Specialist Medical Review Council

Declaration and Reasons for Decisions

Section 196W
Veterans’ Entitlements Act 1986

Re: Statements of Principles Nos. 69 and 70 of 2012
in respect of Myeloma
Request for Review Declaration No. 23

1. In relation to the Repatriation Medical Authority (the RMA) Statement of Principles No. 70 of 2012 concerning myeloma and death from myeloma, made under subsection 196B (3) of the Veterans’ Entitlements Act 1986 (the VEA), the Specialist Medical Review Council (the Council) under subsection 196W of the VEA:

   DECLARES that the sound medical-scientific evidence available to the RMA is insufficient to justify an amendment to Statement of Principles No. 70 of 2012 to include a factor or factors in the same or similar terms to existing factors 6(c) and 6(d) in Statement of Principles No. 69 of 2012.

2. In relation to the RMA Statements of Principles Nos. 69 and 70 of 2012 concerning myeloma and death from myeloma, made under subsections 196B (2) and 196B (3) of the VEA, the Council under subsection 196W of the VEA:

   DECLARES that there is sound medical-scientific evidence on which the RMA could have relied to amend both the Statements of Principles to include the factor set out below; and

   DIRECTS the RMA to amend both Statements of Principles Nos. 69 and 70 of 2012 by including the following factor:

   Having exposure to 2,3,7,8 tetrachlorodibenzo-para-dioxin (TCDD) sufficient to produce an expected initial serum TCDD level of at least 1500 parts per trillion before the clinical onset of myeloma.
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REASONS FOR DECISIONS

INTRODUCTION TO THE COUNCIL AND ITS FUNCTIONS

3. 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.

4. Again in general terms, in conducting a review, the Council must review all the information that was available to (before) the RMA when it determined, amended, or last amended the Statement/s of Principles (or decided, or last decided not to determine or amend a Statement/s of Principles) in respect of a particular kind of injury, disease or death. The Council is constrained to conduct its review by reference to the available information only.¹

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

6. Appendix A sets out further details:
   – of the composition of the Council for this review;
   – consideration by a previously constituted Council of Statements of Principles previously in force in respect of myeloma and death from myeloma;
   – the legislative scheme; and
   – the information that was available to (before) the RMA.

THIS REVIEW

7. The Applicant in his application sought review of the contents of Statements of Principles Nos. 69 and 70 of 2012 concerning myeloma.² However, in

¹ 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.
² Statements of Principles Nos. 69 and 70 of 2012 each define myeloma as:
   …a malignant disease of plasma cells, in which a single line of plasma cells accumulates and produces a monoclonal immunoglobulin. This definition includes plasma cell leukaemia, multiple myeloma and solitary plasmacytoma of bone or extramedullary plasmacytoma, but excludes monoclonal gammopathy of undetermined significance.

The Council noted the statement on the RMA website that Myeloma was “previously known as - multiple myeloma”. The Council considered the two descriptions are of the same disease and
the Council's view, the Applicant did not raise a valid ground for review of the contents of Statement of Principles No. 69 of 2012, as the Applicant's contentions concerning that Statement of Principles were that it should apply to veterans other than those who had had (in general terms) operational service. The VEA specifies to whom Statement of Principles No. 69 of 2012 applies. In the Council's view the Applicant's contentions in this regard raised a question of law, and so were not a matter in respect of which the Council had jurisdiction.

3. The VEA specifies to whom Statement of Principles No. 69 of 2012 applies. In the Council's view the Applicant's contentions in this regard raised a question of law, and so were not a matter in respect of which the Council had jurisdiction.

4. The Applicant clarified that his contention was that there was sound medical-scientific evidence on which the RMA could have relied to include in Statement of Principles No. 70 of 2012 a factor or factors in the same or similar terms to existing factors 6(c) and 6(d) in Statement of Principles No. 69 of 2012.

5. The Council later expanded the scope of its review to include exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) at very high doses.

6. Appendix B sets out further details of the background to this review.

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8. The Council later expanded the scope of its review to include exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) at very high doses.

9. The Council later expanded the scope of its review to include exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) at very high doses.

10. Appendix B sets out further details of the background to this review.

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3. See footnote 9 for the relevant service to which the reasonable hypothesis Statement of Principles No. 69 of 2012 applies.

4. The Council advised the Applicant of its preliminary view in a letter dated 21 February 2013, and provided the Applicant an opportunity to comment.

5. There are no existing factors in Statement of Principles No. 70 of 2012 dealing with the exposures in existing factors 6 (c) and 6 (d) of Statement of Principles No. 69 of 2012.

Existing factor 6(c) in Statement of Principles No. 69 of 2012 provides:

inhaling, ingesting or having cutaneous contact with a phenoxy acid herbicide from the specified list, for a cumulative period of at least 1000 hours, within a consecutive period of ten years before the clinical onset of myeloma, where the first exposure occurred at least five years before the clinical onset of myeloma; and

Existing factor 6(d) in Statement of Principles No. 69 of 2012 provides:

inhaling, ingesting or having cutaneous contact with a chemical agent contaminated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), for a cumulative period of at least 1000 hours, within a consecutive period of ten years before the clinical onset of myeloma, where the first exposure occurred at least five years before the clinical onset of myeloma.

'A phenoxy acid herbicide from the specified list' and 'Inhaling, ingesting or having cutaneous contact with a chemical agent contaminated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)' are terms defined in paragraph 9 of Statement of Principles No. 69 of 2012 (see [149]).

6. The details of the expanded scope are set out at paragraph 150.
Appendix C sets out the details of the preliminary and amended scope of this review.

The Council accordingly reviewed the sound medical-scientific evidence relevant to the Applicant’s contentions (essentially, inhaling, ingesting or having cutaneous contact with a phenoxy acid herbicide from the specified list and/or inhaling, ingesting or having cutaneous contact with a chemical agent contaminated by TCDD as set out by the Council in the scope of review (See Appendix C).

THE COUNCIL’S PROCESS

In conducting a review, the Council identifies from all of 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 [133]) - which in its view ‘touches on’ (i.e. is relevant to) the issue of whether a particular kind of injury, disease or death (in this review, myeloma) can be related to service with the exposure under consideration.

Considering all the relevant information, the Council decides whether or not there is sound medical-scientific evidence that indicates a reasonable hypothesis connecting the particular kind of injury, disease or death to relevant service. 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.’

If Council is of the opinion that there is a reasonable hypothesis, members then determine, in addition, whether a connection exists to relevant service on the balance of probabilities, i.e. whether the connection is more

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7 The Council did not consider information about other chemicals mentioned by the Applicant such as Phenyl mercury acetate; Chlordane; Dieldrin; Azinphos-methyl; Tecto 90 as the Council considered them outside the scope of the Applicant’s contentions.

8 Given the Council’s proposed expansion to the scope of review to include a potential factor concerning exposure to high doses of TCDD, the Council also reviewed the sound medical-scientific evidence which touched on that contention (see Appendix C).

9 Relevant service in reasonable hypothesis statements of principles 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.

10 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].

11 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].

12 Relevant service in balance of probabilities statements of principles 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.
probable than not. The balance of probabilities test of association between relevant disease and service is less easily satisfied than in a reasonable hypothesis, so if the balance of probabilities test was satisfied, the reasonable hypothesis test must also be met. If, however, the reasonable hypothesis test was not met, the balance of probabilities test could not be met.

16. In these Reasons the association for both the reasonable hypothesis test (at [14]) and the balance of probabilities test (at [15]) are respectively referred to as the ‘relevant association’.

17. Noting that Councillors are appointed to a particular review because of their specialist expertise in the particular condition (in this case, myeloma) and the matters within the scope of the Review, the Council exercises its scientific judgement in weighing the evidence about the relevant association. Appendix A sets out further details of the legislative framework for the Review.

SCOPE OF REVIEW AND POOL OF INFORMATION

18. Appendix C sets out:

– the Council’s preliminary and final decisions on the scope of review;
– the Council's preliminary and final decisions on the pool of information; and
– the steps taken by the Council to discharge its procedural fairness obligations regarding the scope of review and pool of information.

WRITTEN AND COMPLEMENTARY ORAL SUBMISSIONS

19. The Council took into account all the submissions made to it, both written and oral. The Council's summaries of the respective submissions of the Applicant and the Commissions are set out at Appendix D.

COUNCIL’S EVALUATION OF THE INFORMATION IN THE POOL

20. The Council noted that myeloma is a rare cancer (prevalence of 4 - 5 of 100,000 13), and considered that this was reflected in the low case numbers in the studies in the pool.

21. The Council focussed on the information relevant to those chemicals in scope (see below and the lists at [149] Appendix C – Scope of Review), noting that many of the studies did not sufficiently identify specific chemicals but only referred to the class of chemicals (phenoxy acid

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13 Kyle, RA et al 2004, ‘Incidence of multiple myeloma in Olmsted County Minnesota: Trend over 6 decades’, Cancer, vol. 1, no. 11, pp. 2667-74. This information was not available to the RMA, and so was not considered by the Council in determining the matters within the scope of the review.
herbicides). The Council took into account studies with outcomes for phenoxy acid herbicides to the extent that they provided evidence that touched on either or both of:

- Inhaling, ingesting or having cutaneous contact with a phenoxy acid herbicide [from the specified list in Statement of Principles No. 69 of 2012], that is, 2,4-dichlorophenoxyacetic acid (2,4-D), and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T); and

- Inhaling, ingesting or having cutaneous contact with a chemical agent [as specified in Statement of Principles No. 69 of 2012] contaminated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD);

22. While most of the chemical agents specified in Statement of Principles No. 69 of 2012 as potentially contaminated by TCDD were included in the relevant sound medical-scientific evidence in the pool by reference to the class of chemical to which they belong, the sound medical-scientific evidence did provide outcomes specific to 2,4,5-T (as a phenoxy acid herbicide by itself, and as a chemical agent that is considered to be contaminated by TCDD).

EVALUATION OF ARTICLES TOUCHING ON THE APPLICANT’S CONTENTIONS

23. For the Council, consideration of the statistical data was a necessary, but not a sufficient, consideration of whether the statutory tests were met. The Council, in considering the matters within the scope of the review, evaluated all the studies in the pool of information. The Council, having closely evaluated all the information in the pool, placed particular weight on the articles discussed in detail below.

24. The Council did not focus in its evaluation on those articles that:

- were reviews of available information that the Council has evaluated in these reasons for decisions;

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15 In considering the Applicant's contention in this review the Council did not need to consider the reasonable hypothesis test given the Applicant's clarification of his contentions as set out in [8] above. With respect to the possibility of a factor or factors concerning exposure to TCDD in very high doses if the Council concluded that the sound medical-scientific evidence satisfied the balance of probabilities test, it necessarily met the reasonable hypothesis test. If the Council concluded that the sound medical-scientific evidence concerning such an exposure did not satisfy the balance of probabilities test, whether it met the reasonable hypothesis test would require separate consideration.
- did not provide data that the Council could draw conclusions on about the phenoxy acid herbicides or chemicals contaminated by TCDD (as specified) and myeloma;
- had such small numbers of cases of myeloma that the Council could not draw conclusions concerning any associations with myeloma.

25. In the Council’s view the Agricultural studies and the Vietnam veteran studies were the most relevant evidence for its consideration of the Applicant’s contention that existing factors 6(c) and 6(d) in Statement of Principles No. 69 of 2012 (see [21] above) should be replicated in the same or similar terms in Statement of Principles No. 70 of 2012 (the balance of probabilities Statement of Principles)

**Agricultural Studies**

26. **Landgren, et al 2009**\(^{16}\) found that the prevalence of MGUS (monoclonal gammopathy of undetermined significance), a potential precursor of multiple myeloma, was twice that in matched non-applicants in restricted-use pesticide applicators aged over 50 (555 of the 678 study subjects).

27. Insecticides, herbicides and fungicides showed non-significant excess risk, including the herbicide 2,4-D (OR= 1.8, 95% CI 0.7 – 4.8; 33 cases)\(^{17}\).

28. The Council noted that serum samples were analysed for MGUS, but there was no indication that serum TCDD levels were determined. Self-administered questionnaires were used to assess exposure to pesticides with no specific level of exposure data provided.

29. The Council considered that since no MGUS was detected in applicators aged under 50 (n = 123), and that the prevalence increased with age thereafter to a total of 38/555 subjects, it is not possible to extrapolate these findings to Myeloma, as no cases of myeloma were found.

30. **Eriksson, M et al 1992**\(^{18}\) compared 275 cases (156 alive and 119 deceased) with confirmed multiple myeloma with controls matched by age, sex and county extracted from the Swedish National Population.

31. Exposure by univariate analysis to phenoxy acids gave a relative risk (RR) = 2.22, 90% CI 1.15 - 4.66 (20 exposed cases)\(^{19}\)

\(^{16}\) Landgren, O et al 2009, ‘Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study’, *Blood*, vol. 113, no. 25, pp. 6386-91. RMA ID 58798 / 58816

\(^{17}\) OR = Odds Ratio; CI = Confidence Interval

32. On multivariate analysis the authors noted that for phenoxy acid herbicides:

...risks decreased somewhat, and were non-significantly...increased.20

33. In the Council’s view the absence of a duration-response relationship and the not significantly elevated risk were important factors, limiting extrapolation from the study.

34. Mills, PK et al 200521 identified a total of 131 lymphohematopoietic cancers (LHC) diagnosed between 1998 and 2001 in Californian farm workers who had been exposed to pesticides (15 high use chemicals including the herbicide 2,4-D). Each case was compared with five members drawn from the 139,000 ever-members of the United Farm Workers of America matched on age, gender and cancer-free status.

35. The Council noted that for the 20 cases of multiple myeloma (14/94 males, 6/37 females), the authors found no elevated risks from exposure to pesticides, but the data were not further detailed and thus Council assigned little weight to the study. The Council considered that the study does not support an association for 2,4-D with myeloma.

36. Morris-Brown, et al 199322 provided a population-based case-control study of 173 subjects with multiple myeloma and 650 controls in a farming area in Iowa. The study collected information about exposure to 24 animal insecticides, 34 crop insecticides, 38 herbicides, and 16 fungicides, including whether the chemical agents were mixed, handled, or applied, together with the use of protective equipment.

37. The Council noted that the authors provided data23 on the specific phenoxy acid herbicides referred to by the Applicant and found no difference in risk for multiple myeloma in farmers who handled:

a. 2,4-D (35 cases) OR = 1.0; 95% CI 0.6 – 1.6; or

b. 2,4,5-T (7 cases) OR = 0.9; 95% CI 0.4 – 2.1.

38. The Council regarded this as a well-conducted study with appropriate controls, showing no evidence for an increased prevalence of myeloma in subjects exposed to 2,4-D or 2,4,5-T.

19 Ibid Table 1 at p. 98
20 Ibid at p. 101
23 Ibid, Table 2 at p. 154.
39. A French hospital-based case-control study by Orsi, L et al 2009\(^{24}\) conducted in six centres in between 2000 and 2004 amassed 491 cases of lymphoid neoplasm (excluding acute lymphoid leukemia), of which 56 were multiple myeloma.

40. For phenoxy herbicides, in seven exposed subjects (farm workers) the OR for myeloma = 2.6, 95% CI 0.9 - 7.0.

41. The Council noted that the data for phenoxy herbicides, which could include 2,4-D and 2,4,5-T were consistent with, but not strong evidence for an increased risk in that the number of cases was small and the confidence intervals were wide, so decreasing the weight the Council gave to this study.

42. The population-based study Canadian study by Pahwa, P et al 2006\(^{25}\) of DEET (N, N-diethyl-m-toluamide - insect repellent), rubber gloves, sunlight and phenoxy herbicides included 342 cases of multiple myeloma, plus a total of 1506 controls.

43. Exposure to 2,4-D, was not associated with myeloma:
   - Characterisation of exposure to 2,4-D in the presence / absence of DEET\(^{26}\):
     - 2,4-D, no DEET (29 cases) OR = 1.00 95% CI 0.62 – 1.61;
     - DEET and 2,4-D (51 cases) OR = 1.08 95% CI 0.73 – 1.59.

44. Pahwa, P et al 2012\(^{27}\), re-evaluated in 2012 the 342 cases/1506 controls from their 2006 study and found that for subjects with a cumulative exposure ≥ 10 hours per year, using different statistical analyses and including all 80 cases:\(^{28}\)
   - 2,4-D (for 80 cases) OR = 1.28, 95% CI 0.93 - 1.76.

45. The Council found that an OR of close to 1.0 was not consistent with an association of 2,4-D with or without DEET in the earlier study, and that there was no significant change when data were combined in the later study.

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\(^{26}\) See Table 3 at p. 268.


\(^{28}\) ibid, Table 3 at p. 45.
46. **Pearce et al 1986**,\(^2^9\) published the second phase of their 1985 New Zealand agricultural workers study and found:

- Among 76 cases of myeloma there was no significant difference regarding exposure to phenoxy herbicides compared with 315 controls:

\[
\text{OR} = 1.3, \quad 95\% \text{ CI } 0.8 - 2.2, \quad 43 \text{ cases}, \quad p \text{ value of 0.30.}
\]

In Council's view this is a careful study with a large cohort of subjects with myeloma workers at a ratio of 1:4 with controls, and shows no association between exposure to phenoxy herbicides and the prevalence of myeloma.

**Manufacturing - Production Studies**

47. **‘t Mannetje et al 2005**, followed sprayers (n=703) from 1973 to 31 December 2000. The authors classified a total of 699 sprayers as exposed to dioxin and phenoxy herbicides.

48. There were no cases of multiple myeloma in sprayers, against an expected incidence of 0.7 (SMR\(^3^0\) = 0.0; 95\% CI 0.00 – 5.29). Further, the number of deaths for the sprayers' cohort was below that expected, and longer duration of sprayer employment was not associated with higher cancer mortality.

49. For sprayers the authors cited another New Zealand study\(^3^1\) of nine pesticide applicators for an indicative level of TCDD exposure. That study found an average TCDD serum level of 53 ng/kg lipid (3.0 – 131) compared with control subject levels of 5.6 ng/kg lipid. When the applicators' levels were back extrapolated to 1970 the average level was around 300 ng/kg lipid (ng/kg = nanograms per kilogram and is equivalent to 300 parts per trillion (ppt)).

50. In the Council’s view, in such a small study no relevant conclusion could be reached. It thus provided no evidence for or against an association between phenoxy herbicide exposure and myeloma, despite the back-extrapolation value of moderately high TCDD levels at the time of exposure.

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\(^2^9\) Pearce, NE et al 1986, ‘Case-control study of multiple myeloma and farming’, *British Journal of Cancer*, vol. 54, pp. 493-500. RMA ID 16002

\(^3^0\) SMR = Standard Mortality Ratio


This article was not available to the RMA at the relevant times, and so could only be considered by the Council as new information.
51. Lynge, E 1998\textsuperscript{32} studied 2119 workers potentially exposed to phenoxy herbicides (2,4-D and MCPA) in two Danish factories over 50 years, between 1947-1993.

52. The authors noted that neither of 2,4-D nor MCPA (2-methyl-4-chlorophenoxyacetic acid) are known to be contaminated with TCDD. The factories produced negligible amounts of 2,4,5-T, which is known to be contaminated with TCDD. The authors stated\textsuperscript{33}:

> [This]...study indicates that the manufacture of MCPA, MCPP and 2,4-D does not influence the overall risk of cancer.

> ...the overall cancer mortality among persons exposed to phenoxy herbicides not potentially contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was equal to that of their national population.

53. No cases of multiple myeloma in men were identified (expected 1.89), but two cases in women were found (expected 0.44), RR = 4.55, CI 0.5 - 16.5.\textsuperscript{34} The authors considered the results for women to be at the borderline of statistical significance saying:

> Two case of multiple myeloma occurred among women in the study. Although there are some indications in the literature for a possible association between exposure to phenoxy herbicides and multiple myeloma, the literature is not consistent. It therefore seems prudent not to over interpret the finding of an excess risk in the Danish study based on two cases.\textsuperscript{35}

54. Council agreed with the authors, noting that the higher than expected number in women was not a significant increase, and offset by the much lower than anticipated prevalence in exposed men.

55. Burns, CJ et al 2001\textsuperscript{36} compared Dow chemical workers potentially exposed to 2,4-D between 1945-1996 with 40,000 other company employees working at the same location. The analysis was confined to men, (1517 males, 39,799 person years, 330 deaths). Fewer deaths than expected were found either due to all causes or to malignant neoplasms.

56. Myeloma mortality (RR = 0.8, CI 0.02 - 4.46) was not elevated in the workers exposed to 2,4-D.


\textsuperscript{33} Ibid, at p. 686-687.

\textsuperscript{34} Ibid, Table 4, p.685

\textsuperscript{35} Ibid, p.687

\textsuperscript{36} Burns, CJ et al 2001, ‘Mortality in chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) 1945-94: an update’, \textit{Occupational and Environmental Medicine}, vol. 58, pp. 24-30. RMA ID 24760 26080
57. In the Council’s view this is a major study with over 1500 potential 2,4-D exposed workers compared with a ≥ 25 fold larger control group on the same sites. The finding that the prevalence of myeloma was not different between the two groups provides no evidence for an association between 2,4-D exposure and myeloma.

**Vietnam Veterans’ Study**

58. Ketchum, NS et al 1999\(^{37}\) compared Ranch Hand Vietnam veterans with matched (age, race, military operations) non-exposed veterans. Dioxin was measured in parts per trillion (ppt), and adjusted values determined on a half-life of 8.7 years. No subject in the comparison group (n = 1,275; Dioxin (ppt) median 4.0, range 0 - 10) had myeloma; two subjects in the low exposure group (n = 276; Dioxin (ppt) median 52.3, range 27 - 94) had myeloma; but none in the high exposure (n = 283; Dioxin (ppt) median 196, range 94 – 3,290) or background (n = 421; Dioxin (ppt) median 5.7, range 0 - 10) groups had myeloma.

59. The authors stated:

No association was found between any cancer (all sites and any type) and dioxin category...Counts of veterans with specific cancers [including myeloma], all of which were too small to analyse are shown in table 5.\(^{38}\)

Overall we found no consistent evidence of a dose-response gradient and no significant increase in cancer risk in the high dioxin exposure category, the subgroup of highest a priori interest. \(^{39}\)

60. Based on the authors’ conclusions, the Council did not consider that this study supported the relevant association.

**COUNCIL’S CONCLUSIONS ON ARTICLES TOUCHING ON THE APPLICANT’S CONTENTIONS**

61. In the Council’s view the agricultural studies and production studies (above) in the pool were the studies most relevant to the Applicant’s contention. The Applicant contended that existing factors 6(c) and 6(d) in Statement of Principles No. 69 of 2012 concerning inhaling, ingesting or having cutaneous contact with:

   – a phenoxy acid herbicide [from the specified list in Statement of Principles No. 69 of 2012], that is, 2,4-dichlorophenoxyacetic acid (2,4-D), and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T); and/or

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\(^{38}\) Ibid, p. 635.

\(^{39}\) Ibid, at p.638.
– a chemical agent [as specified in Statement of Principles No 69 of 2012] contaminated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD); should be replicated in the same or similar terms in Statement of Principles No. 70 of 2012 (the balance of probabilities Statement of Principles).

62. The Council considered that the same evidence was the most relevant to, and the most likely to provide data on, the level of exposure to TCDD, as contended by the Applicant, i.e. an exposure to TCDD produced by decanting, mixing and spraying chemical agents and/or by consuming food potentially contaminated by those same chemical agents.

63. The Council noted the Commissions' submission (see [184] to [220]) that the sound medical-scientific evidence for the phenoxy herbicide 2,4,5-T and TCDD collectively, or for TCDD alone, was limited, and did not satisfy the balance of probabilities test. In regard to phenoxy herbicides the Commissions submitted that 2,4,5-T was contaminated with TCDD and submitted further that they could not find any direct evidence for 2,4-D exposure being associated with myeloma.

64. The Council understood that the Applicant’s submission (see [172] to [183]) was that the Council should apply the possible links in the evidence, such as the findings by the US Institute of Medicine described in its Veterans and Agent Orange series as ‘limited or suggestive evidence’ as meeting the balance of probabilities standard of proof. The Council considered that that was not a correct application of the balance of probabilities test. Further, the Council considered that the sound medical-scientific evidence did not satisfy the balance of probabilities test.

65. The Council noted that while some studies produced an OR > 1.0 this was not a statistically significant increase. Many studies, including some with a relatively high number of cases of myeloma, found no evidence for any association. The Council was of the view that the overall combined effect of the studies with outcomes for the chemical agents specified in existing factors 6 (c) and 6 (d) of Statement of Principles No. 69 of 2012 (see [61] above and Appendix C and [149]) by:

– Landgren et al 2009 (2,4-D);
– Eriksson & Karlsson 1992, (phenoxy herbicides);
– Morris-Brown et al 1993, (2,4-D and 2,4,5-T);
– Orsi et al 2009, (phenoxy herbicides);

40 Noting that the reasonable hypothesis test was not within scope in so far as the Applicant's contentions were concerned.
- Pahwa et al 2012, (phenoxy herbicides; 2,4-D);
- Pearce et al 1986 (phenoxy herbicides);
- ‘t Mannetje et al 2005, (mortality in sprayers - TCDD);
- Lynge, E 1998 (2,4-D and 2,4,5-T); and
- Burns, CJ et al 2001 (2,4-D)
- Ketchum, NS et al 1999 (sprayers Vietnam - TCDD)

did not satisfy the balance of probabilities test for clinical onset of myeloma.

66. The evidence concerning phenoxy herbicides for farmers covering occupational exposure of handlers, applicators and sprayers was in the Council’s view most consistent with a positive association. However in the Council’s view the combined effect of these studies (noted below) did not satisfy the balance of probabilities test:

- Eriksson & Karlsson 1992;
- Orsi et al 2009;
- Pearce et al 1986.

67. In conclusion, the Council considered that the information available to the RMA at the relevant times touching on the Applicant’s contentions was insufficient to justify an amendment to Statement of Principles No. 70 of 2012 (the balance of probabilities Statement), to include factors for low level exposure by agricultural workers and sprayers or at all to:

b. Inhaling, ingesting or having cutaneous contact with a phenoxy acid herbicide [from the specified list in Statement of Principles No. 69 of 2012], that is, 2,4-dichlorophenoxyacetic acid (2,4-D), and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T); and/or

c. Inhaling, ingesting or having cutaneous contact with a chemical agent [as specified in Statement of Principles No. 69 of 2012] contaminated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).
EVALUATION OF ARTICLES TOUCHING ON THE COUNCIL’S REVIEW CONCERNING VERY HIGH DOSE EXPOSURE TO TCDD

Manufacturing Studies

Seveso industrial accident studies

An industrial accident in a chemical plant which manufactured pesticides and herbicides in Seveso, Italy in 1976, resulted in the release of 2,900 kg of matter in a cloud containing several kilograms of TCDD. No immediate fatalities were reported, but land and vegetation were contaminated; more than 600 people were evacuated from their homes with up to 2000 people treated for dioxin poisoning.

[The accident]…in the trichlorophenal production department of a chemical plant….A chemical cloud containing several kilograms of TCDD was released into the environment and contaminated a vast and densely populated area.

Consonni, D et al 2008 describe TCDD as:

The most toxic member of a large family of poly-chlorodibenzodioxins is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a non-wanted by-product of numerous chemical reactions involving chlorine compounds, highly persistent in the environment and biologic organisms.

The Council identified six main studies relating to this accident that examined cancer incidence and mortality covering a 25-year follow-up period. The area of Seveso was divided into three dioxin contaminated zones of decreasing mean soil levels:

A = highest exposure to dioxin
B = the next, and

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Pesatori, AC et al 2009, ‘Cancer incidence in the population exposed to dioxin after the “Seveso accident”: twenty years of follow-up’, Environmental Health, vol. 8, no. 39. RMA ID 63465


42 Consonni, D et al 2008 at p. 848

43 Consonni, D et al 2008 at p. 847
R = the lowest level of contamination.

The population of the surrounding non-contaminated area was used as a reference group.

70. Bertazzi, PA et al 1993 noted in relation to dose for zone A, that:

Information on TCDD blood levels was available for few subjects. Ten children from zone A affected by chloracne (an established marker of TCDD toxicity) showed lipid-adjusted blood levels as high as 56,000 parts per trillion (ppt). Nine adults without chloracne, from the same area, showed values ranging from 1,770 ppt to 10,400 ppt. 44

71. For zone B the authors reported a range for a limited group of 13 subjects:

.. results for a group of 13 subjects from zone B have become available; their blood concentrations ranged from 74 to 526 ppt. 45

72. Bertazzi AB et al 2001 provided a more detailed summary of the level of contamination of the soil related to the equivalent levels of serum dioxin in residents of each zone provided relevant information 46:

<table>
<thead>
<tr>
<th>Zone</th>
<th>Soil TCDD (µg/m²) Minimum - Maximum</th>
<th>Serum TCDD no. of subjects</th>
<th>Median (ppt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1976 15.5 - 580.4</td>
<td>296§</td>
<td>447.0</td>
</tr>
<tr>
<td></td>
<td>1993-4</td>
<td>7¶</td>
<td>73.3</td>
</tr>
<tr>
<td>B</td>
<td>1976 1.7 – 4.3</td>
<td>80§</td>
<td>94.0</td>
</tr>
<tr>
<td></td>
<td>1993-4</td>
<td>51¶</td>
<td>12.4</td>
</tr>
<tr>
<td>R</td>
<td>1976 0.9 – 1.4</td>
<td>48§</td>
<td>48.0</td>
</tr>
<tr>
<td>Reference Zone</td>
<td>1993-4 n.a*</td>
<td>52¶</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Source: Bertazzi AB et al 2001, Table 1 at p. 1032.

73. The Council observed that there was high agreement between exposure, soil contamination and serum blood levels for dioxin. Further, the Council noted that the chemicals, other than dioxin (detailed below) that were measured in the blood tests, did not reach above background levels

44 Bertazzi, PA et al 1993 at p. 399
45 ibid at p. 399
46 Pesatori, AC et al 2009, Table 1 at p. 3.
The serum levels of six other PCDDs [polychlorinated dibenzo-dioxins], 10 PCDFs [polychlorinated dibenzo-furans], and four coplanar PCBs [polychlorinated biphenyls] were also measured...  

74. These two factors convinced the Council that exposure to TCDD was the only relevant chemical agent of exposure.

75. The Council expected that there would be a delay in the observation of disease and death and hence considered the follow-up studies that provided cumulative incidence and mortality data to be the most relevant.

**Seveso Incidence Studies**


77. In the first of the papers, Bertazzi, et al 1993 described the incidence of cancer at the 10 year point following the incident and showed a statistically significant increased risk of myeloma for women in Zone B
   
   − for women (2 cases; RR = 5.3, 95% CI 1.2 – 22.6),
   
   − but for men (2 cases; RR = 3.2, 95% CI 0.8 – 13.3).

78. The 20 year follow up incidence study by Pesatori et al 2009 found cases of myeloma for the period 1977 – 1996 as follows:

   − Zone A - 1 case
     
     RR = 2.88  
     95% CI 0.40 – 20.70
   
   − Zone B - 6 cases
     
     RR = 2.77  
     95% CI 1.20 - 6.32
   
   − Zone R - 18 cases
     
     RR = 1.15  
     95% CI 0.70 - 1.91

79. In the Results section, in reference to cancer incidence from the time of the accident, the 2009 study authors noted:

   Steadily increased risks for multiple myeloma were observed in each category [0-4 yrs, 5-9, 10-14 and 15+ years] within 15 years since the accident.

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47 Pesatori, AC et al 2009 at p. 2 of 11.
49 ibid Table 3 at p.6
50 The Bertazzi et al 1993 provided no data for myeloma incidence in Zone A, and for Zone R,  
   − for women (2 cases; RR = 0.6, 95% CI 0.2 – 2.8),
   
   − for men (1 case; RR = 0.2, 95% CI 0.0 – 1.6).
and

In zone R, a numerical increase of the RR values with time since initial exposure was observed; however, none of the values was significantly above unity with the exception of multiple myeloma after 15 years since the accident.52

Seveso Mortality Studies

80. Mortality studies by Bertazzi et al 1997 and Bertazzi et al 1999 at 15 years, Bertazzi et al 2001 at 20 years and Consonni et al 2008 at 25 years were also considered.

81. The Council noted that the 15 year follow-up mortality study by Bertazzi et al 1997 (for the period 1976-1991), identified that in:53

Zone B; the excess of cases became significant for

women (4 deaths) RR = 6.6, 95% CI 1.8 - 16.8,

but not for men (1 death) RR = 1.1, 95% CI 0.0 - 6.2.

The authors noted that:

Multiple myeloma excess risk occurred among zone B females, with an increasing trend by latency and length of stay in the area; previous studies support its association with dioxin exposure.

82. The Bertazzi et al 2001, 20 year mortality study (for the period 1976-1996) reported no further deaths since those reported in the Bertazzi et al 1997 study, above. The authors commented:

In zone B, nearly twice as many as expected lymphohemopoietic neoplasms occurred, a significant increase that in particular included Hodgkin's disease, multiple myeloma, and myeloid leukemia.54

83. The 25 year follow up mortality study by Consonni et al 2008 for the period 1976 – 200155 detailed results for myeloma deaths as follows:

- Zone A - 2 myeloma deaths

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51 Pesatori, AC et al, 2009, p. 6 and Table 4 at p. 7-8.
52 Pesatori, AC et al, 2009, p. 6
53 The Bertazzi et al 1997 data for the other zones is:
   - Zone A; there had been no deaths from multiple myeloma; and
   - Zone R; for women (5 deaths) RR = 1.0, 95% CI 0.3 - 2.3, and for men (5 deaths) RR = 0.8, 95% CI 0.3-1.9.
54 Bertazzi, PA et al 2001, p. 1033
55 Consonni, D et al 2008, Table 5 at p.851
RR = 4.34  \quad 95\% \text{ CI} \quad \text{1.07 - 17.52}

- Zone B – 5 deaths
  \quad RR = 1.68 \quad 95\% \text{ CI} \quad \text{0.69 - 4.10}

- Zone R – 24 deaths
  \quad RR = 1.1 \quad 95\% \text{ CI} \quad \text{0.71 - 1.69}

84. The authors commented that:

…the most notable finding was increased mortality from cancers of the lymphatic and hematopoietic tissues in the two most polluted zones, with a significant \((p = 0.04)\) test for trend of rate ratios across zones \((A > B > R)\).\(^{56}\)

and noted that:

The increases were stronger for females … myelomas \((\text{zone B: four deaths, RR = 3.07, 95 percent CI: 1.12, 8.42})\).\(^{57}\)

85. The Bertazzi et al 2001 at 20 years and Consonni et al 2008, at 25 years mortality studies reported no further deaths for Zone B than were reported in the Bertazzi et al 1997 study, above. In contrast, the Council considered that the Consonni et al 2008, 25-year follow-up study (see \([80]\) above) showed statistically significant increased risk in Zone A.

86. In the Council’s view, incidence and mortality data from all the Seveso studies (particularly when combined for Zones A and B, the most contaminated zones), and the data that reached significance, supported the relevant association for high doses of dioxin.

87. Taken together these Seveso incidence and mortality studies also provide data on the high level of dioxin exposure at which an association with myeloma was evident. As mentioned above \([76]\), in relation to dose for zone A, the authors noted levels as high as 56,000 ppt in children and 1,700 to 10,400 ppt in some adults.\(^{58}\) And in Zone B results were available for a small number of subjects, showing a range from 74 to 526 ppt.\(^{59}\).

88. The Council considered the series of Seveso studies provided evidence of a strong association for very high exposure to TCDD and myeloma. In support of such an association were statistically significant results in Zones A and B for both incidence and mortality. The mean soil and median serum TCDD data were in agreement (high to low levels) and the blood tests showed TCDD was the only chemical agent above background levels. Zone A provided evidence on the exposure dose with adult values ranging from 1,770 ppt to 10,400 ppt of TCDD in blood serum.

\(^{56}\) Consonni, D et al 2008, p. 850
\(^{57}\) Consonni, D et al 2008, p. 850
\(^{58}\) Bertazzi, PA et al 1993 at p. 399
\(^{59}\) ibid at p. 399
89. Important in the Council’s view were:

- the data for an increased risk of myeloma;
- the incidence dose-positive relationship and incidence versus time positive relationship; and
- that the results were both scientifically and statistically significant.

Other industrial accident study

90. The Council considered the Hooiveld, M et al 1998\textsuperscript{50} to be an important study, as some of the workers were exposed to chemical agents from an accident, some through production of chemical agents, and a non-exposed group. In the Council’s view, this study provided data on different dose levels of TCDD in response to different levels of exposure.

91. The period studied was 1955-85 (all employees over all or part of that period): 562 subjects were exposed, and 567 non-exposed. The authors found an increased incidence of cancer in Dutch chemical plant workers exposed to phenoxy herbicides, chlorophenols and contaminants (TCDD and other polychlorinated dioxins and furans). Levels of serum TCDD were established in 47 subjects (14 exposed to an accident, 17 exposed elsewhere, and 16 non-exposed).

92. Levels of serum TCDD in the first group (accident) were higher than in the second (exposed, no accident), and the second was higher than the third (non-exposed):

Extrapolated serum TCDD max concentrations (on lipid-adjusted basis) had a nonnormal, right-skewed distribution and ranged between a geometric mean of 40.8 ppt in exposed workers in nonproduction departments to a geometric mean of 2,148.0 ppt in workers exposed as a result of the accident and working in main production\textsuperscript{61}.

93. The Council noted that any increased mortality was for 'all cancers', not from myelomas. However, in the Council’s view the exposure dose data, as measured by serum lipid TCDD levels, supported very high dose levels for workers exposed by the accident (exposure to polychlorinated dioxins, including TCDD) and similar TCDD dose levels for workers in main production, but not for exposed workers with no main production work (both exposed to phenoxy herbicides or chlorophenals contaminated with TCDD), and not for those non-exposed workers.

94. Further, the relevant exposure to a very high dose was in the order of a mean of 2,148 ppt of TCDD in blood serum (lipid adjusted). The Council

\textsuperscript{50} Hooiveld, M et al 1998, ‘Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants’, \textit{American Journal of Epidemiology}, vol. 147, no. 9, pp. 891-901. RMA ID 24770 26075

\textsuperscript{61} p. 894
noted that this very high dose was similar to the 1,770 ppt of TCDD lower end value of the range for Zone A adults in the Seveso studies (See [88]).

95. Despite 14 subjects being exposed to the accident, resulting in a high mean dose of TCDD $\approx 2000$ ppt serum, there were no cases of myeloma in those subjects. In the Council’s view, this is consistent with the rarity of the disease and reflecting the small number of exposed subjects.

96. The Council’s view was that this study provides some evidence for levels of TCDD in serum which might result from an accidental exposure but reflecting the small number of exposed subjects, it did not contribute to the Council’s view about the association of onset of myeloma.

**Other Manufacturing - Production Studies**

97. The Council considered a number of studies that were available to the RMA concerning workers exposed to a range of pesticides and herbicides including phenoxy herbicides, chlorophenols and contaminants such as TCDD and other polychlorinated dioxins in the manufacturing process. The Council considered these studies were important, given the data from the Seveso studies, in identifying any potential relevant association for TCDD, and particularly if that were so, the level of exposure (given workers’ employment over a number of years and the dose at which any association was shown).

98. **Steenland, K et al 1999**$^{62}$ studied 5132 workers at 12 U.S. chemical plants that produced (1942 - 1984) TCDD contaminated chemicals (including Agent Orange (50:50 mixture of 2,4-D and 2,4,5,-T). Exposure was measured by the presence of TCDD in process material, a job-exposure matrix (time spent in specific jobs) and estimates on potential exposure by cutaneous contact or inhaling of TCDD. Serum dioxin evaluations were used to estimate cumulative exposure levels.

99. The authors found 377 deaths from all cancers:

$$\text{RR} = 1.13 \quad \text{CI 1.02 - 1.25; and}\$$

of these multiple myeloma accounted for 10 cases:

$$\text{RR} = 2.07 \quad \text{CI 0.99 - 3.80}\$$

100. In relation to dose, Steenland et al noted that in the largest of the four industrial cohorts considered by the IARC study in the US:

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$^{62}$ Steenland, K et al 1999, ‘Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin’, *Journal of the National Cancer Institute*, vol. 91, no. 9, pp. 779-86. RMA ID 24794 25814
workers were exposed to high levels of TCDD. Blood drawn from a sample of these workers \((n = 253)\) indicated an estimated mean serum level of 2000 parts per trillion in lipids at the time of last exposure compared with six to eight parts per trillion for the general population.\(^63\)

101. The Council noted the elevated risk for myeloma above was in relation to production workers for exposure to chemicals contaminated by TCDD, where the mean serum level (dose) of 2000 ppt of TCDD was in a similar order to the lower range value (1,770 ppt to 10,400 ppt) for adults in the most contaminated zone A in the Seveso studies. The Council initially concluded from the mean value in the Steenland study and the range value from the Seveso studies that a serum blood level for TCDD in the vicinity of 2000 ppt would be required for the relevant association.

- In the Council’s view the data were based on a high number of cases \((10/5132\) is very high for such a rare cancer). The RR showed a doubling of risk and was supportive of an association between very high dose (see above) exposure to TCDD and Myeloma.

102. The following two studies by \textquoteleft t Mannetje, A et al 2005\textquoteright and McBr 
Be II et al 2009\textquoteright provided a comparison between the levels of potential exposure to TCDD by manufacturing production workers and agricultural sprayers. However, a range of other chemicals were also manufactured at the plant in question, which raises doubt about the weight the Council could assign to the results.

103. Both 2,4,5-T trichlorophenol (TCP) and TCDD were manufactured in New Plymouth, New Zealand from 1962 to 1988. The mortality rates of the workers at the site were compared to standard mortality in the background population.

104. \textquoteleft t Mannetje et al 2005\textquoteright, followed production workers \((n=1025)\) from 1969 to 31 December 2000. The authors classified a total of 813 producers as exposed to dioxin and phenoxy herbicides.

105. The authors reported what they considered to be “a significant excess for multiple myeloma” with three multiple myeloma deaths in the producers’ cohort against an expected number of 0.5 resulting in an SMR of 5.51 \((95\% \ CI 1.14 - 16.1)\).

\(^63\) Ibid, at p. 779

\(^64\) \textquoteleft t Mannetje, A et al 2005\textquoteright, ‘Mortality in New Zealand workers exposed to phenoxy herbicides and dioxins’, \textit{Occupational and Environmental Medicine}, vol. 63, no. 34-40. RMA ID 34856

\textquoteleft McBr 
Be II et al 2009\textquoteright, \textquoteright Mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin at a trichlorophenol plant in New Zealand\textquoteright, \textit{Journal of Occupational & Environmental Medicine}, vol. 51, no. 9, pp. 1049-56. RMA ID 24922 / 56055
Two cases had worked in packing and transport and one had worked in an unspecified exposed department. Including these three cases, in total five lymphohematopoietic cancer deaths occurred in the producers cohort (SMR = 1.65, 95% CI 0.53 to 3.85).\(^{65}\)

106. **McBride et al 2009** studied the same cohort as ‘t Mannetje et al 2005. They found in exposed workers (n=1134, 196 deaths) two cases of multiple myeloma representing a SMR = 2.2 (95% CI 0.2 - 8.1), which the authors stated were greater than expected. There were 51 deaths among 465 non-exposed workers, but none from multiple myeloma.

107. Serum TCDD levels were collected from 22% of the study cases.

The current serum lipid adjusted TCDD levels for workers with exposure to TCP [2,4,5-trichlorophenol] or 2,4,5-T averaged 9.9 ppt. The highest levels were found in the TCP operation (23.4 ppt), particularly those involved in a release in 1986 (37.9 ppt). The unexposed workers averaged 4.9 ppt, which was very close to what would be considered New Zealand background level of 3.9 ppt for persons of similar age.\(^{66}\)

108. The Council noted that the study by McBride et al 2009 listed only two multiple myeloma deaths in the same cohort compared with three identified by ‘t Mannetje et al 2005, suggesting that one case in the ‘t Mannetje et al 2005 study was misclassified.

109. The Council considered that ‘t Mannetje and McBride did not provide significant evidence but the studies leave open the possibility of relevant association for TCDD with myeloma (see [47]).

**COUNCIL’S CONCLUSIONS ON ARTICLES FOR VERY HIGH DOSE EXPOSURE TO TCDD**

110. Having evaluated all the evidence in the pool, the Council was of the view that the combined effect of the studies concerning high doses of TCDD by:

- Seveso studies
  - Bertazzi, PA et al 1993
  - Bertazzi, PA et al 1997
  - Bertazzi, PA et al 1999
  - Bertazzi, PA et al 2001
  - Pesatori, AC et al 2009
  - Consonni, D et al 2008

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\(^{65}\) ‘t Mannetje, A et al 2005 at p. 37

\(^{66}\) Ibid, at p. 1050-1051.
And

- Steenland, K et al 1999.

pointed to the relevant association for clinical onset of myeloma.

111. Still regarding high doses, the Council was of the view that the combined effect of the studies concerning TCDD by:

- The Seveso studies:
  - Bertazzi, PA et al 1993
  - Bertazzi, PA et al 1997
  - Bertazzi, PA et al 1999
  - Bertazzi, PA et al 2001
  - Pesatori, AC et al 2009
  - Consonni, D et al 2008

And

- Steenland, K et al 1999

satisfy the relevant association on the balance of probabilities, when considered with all the other evidence in the pool.

112. Overall the Council noted that these studies, which detailed TCDD concentrations in plasma lipids/serum, supported an association for very high doses of TCDD exposure only.

113. The Council considered it important that the Seveso studies found an excess risk up to six-fold, following a chemical accident, which was statistically significant for myeloma, in the most highly exposed Zones A and B.

114. In addition, the study by Steenland et al 1999 found 10 cases of multiple myeloma in U.S. pesticide manufacturers (RR = 2.07; CI 0.99-3.80), which the Council considered was highly suggestive of an association, and close to but not statistically significant for high doses.

DOSE

115. In considering what threshold dose of TCDD would be supported by the sound medical-scientific evidence, the Council noted in particular that the studies detailing TCDD concentrations in lipids or serum, supported an association for very high doses of TCDD exposure only. While not many studies included blood TCDD level evaluation, the following data remained persuasive for only a very high dose (industrial accident and manufacturing
chemical production) exposure being potentially relevant to any relevant association with myeloma.

- Steenland et al 1999\textsuperscript{67} found a high concentration mean in myeloma cases based on concentration of TCDD of about 2000 ppt in lipids.

- Bertazzi et al 1993, Pesatori et al 2009 found shortly after the accident that Zone A had a median serum concentration of 447 ppt, but that nine adults had 1,770 ppt to 10,400 ppt.

- Hooiveld et al 1998 found an (extrapolated) geometric mean of 2,148 ppt (95\%CI 1375-3,355) of TCDD in workers exposed.\textsuperscript{68}

116. The TCDD blood levels measured in \textquote{t}Mannetje et al 2005 and Ketchum et al 1999 for agricultural workers and Vietnam veterans, were only moderately elevated, and no increased risk was detected.

- \textquote{t}Mannetje et al 2005 found that sprayers / pesticide applicators had average concentrations of around 300 ng/kg lipid (back extrapolated to the approximate time of exposure).

- Ketchum et al 1999 found for Vietnam Ranch Hand veterans that the highest exposed group had a median TCDD level of 196 ppt, in the range 94 – 3,290 ppt. As in the Hooiveld study, no cases of myeloma were detected at the highest TCDD concentrations.

117. Overall, based on the above evaluation of the studies and its consideration of all submissions, the Council believes that, on the balance of probabilities, there is sound medical-scientific evidence connecting TCDD exposure at very high levels (in the vicinity of 2000 ppt), with myeloma. The Council noted that the half life of TCDD in sera and lipids ranges from 7 to 8.7 years, and that it is reported that TCDD levels in control subjects is approximately 5 ppt.

118. After considering comments submitted by the Applicant and the Commissions on the Council’s proposed factors\textsuperscript{69}, the Council decided that a minimum threshold of at least 1500 ppt at the time of exposure would provide an acceptable margin to allow for individual variances such as gender and body type.

119. The Council also considered that a serum TCDD level of at least 1500 ppt allows for the successful inference by back-extrapolation some decades after exposure, and is consistent with the sound medical-scientific evidence from the studies set out above.

\textsuperscript{68} p. 894

\textsuperscript{69} See Appendix C under Revised Scope and Proposed Factor
120. In the Council’s view the sound medical-scientific evidence was sufficient for exposure at the dose discussed above to be applied to both the reasonable hypothesis and balance of probabilities statements of principles.

DECISION

121. On this basis, the Council decided that having exposure to 2,3,7,8 tetrachlorodibenzo-para-dioxin (TCDD) sufficient to produce an expected initial serum TCDD level of at least 1500 parts per trillion before the clinical onset of myeloma is sufficient to satisfy the balance of probabilities for association between TCDD at very high doses and the subsequent onset of myeloma.

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

COUNCIL’S VIEW ON THE NEW INFORMATION SUBMITTED BY THE APPLICANT

123. Given the Council’s decision, it was of the view that there was no need for it to consider any of the ‘new information’ with respect to the contended factors in order to form a view as to whether any directions or recommendations should be made to the RMA.
EVIDENCE THAT THE COUNCIL COMMENTS ON

**Agricultural Studies**


Pearce, NE et al 1986, ‘Case-control study of multiple myeloma and farming’, *British Journal of Cancer*, vol. 54, pp. 493-500. RMA ID 16002

**Manufacturing Studies**


Burns, CJ et al 2001, ‘Mortality in chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) 1945-94: an update’, Occupational and Environmental Medicine, vol. 58, pp. 24-30. RMA IDs 24760 & 26080

Seveso studies


Pesatori, AC et al 2009, ‘Cancer incidence in the population exposed to dioxin after the "Seveso accident": twenty years of follow-up’, Environmental Health, vol. 8, pp. 39. RMA ID 63465


Manufacturing – industrial accident and production Study

Hooiveld, M et al 1998, ‘Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants’, American Journal of Epidemiology, vol. 147, no. 9, pp. 891-901. RMA IDs 24770 & 26075
Manufacturing Studies

Steenland, K et al 1999, ‘Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin’, Journal of the National Cancer Institute, vol. 91, no. 9, pp. 779-86. RMA IDs 24794 & 25814


Vietnam Veterans Studies

The Specialist Medical Review Council

124. As mentioned in [3], the Council is a body corporate established under section 196V of the VEA. It 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. 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.

125. The composition of each Review Council changes from review to review depending on the issues relevant to the particular Statement/s of Principles under review. When a review is undertaken three to five Councillors selected by the Convener constitute the Council.

126. 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.

127. Professor John Funder was the Presiding Councillor for this review. He is a Senior Fellow at Prince Henry’s Institute of Medical Research at Monash Medical Centre, and holds honorary professorial appointments at Monash, Melbourne University and the University of Queensland. He has been President of the Australian Society for Medical Research (1979) and the Endocrine Society of Australia (1984), and Chairman of the International Society for Endocrinology (1996-2000).

128. The other members of the Council were:

- Professor Lin Fritschi, who is Professor of Epidemiology at Curtin University in Western Australia. She holds a National Health and Medical Research Council Senior Research Fellowship. Her research interests include cancer epidemiology, occupational causes of cancer, and exposure assessment in epidemiological studies.

- Professor Doug Joshua, who is the Alan Ng Professor of Haematology at the University of Sydney and was until January 2014 Head of the Haematology Department of the Royal Prince Alfred Hospital and Concord Hospital, returning to the Royal Prince Alfred Hospital as a consultant from 1 April 2014. Professor Joshua is a scientific advisor and member of the International Myeloma Foundation.
– Dr Hang Quach, who is a consultant clinical and laboratory haematologist at St Vincent’s Hospital, Melbourne, a Clinical Fellow of the University of Melbourne and Member of the International Myeloma Foundation. Dr Quach’s research interests include the study of mechanisms of immune modulation in myeloma and the impact of immune modulation on clinical outcome based on correlative studies.

**Previous Councils’ Review of the Statement of Principles then in force in respect of Myeloma**

129. In or about 2003 the Council conducted a review of the contents of Statement of Principles No. 72 of 1999 which was a Statement of Principles previously in force in respect of myeloma. The contended factors considered by the Council in that review were:

(i) parasitic diseases, including malaria;

(ii) antigenic stimulation; and/or

(iii) parasitic disease, including malaria, precipitating antigenic stimulation.

130. The Council published a Declaration dated 7 February 2003, which was published by Gazette Notice 7 of 19 February 2003, pp. 560 - 561.

131. The Minister appointed, and the Convener selected, a newly constituted Council to conduct this review to ensure that there was no apprehension of bias or prejudgement (notwithstanding that the Statements of Principles under review and contended factors were different). The previous Council’s decision was not included in the information available to the RMA and forwarded by the RMA to the Council under section 196K of the VEA, and so was not taken into account by the Council in this review.

**The Legislation**

132. 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. They are determined by the RMA, and set out those criteria (conditions or exposures), known as factors, that must as a minimum exist before it can be said that an injury, disease or death can be connected with service, on either or both of the two statutory tests, the reasonable hypothesis test \(^70\) and the balance of probabilities test. \(^71\) Statements of

\(^{70}\) The reasonable hypothesis test is set out in section 196B(2) of the VEA which 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
Principles 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).  

133. As noted in [5] the concept of ‘sound medical-scientific evidence’ as defined in section 5AB(2) of the VEA is fundamental to Statements of Principles. 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.  

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(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.

The balance of probabilities test is set out in section 196B(3) of the VEA which 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.

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

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

73 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.
The functions of the Council are set out in section 196W of the VEA. In this review 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. 69 of 2012 concerning myeloma and death from myeloma, being a Statement of Principles determined by the RMA under section 196B(2) of the VEA (‘the reasonable hypothesis test’), and

- Statement of Principles No. 70 of 2012 concerning myeloma and death from myeloma, being a Statement of Principles determined by the RMA under section 196B(3) of the VEA (‘the balance of probabilities test’).

The information

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 myeloma 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 October 2012 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 myeloma which was in the possession of the RMA at the time it (the RMA) made the decision that triggered the Council's review.

By email dated 21 March 2013 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 Table 2.

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 Applicant, the Commissions and other participants in the review via confidential password.
Lists at Appendix E of the Information sent to the Council by the RMA under section 196K

138. The list of the preliminary and final pool of information, as advised to the Applicant and the Commissions at the hearing of oral submissions on 30 October 2013 is listed in Table 1.

139. 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 Table 2.

140. The 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 is also listed in Table 2.

141. 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 Table 3.

142. The information upon which the Council understands 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 also listed in Table 2.
APPENDIX B: DETERMINATION OF THE STATEMENTS OF PRINCIPLES AND APPLICATION TO THE COUNCIL FOR REVIEW

143. On 22 October 2012 the RMA under subsections 196B(2) and (3) of the VEA determined Statements of Principles Nos. 69 and 70 of 2012 concerning myeloma. The Statements of Principles took effect from 31 October 2012.

144. On 25 October 2012 the Statements of Principles were registered on the Federal Register of Legislative Instruments.

145. On 29 October 2012 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.


147. 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 myeloma and invited eligible persons or organisations so authorised to make submissions to the Council.\(^75\)

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75 Gazette Notice GN 8 of 27 February 2013.
APPENDIX C: THE COUNCIL’S PRELIMINARY AND FINAL DECISIONS ON THE SCOPE OF REVIEW AND THE POOL OF INFORMATION AND THE COUNCIL’S NOTIFICATIONS ON THE SCOPE AND POOL

The Scope of Review

148. As noted in [7], the Council considered that the Applicant had not raised a valid ground of review referable to his contentions concerning the application of Statement of Principles No. 69 of 2012.

149. Taking into account the Applicant’s clarification of his contentions, the Council’s preliminary decision on the scope of the review, as advised to the Applicant and Commissions on 24 September 2013, was as follows:

Without limiting the scope of the Council’s review of (some or the whole of) the contents of Statements of Principles Nos. 69 and 70 of 2012, 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:

Statement of Principles No. 70 of 2012 in the following way for the clinical:
- onset; and/or
- worsening of myeloma.

That is, the possible inclusion in Statement of Principles No. 70 of 2012 of a factor or factors in the same or similar terms to existing factors 6(c) and 6(d) in Statement of Principles No. 69 of 2012, which respectively provide for:

- inhaling, ingesting or having cutaneous contact with a phenoxy acid herbicide from the specified list, for a cumulative period of at least 1000 hours, within a consecutive period of ten years before the clinical onset of myeloma, where the first exposure occurred at least five years before the clinical onset of myeloma;

and/or

- inhaling, ingesting or having cutaneous contact with a chemical agent contaminated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), for a cumulative period of at least 1000 hours, within a consecutive period of ten years before the clinical onset of myeloma, where the first exposure occurred at least five years before the clinical onset of myeloma.

As defined in paragraph 9 of Statement of Principles No. 69 of 2012:

"a phenoxy acid herbicide from the specified list" means:
- (a) 2,4-dichlorophenoxyacetic acid (2,4-D); or
- (b) 2,4,5-trichlorophenoxyacetic acid (2,4,5-T);

and

"inhaling, ingesting or having cutaneous contact with a chemical agent contaminated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)" means:
- (a) decanting or spraying;
(b) cleaning or maintaining equipment used to apply;
(c) being sprayed with;
(d) handling or sawing timber treated with;
(e) being in an environment shrouded in dust from timber treated with; or
(f) using cutting oils contaminated with;
one of the following chemicals:
(i) 2,4,5-trichlorophenoxyacetic acid;
(ii) 2,4,5-trichlorophenoxypropionic acid;
(iii) 2,4,5-trichlorophenol;
(iv) 2-(2,4,5-trichlorophenoxy)-ethyl 2,2-dichloropropionate;
(v) o,o-dimethyl-o-(2,4,5-trichlorophenyl)-phosphorothioate;
(vi) pentachlorophenol;
(vii) 2,3,4,6-tetrachlorophenol;
(viii) 2,4,6-trichlorophenol;
(ix) 1,3,4-trichloro-2-(4-nitrophenoxy)benzene;
(x) 2,4-dichloro-1-(4-nitrophenoxy)benzene; or
(xi) 2,4-dichloro-1-(3-methoxy-4-nitrophenoxy)-benzene.

150. In analysing the information (and particularly the industrial accident studies), it became apparent to the Council that there was sound medical-scientific evidence available to the RMA at the relevant times which potentially could justify an amendment to the Statement/s of Principles by the inclusion of a factor or factors concerning exposure to TCDD in very high doses. Accordingly, the Council considered that the scope of review needed to be expanded. After affording procedural fairness, the Council’s final view on the scope of the review was:

(a) as set out in [149]; and

(b) whether there was sound medical-scientific evidence on which the RMA could have relied to amend Statement/s of Principles Nos. 69 and 70 of 2012 by the possible inclusion of a factor or factors for the clinical onset and/or clinical worsening of myeloma concerning:

Any exposure to 2,3,7,8 tetrachlorodibenzo-para-dioxin (TCDD) that provides an initial serum/lipid level of TCDD in the vicinity of 2000 parts per trillion (where the normal level is approximately 5 parts per trillion) before the clinical onset of myeloma.

The Pool of Information

151. The Council considered that the pool of information should comprise 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;

76 Discussed at [68] - [96].
which was considered by the Council to be sound medical-scientific evidence as defined in section 5AB(2) of the VEA being information which:

b. epidemiologists would consider appropriate to take into account; and

c. in the Council's view 'touches on' (is relevant to) matters within the scope of review.

152. The Council took into account and accepted the submissions on the proposed pool of information made by both the Applicant (see [157]) and the Commissions (see [158]). The Council's final decision on the pool of information was that it should comprise the information listed in Table 1.

153. The Council noted the Applicant's references to and submissions concerning information which was not available to (not before) the RMA (see Table 3). 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' (see [123]).

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

154. In separate letters to each of the Applicant and the Commissions dated 24 September 2013 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 11 October 2013; 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.

155. No comments were received on the proposed scope of the review.

156. Comments were received from both the Applicant and the Commissions in relation to the proposed pool of information.

157. The Applicant submitted in his submission dated 3 October 2013 that the pool of information should include\textsuperscript{77}:

\textsuperscript{77} The Applicant made no specific submissions concerning Pearce, NE at al. 1985, other than his request to the Council to include the article in the Pool of Information.

158. On 29 October 2013 the Council received an email from the Commissions submitting that the pool of information should include:


159. A copy of the Council’s revised preliminary list of the proposed pool of information, (which included the articles which the Applicant and the Commissions had respectively submitted should be added to the proposed pool) was provided to the Applicant and the Commissions’ representative at the Council’s hearing of oral submissions on 30 October 2013 and is attached at Table 1.

160. No comments were received on the Council’s revised proposed pool of information.

161. By letters dated 28 March 2014 the Council advised the Applicant and the Commissions of an expanded proposed scope of review and provided an opportunity to comment by 28 April 2014.

162. Having considered the expansion of the proposed scope of review (see [150]), the Council considered whether any changes to the proposed pool of information were required. The Council took into account the comment made by the Commissions (see [166]) and decided not to make any changes, as in the Council’s view the revised proposed pool contained all the information that ‘touches on’ (is relevant to) matters within the expanded scope of review.

**Notification of Preliminary Decisions on Proposed New Factor**

163. In its letters of 28 March 2014, the Council also provided the Applicant and the Commissions with an opportunity to comment on the wording of a proposed new factor in respect of TCDD exposure in both of Statements of Principles Nos. 69 and 70 of 2012.

164. The proposed new factors were:
Reasonable Hypothesis Statement of Principles No. 69 of 2012:

Any exposure to 2,3,7,8 tetrachlorodibenzo-para-dioxin (TCDD) that provides an initial serum/lipid level of TCCD in the vicinity of 2000 parts per trillion (where the normal level is approximately 5 parts per trillion) before the clinical onset of myeloma;

Balance of Probabilities Statement of Principles No. 70 of 2012:

Any exposure to 2,3,7,8 tetrachlorodibenzo-para-dioxin (TCDD) that provides an initial serum/lipid level of TCCD in the vicinity of 2000 parts per trillion (where the normal level is approximately 5 parts per trillion) before the clinical onset of myeloma.

165. In emails dated 31 March 2014 and 1 April 2014 the Applicant sought clarification of the wording of the proposed factor and asked the Council questions of a technical nature about the level of serum/lipid TCDD as set out in the proposed factor and the half-life of TCDD. The Council has attempted to address these issues in its discussion above.

166. In a letter dated 9 April 2014, the Commissions contended that a report to the DVA by Muller et al 2002 should be included in the pool of information for this review; and

“If the Council has formed a view that the minimum level of TCDD exposure necessary to cause myeloma is as specified in the proposed new factor, then the Commissions would see the existing two TCDD factors [factor 6(d) and 6(e)(iii)] in instrument 69 of 2012 as being both unnecessary and potentially inconsistent with that view.”

167. The Commissions also proposed alternative wording of the factor.

168. The Council considered the Commissions’ comments.

169. Regarding the NRCET [Muller, et al 2002] report, the Council noted that its scope of review did not extend to the 6(e)(iii) ‘potable water’ factor. It follows that the Council decided not to add the NRCET report about potable water to the pool of information.

170. In so far as that factor 6(e)(iii) and the existing 6(c) and 6(d) factors are concerned the Council was satisfied that the factor it directs the RMA to include in both the Statements of Principles concerning myeloma, did not render those existing factors unnecessary in instrument 69 of 2012, or that the directed factor is inconsistent with those factors. These factors were not in the Council’s scope at the reasonable hypothesis level. On the other hand, the Council’s examination of blood serum evidence was from a different
subset of data (measure of exposure). The Council recognises that under the VEA the Commissions may take this matter up directly with the RMA.

171. The Council took into account all of the comments it received and considered that it should amend its proposed factor to that set out at [2] above.
APPENDIX D: WRITTEN AND COMPLEMENTARY ORAL SUBMISSIONS

Applicant's submissions

172. The Applicant made:
– a written submission dated 3 October 2013 and
– an oral submission complementing his written submissions on 30 October 2013
both of which were taken into account by the Council.\(^78\)

173. The Applicant contended that:

...the current available scientific evidence supports the inclusion of factors 6 (c) and 6 (D) from instrument SOP 69/2012 to instrument SOP 70/2012.

174. The Applicant contended that there is a small number of service personnel who did not serve outside Australia but who:

...were exposed to the herbicides mentioned in the “specified list” in instrument SOP 69/2012.

They were exposed over a much longer period than those who served in Vietnam (due to the nature of their job description - over 1000 hours per year).

175. In support of his contentions the Applicant cited the National Defence and Canadian Armed Forces study on the use of herbicides\(^79\), which stated:

The IOM [Institute of Medicine] has also found a limited or suggestive evidence of an association for seven other outcomes one of these outcomes is Myeloma.\(^80\)

176. The Applicant also cited a recent case-control study conducted in men by Kachuri et al 2013\(^81\) which he contended concluded that:

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\(^78\) 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 Table 2 and 3.

This article was not available to the RMA at the relevant times, and so could only be considered by the Council as new information.

\(^80\) Ibid, at p. 7

This article was not available to the RMA at the relevant times, and so could only be considered by the Council as new information.
Multiple Myeloma has been linked to certain agricultural exposures, including pesticides. Significant associations observed for certain chemical classes and individual pesticides suggest that these may be MM risk factors.

177. The Applicant also referred the Council to Table 1 of a Western Australian Government review by Harper 2003\textsuperscript{82}, and contended:

...Myeloma is listed as a "possible causal link". The very word possible means there is sound scientific and medical evidence without doubt.

178. In his oral submission the Applicant submitted that:

Myeloma is one of the rare cancers, and there is now scientific evidence that links exposure to certain herbicides and pesticides to this disease.

179. The Applicant submitted that a soldier, working on Australian bases:

...used herbicides and chemicals – both mixing and spraying – up to five times per week, six hours per day over a six-year period. These chemicals were stored and mixed in the same area where food was stored and consumed. There was no protective clothing or equipment supplied and no instruction given.

No occupational risk assessment was ever undertaken.

180. The Applicant contended in relation to a possible factor that:

...a time-exposure factor be applied along with the relevant factors to Instrument 69 of 2012 and to Instrument 70 of 2012.

181. The Applicant further contended that:

Most studies on Vietnam veterans have shown no increase in myeloma. Agricultural workers show a marked increase in non-Hodgkin’s lymphoma and myeloma – both of those have now been classified as B-cell cancers – blood cancers.

182. The Applicant concluded\textsuperscript{83} that:

[The Council]...should take into account the stated causal links between herbicide exposure and Myeloma where the case has been proven for even "possible links" for other than those who have served in Vietnam, but were exposed over longer periods of time.

\textsuperscript{82} Harper, A 2003, Report of expert medical panel to evaluate recommendations of the Kimberley chemical use review, final report, West Australian Government, Perth WA, pp. 1-58. This article was not available to the RMA at the relevant times, and so could only be considered by the Council as new information.

\textsuperscript{83} At page 7 of 2013, Written Submission.
The Applicant also suggests an additional addendum [of the relevant factor 6 (C) and (D) from SoPs No. 69 of 2012 to be included in SoPs No. 70 of 2012] in regard to hours per year (e.g. 1000) to exposure for a consecutive number of years prior to the onset of the disease.

183. References provided by the Applicant to material that was not available to the RMA at the relevant times are listed at Table 3.

Commissions’ submissions

184. The Commissions made a written submission dated 25 June 2013, and 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 30 October 2013.84

185. The Commissions identified papers describing exposures for the following groups:

- US and Australian Vietnam veterans;
- Chemical production workers;
- Agricultural workers;
- Other pesticide applicators;
- Forestry workers; and
- Environmentally exposed subjects.

Vietnam veterans

186. In terms of exposure experienced by Australian forces in Vietnam, the Commissions stated that they:

….did not directly use 2,4,5-T (with two small scale exceptions). Australian personnel in Vietnam utilised and were exposed to non-phenoxy herbicides, particularly bromacil, diquat, borate and chlorate. Limited use was also made of Tordon 50-D (80% picloram, 20% 2,4-D) along with paraquat and creosote. Potential exposure of Australian personnel in Vietnam to 2,4,5-T and to TCDD came from being in areas that had been sprayed by US forces or via other pathways such as contaminated food.

187. The Commissions identified three original reports85 on the Vietnam veterans’ cohort that were available to the RMA. About these it concluded that:

84 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 - Table 2.
none provided any results for myeloma risk. One of these reports (Ketchum et al 1999\textsuperscript{86}) does provide information on measured and extrapolated serum TCDD levels in Ranch Hand and other US Air Force veterans.

188. The Commissions cited a 2011 review of the medical scientific information on dioxins (agent orange) and Vietnam veterans by the Institute of Medicine\textsuperscript{87} and concluded that:

Not one of the Vietnam veterans studies cited in VAO 2010 found a statistically significant elevated risk of multiple myeloma in veterans.

189. The Commissions submitted that evidence from Vietnam veteran studies were not helpful when looking at TCDD.

...general veterans, if they were exposed, they were exposed to quite low levels. We have got no meaningful exposure assessment in that group, and no evidence of increased Myeloma risk in that population.

...in the subset of veterans who were exposed, the Ranch Hand and the Chemical Corps people, some of whom have had TCDD measurements, we don't have any useful data on Myeloma.

**Chemical Production Workers**

190. The Commissions submitted that the best available evidence for phenoxy herbicide and TCDD exposure come from studies of:

...workers involved in the production of either phenoxy herbicides (including 2,4,5-T, contaminated by TCDD) or chlorophenols (which can be contaminated by TCDD or other higher chlorinated dioxins).

191. The Commissions contended that while the small case numbers described in these studies for myeloma limit the usefulness of the data, the advantages of these studies include:

...higher exposure levels, better quantification of exposure (with serum levels of TCDD in some cases) and less potential confounding by other exposures, when compared to studies in other populations.

192. The Commissions cited Steenland et al 1999,\textsuperscript{88} which they contended provided six year follow-up data on the IARC cohort\textsuperscript{89}. The Commissions

\textsuperscript{87} Institute of Medicine 2011, Veterans and Agent Orange (VAO): Update 2010, National Academy Press, Washington DC, p 489-97.
\textsuperscript{88} Steenland, K et al 1999, ‘Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin’, Journal of the National Cancer Institute, vol. 91, no. 9, pp. 779-86. RMA ID 25814
noted that the Steenland et al 1999 study used a job-exposure matrix to assess TCDD exposure levels, and reported for multiple myeloma that:

...there were 10 deaths in the cohort and the SMR was 2.07 (95% CI, 0.99 to 3.80).

...There was no excess of haematopoietic cancers in the most highly exposed subjects (3 cases, 4.8 expected).

193. The Commissions submitted that other studies of cancer risk in chemical production workers exposed to phenoxy herbicides / TCDD all had very small numbers of exposed myeloma cases.

- Despite this, there were three studies cited in VAO 2010 that reported statistically significant associations (based on either two or three cases). These were Lynge 1993, Becher et al 1996 and ‘t Mannetje et al 2005.

194. Concerning ‘t Mannetje et al 2005, the Commissions submitted that:

...the phenoxy herbicide exposure was predominantly to 2,4,5-T. Exposure information was limited to years worked and in which department of the production plant an individual worked. There were three myeloma cases in the production workers vs. 0.5 expected, giving an SMR of 5.51 (95% CI, 1.14 to 16.1). Two of the cases worked in packing and transport and the location for the other wasn’t specified. There were no myeloma cases in the sprayers, vs. 0.7 expected.

195. The Commissions contended that ‘t Mannetje et al 2005:

...found an increased risk in the production workers but not in the sprayers.

In the production workers, that was based on three cases. They didn’t have much information on exposure levels in the production workers in particular. They did some testing in the sprayers, and they found them to have an average TCDD in 1988, well

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89 Kogevinas M, Becher H, Benn T et al (1997). Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. American Journal of Epidemiology, 145(12): 1061-75. This article was not available to the RMA at the relevant times, and so could only be considered by the Council as new information. The Commissions cited this article in its written submission stating it was not relied upon by the Commissions.


91 Becher H, Flesch-Janys D, Kauppinen T et al 1996, ‘Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins. Cancer Causes Control, vol. 7, pp. 312-21. This article was not available to the RMA at the relevant times, and so could only be considered by the Council as new information. The Commissions cited this article in its written submission stating it was not relied upon by the Commissions.

after their exposure, of around 53.3 ppt\textsuperscript{93} which they back-extrapolated to a level of 300 ppt during their exposure.

196. The Commissions commented that the 't Mannetje et al 2005 study was looking at:

\ldots a whole bunch of associations - many different cancers associations - and it's possible in that setting that they're finding for Myeloma of a statistically significant association\ldots maybe \ldots about chance.

197. The Commissions cited a later study by McBride et al 2009\textsuperscript{94} which reported on an expanded cohort from the same production plant as 't Mannetje et al 2005.

This study used similar methods but more comprehensive exposure assessment, including serum dioxin testing in a proportion of subjects. This study identified only two myeloma cases and reported an SMR of 2.2 (95% CI, 0.2 to 8.1).

\ldots did some measuring of TCDD in the production workers, \ldots quite a long time after their exposure.

They looked at exposure months, and they did not back-extrapolate.

\ldots from this larger cohort they could find\ldots only two cases of Myeloma \ldots versus three for 't Mannetje.

\ldots going from three cases to two in a bigger cohort reduced the magnitude of the risk estimate, and reduced it to below statistical significance.

198. The Commissions cited a study by Lynge 1998\textsuperscript{95} about which the Commissions submitted:

No incident cases of multiple myeloma were observed in men potentially exposed to phenoxy herbicides vs. 1.89 expected. In women there were two observed cases vs. 0.44 expected, giving an SIR of 4.55 (95% CI, 0.6 to 16.4).

199. The Commissions cited a study be Burns et al 2001\textsuperscript{96} and submitted:

\textsuperscript{93} ppt – 'parts per trillion'

\textsuperscript{94} McBride, DI et al 2009, 'Mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin at a trichlorophenol plant in New Zealand', Journal of Occupational & Environmental Medicine, vol. 51, no. 9, pp. 1049-56. RMA ID 56055


\textsuperscript{96} Burns, CJ et al 2001, 'Mortality in chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) 1945-94: an update', Occupational and Environmental Medicine, vol. 58, pp. 24-30. RMA ID 26080
A job exposure matrix was used to calculate cumulative 2,4-D exposure. There was one death from myeloma in the cohort vs. 1.2 expected, giving an SMR of 0.80 (95% CI, 0.02 to 4.46). No association was found between exposure level and cancer risk for any of the cancer types evaluated in the study.

200. The Commissions cited a cohort mortality study by Hooiveld et al 1998\(^7\) about which the Commissions submitted:

In this relatively small cohort (549 male workers) there were no deaths from multiple myeloma. However, the study did involve serum dioxin testing and provides information on measured and extrapolated TCDD levels in a subset of the subjects.

201. In conclusion, the Commissions submitted that the study of exposed workers by Steenland et al 1999\(^8\) provided the strongest evidence in favour of TCDD as a risk factor for Myeloma.

We have some details on their serum TCDD levels, and ... we can compare that to levels in other groups. So in this cohort their mean serum TCDD was recorded to be around 2000 ppt based on a limited sample of the cohort. That compares to a general population figure - that varies over time - but it's somewhere less than 10; in Australia it's probably less than five. But in the US a contemporary figure at the time ... these workers were being exposed was probably in the 10 to 20 range.

202. The Commissions further submitted that:

TCDD exposure peaked in the general population in the late sixties, early seventies and has declined fairly substantially since then. And there's no actual testing of the general populations from that date, so you would have to try and recreate the numbers (2000 ppt in these workers versus a figure two orders of magnitude less than the general population).

And we have also got some numbers from elsewhere for the Ranch Hand subjects; the people who were part of the US spraying program in Vietnam. ... there has been some testing in them. ... there's evidence of a median figure in that population of the heavily exposed people in that population of around 200 ppt.

**Agricultural workers**

203. The Commissions cited a number of studies in relation to risk of multiple myeloma in farmers, other agricultural workers, pesticide sprayers, forestry workers and other subjects with occupational exposure to pesticides, submitting that very little of the evidence from these studies, provides

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\(^7\) Burns, CJ et al 2001, ‘Mortality in chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) 1945-94: an update’, Occupational and Environmental Medicine, vol. 58, pp. 24-30. RMA ID 26080

\(^8\) Steenland, K et al 1999, ‘Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin’, Journal of the National Cancer Institute, vol. 91, no. 9, pp. 779-86. RMA ID 25814
information on risk of myeloma from exposure specifically to 2,4-D, 2,4,5-T or TCDD.

Workers in such occupations have exposures to a large number of potential carcinogens including a wide array of pesticides. Studies of this type are essentially unhelpful in elucidating the myeloma risk from specific agents, except where data specific to those agents are provided.

204. The Commissions noted that:

...no data specifically on TCDD exposure are available from these studies.

Those studies that report some results for myeloma risk for exposure to 2,4-D, 2,4,5-T, or less specifically, phenoxy herbicides, are briefly summarised below.

205. The Commissions cited Brown et al 1993, and submitted that:

...for 2,4-D there were 35 exposed myeloma cases and the odds ratio relative to non-farmer controls was 1.0 (95% CI, 0.6 to 1.6). For 2,4,5-T there were seven cases and the odds ratio was 0.9 (95% CI, 0.4 to 2.1).

206. The Commissions cited a population-based case-control study by Pahwa et al 2006 and submitted:

The data provided included results for risk of multiple myeloma from exposure to any phenoxy herbicide, the same study (which was not available to the RMA for this investigation), states that gorse spraying in particular almost always used 2,4,5-T, but is silent on whether 2,4,5-T was used for spraying the other plant types in the above list. The cited results from this study in VAO 2010 may thus involve a misclassification of exposure.

207. The Commissions cited Eriksson and Karlsson 1992, and submitted:

Exposure to phenoxyacetic acid herbicides had occurred in 20 cases vs. nine controls. For these results the authors reported the relative risk (2.22) rather than the

This article was not available to the RMA at the relevant times, and so could only be considered by the Council as new information. The Commissions cited this article in its written submission stating it was not relied upon by the Commissions.
odds ratio and the 90% confidence interval (1.15 to 4.46) rather than the 95% interval. These results were on univariate analysis. From the provided data the 95% confidence interval has been calculated, which is 0.99 to 4.98. On multivariate analysis the risk reduced to 1.92 (90% CI, 0.84 to 4.36).

Some dose response data were also provided based on days of work with phenoxyacetic acid herbicides. For three categories of exposure (≤ 5 days, 6 to 20 days and ≥ 21 days) the relative risks were, respectively 3.0, 2.0 and 2.0.

208. The Commissions cited Thorn et al 2000\textsuperscript{103}, and submitted:

This study had some better exposure assessment derived from work records. There were no incident multiple myeloma cases, vs. 0.43 expected (collectively) in exposed subjects.

209. About Orsi et al 2009\textsuperscript{104}, the Commissions submitted:

Results for phenoxy herbicide exposure and risk of multiple myeloma were provided, with an OR of 2.6 (95% CI, 0.9 to 7.0), based on seven exposed cases. No details on the types of phenoxy herbicides were provided.

\textbf{Industrial Accident - Seveso}

210. The Commissions submitted that the main body of evidence concerning environmental exposure to TCDD comes from studies of a population affected by a 1976 industrial accident in Seveso, Italy.

211. The Commissions submitted that the Seveso cohort provides the best evidence for TCDD and Myeloma.

- Consonni et al 2008\textsuperscript{105} for three categories of exposure (≤ 5 days, 6 to 20 days and ≥ 21 days), that the relative risks were, respectively, 3.0, 2.0 and 2.0 after 25 years of follow-up.

- Pesatori et al 2009\textsuperscript{106} and the 20 year mortality follow up by Bertazzi et al 2001\textsuperscript{107}, while providing quite small case numbers.


\textsuperscript{106} Pesatori, AC et al 2009, ‘Cancer incidence in the population exposed to dioxin after the ”Seveso accident”: twenty years of follow-up’, Environmental Health, vol. 8, pp. 39. RMA ID 63465
and not providing formal dose response information, or testing for trend, do provide:

…the suggestion of a response, and a latency period of five to 15 years in the female data, in particular…

So that's some reinforcement for the case for TCDD.

- Pesatori, AC et al 2009 and Consonni et al 2008 for myeloma in the following table.

Table 3. Myeloma incidence and mortality in the Seveso accident population.

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<td></td>
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<td>RR</td>
</tr>
<tr>
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<td>2.88</td>
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<tr>
<td>Zone B</td>
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<td>2.77</td>
</tr>
<tr>
<td>Zone R</td>
<td>18</td>
<td>1.15</td>
</tr>
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</table>

Obs = observed  
RR = risk relative to unexposed population from surrounding area

212. In relation to 2,4-D exposure the Commissions submitted:

[The Commissions]…would suggest it's (2,4-D) struggling to warrant inclusion in the reasonable hypothesis SOP as a factor, and that it's well short of meeting the balance of probabilities standard of proof. So in the Commission's view, there's no basis for having a factor for 2,4-D as a risk factor for Myeloma.

213. However the Commissions submitted that because of the contamination of 2,4,5-T by TCDD:

…it would …. be redundant to also have a factor for 2,4,5,-T because …. one of the main ways of having that exposure [to TCDD] is through exposure to 2,4,5-T.

214. The Commissions submitted that the medical scientific evidence for TCDD warranted the closest attention in determining whether there should be a factor in the Statement of Principles.

215. About the evidence from the Seveso cohort, the Commissions submitted that the most highly exposed group received a median exposure of 447 ppt.

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108 Commissions’ Written Submission, Table 3, p 14
So the production workers, of the people who have been tested and for whom we have data, are certainly the most heavily exposed.

...we are limited in this study by the small number of cases, ten Myeloma deaths in total, which was a two-fold risk versus the general US population and it was just short of statistical significance.

...they weren't able to give us any dose response information for Myeloma, but there was some other evidence for other cancers where they found - they did find an increased risk but it was confined to the most highly exposed workers.

216. The Commissions stated:

So for TCDD it's in the [current] reasonable hypothesis SOP that seems justified. We have got some, at least, suggestive evidence but overall the results are inconclusive. We don't have dose response information in a convincing way, which you would like to have given the uncertainty about the exposure in some of these people.

217. In conclusion the Commissions stated of the available evidence, there was possible confounding in the results by other exposures and the small case numbers.

...as the Commission sees it, [the evidence] falls short of meeting the balance of probabilities standard of proof.

218. The Commissions added however, that if the Council were to conclude otherwise:

...then... you're probably looking at a level of exposure that's not really plausible for anyone in the military setting.

219. In conclusion, the Commissions submitted that:

The quality of the available evidence concerning myeloma risk from exposure to 2,4-D and 2,4,5-T and TCDD is limited in particular by the difficulty of exposure assessment, the high possibility of confounding (by chemical and other exposures) and the generally small numbers of myeloma cases in the available studies.

And noted that:

The RMA has concluded that the available evidence indicates, but does not establish on the balance of probabilities, that myeloma can be causally related to exposure to both 2,4-D and 2,4,5-T.

The RMA has reached the same conclusions regarding exposure to TCDD.
Further, the Commissions concluded that the evidence “for both TCDD alone and for 2,4,5-T and TCDD together, is limited”, and that they “could not identify any direct evidence that myeloma could be causally related to 2,4-D exposure”.

… the evidence that was available to the RMA does not warrant the inclusion of additional SOP factors in Instrument 70 of 2012, concerning 2,4-D and 2,4,5-T, or TCDD exposure.
APPENDIX E: INFORMATION BEFORE THE COUNCIL

TABLE 1 – Pool of Information

<table>
<thead>
<tr>
<th>RMA ID</th>
<th>Title</th>
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Hoiveld, M et al. 1998, ‘Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants’, American Journal of Epidemiology, vol. 147, no. 9, pp. 891-901.


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### TABLE 2 – The Available Information

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<tr>
<th>RMA ID</th>
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Aksoy, M et al. 1984, ‘Clinical observations showing the role of some factors in the etiology of multiple myeloma. A study in 7 patients’, *Acta Haematologica Polonica Polonicaogica*, vol. 71, no. 2, pp. 116-120.


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<td>Rottenburger, C et al. 1999, ‘Clonotypic CD20 plus and CD19 plus B cells in peripheral blood of patients with multiple myeloma post high-dose therapy and peripheral blood stem cell transplantation’, <em>British Journal of Haematology</em>, vol. 106, pp. 542-552.</td>
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<td>52311</td>
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<td>9924</td>
<td>Savitz, D Andrews, KW</td>
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<td>‘Risk of myelogenous leukaemia and multiple myeloma in workers exposed to benzene’</td>
<td>Occupational &amp; Environmental Medicine</td>
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<td>10434</td>
<td>Savitz, DA</td>
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<td>‘Overview of epidemiologic research on electric and magnetic fields and cancer’</td>
<td>American Industrial Hygiene Association</td>
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<td>Savitz, DA Andrews, KW</td>
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<td>‘Risk of myelogenous leukemia and multiple myeloma in workers exposed to benzene’</td>
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<td>Blood</td>
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<td>Schreinemachers, DM</td>
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<td>‘Cancer mortality in four Northern wheat-producing states’</td>
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### TABLE 3 – Applicant ‘New’ Information


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