenyls (PCBs) exposure and rheumatic diseases. Life Sciences, 157: 140-4. **RMA ID 79249**

28. Carpenter DO (2006). Polychlorinated biphenyls (PCBs)- routes of exposure and effects on human health. Reviews on Environmental Health, 21(1)- 1-23. **RMA ID 45909**

29. Agency for Toxic Substances and Disease Registry (ATSDR) (2011). Addendum to the toxicological profile for polychlorinated biphenyls. Retrieved 30 January 2017, from https://www.atsdr.cdc.gov/toxprofiles/pcbs_addendum.pdf" **RMA ID 80554**

30. Agency for Toxic Substances and Disease Registry (ATSDR) (2017). Polychlorinated biphenyls (PCBs) toxicity. What are the adverse health effects of PCB exposure? https://www.atsdr.cdc.gov/csem/csem.asp?csem=30&po=10. Retrieved 1 February 2017, from https://www.atsdr.cdc.gov/csem/csem.asp?csem=30&po=10" **RMA ID 80562**

31. Bigazzi PE (1997). Autoimmunity caused by xenobiotics. Toxicology, 119: 1-21. **RMA ID 79227**

32. Cooper GS, Miller FW, Germolec DR (2002). Occupational exposures and autoimmune diseases. International Immunopharmacology, 2(2-3): 303-13. **RMA ID 30666**

33. Danish Ministry of the Environment (2014). Evaluation of health hazards by exposure to polychlorinated biphenyls (PCB) and proposal of a health-based quality criterion for soil. Environmental Protection Agency, Environmental Project No. 1485. **RMA ID 79225**

34. Fonnum F, Mariussen E, Reistad T (2006). Molecular mechanisms involved in the toxic effects of polychlorinated biphenyls (PCBs) and brominated flame retardants (BFRs). Journal of Toxicology and Environmental Health, Part A, 69: 21-35. **RMA ID 47944**

35. Kimbrough RD & Krouskas CA (2003). Human exposure to polychlorinated biphenyls and health effects. Toxicol Rev, 22(4): 217-33**. RMA ID 47943**

36. Miller FW, Alfredsson L, Costenbader KH, et al (2012). Epidemiology of environmental exposures and human autoimmune diseases: findings from a national institute of environmental health sciences expert panel workshop. J Autoimmun, 39(4): 259-71. **RMA ID 79236**

37. Yoshizawa K, Heatherly A, Malarkey DE, Walker NJ et al (2007). A critical comparison of murine pathology and epidemiological data to TCD, PCB126, and PeCF. Toxicol Pathol, 35(7): 865-79. **RMA ID 67014**

38. Akahane M, Matsumoto S, Kanagawa Y, et al (2018). Long-term health effects of PCBs and related compounds: a comparative analysis of patients suffering from Yusho and the general population. Arch Environ Contam and Toxicol, 74: 203-17. **NEW INFORMATION**

39. Kuwatsuka Y, Shimizu K, Akiyama Y, et al (2014). Yusho patients show increased serum IL-17, IL-23, IL-1b, and TNFa levels more than 40 years after accidental polychlorinated biphenyl poisoning. J Immunotoxicol, 11(3): 246-9. **RMA ID 79247**

40. Furue M, Uenotsuchi T, Urabe K, et al. (2005). Overview of Yusho. J Dermatol Sci, S3-10. **RMA ID 80614**

41. Hill, A. B. (1965). The Environment and Disease: Association or Causation? Proceedings of the Royal Society of Medicine. 58 (5): 295–300

42. Australian Bureau of Statistics (ABS), (2015). National Health Survey: First Results, 2014-15. 4364.0.55.001.