Specialist Medical Review Council

Declaration and Reasons for Decisions

Section 196W
Veterans' Entitlements Act 1986

Re: Statements of Principles No. 28 of 2010 as amended by Statement of Principles No. 57 of 2014 and No. 86 of 2014; and Statement of Principles No. 29 of 2010 as amended by Statement of Principles No. 87 of 2014 in respect to non-Hodgkin's lymphoma

Request for Review Declaration No. 26

1. In relation to the Repatriation Medical Authority (the RMA) Statement of Principles No. 28 of 2010 as amended by Statement of Principles No. 57 of 2014 and No. 86 of 2014 concerning non-Hodgkin's lymphoma and death from non-Hodgkin's lymphoma, made under section 196B of the *Veterans' Entitlements Act 1986* (the VEA), the Specialist Medical Review Council (the Council) under subsection 196W(4) of the VEA:

DECLARES that there is sound medical-scientific evidence on which the RMA could have relied to justify an amendment to Statement of Principles No. No. 28 of 2010 as amended by Statement of Principles No. 57 of 2014 and No. 86 of 2014 to include a factor in that Statement of Principles for exposure to ionising radiation; and

DIRECTS the RMA to amend Statements of Principles No. 28 of 2010 as amended by Statement of Principles No. 57 of 2014 and No. 86 of 2014 by including the following factor:

having received a cumulative equivalent dose of at least 0.1 sievert of ionising radiation to the bone marrow at least five years before the clinical onset of Non-Hodgkin's Lymphoma.

2. In relation to the RMA Statements of Principles No. 29 of 2010 as amended by Statement of Principles No. 87 of 2014 concerning non-Hodgkin’s lymphoma and death from non-Hodgkin's lymphoma made under section 196B of the VEA, the Council under subsection 196W(5) of the VEA:

DECLARES that the sound medical-scientific evidence available to the RMA is insufficient to justify an amendment to the Statement of Principles No. 29 of 2010 as amended by Statement of Principles No. 87 of 2014 to include a factor or factors in that Statement of Principles for exposure to ionising radiation.

INDEX of CONTENTS

REASONS FOR DECISIONS

INTRODUCTION

1. 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.

2. In conducting a review, the Council must review all of the information (and only that information) that was available to the RMA when it made the decision under review. This is information which was actually used by the RMA as opposed to information which was generally available but not accessed by the RMA. A list of the information that was available to the RMA is listed in **Table 1 of Appendix A**.

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

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

5. In a reasonable hypothesis, the evidence 'points to' as opposed to merely 'leaves open' a link between injury, disease or death and the relevant

---

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

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

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

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

"Information about a particular kind of injury, disease or death is taken to be sound medical-scientific evidence if:

a) the information:

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

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

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

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

service. In a reasonable hypothesis, the link is not 'obviously fanciful, impossible, incredible or not tenable or too remote or too tenuous.'[2]

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

7. The Council exercises its scientific judgement in weighing the evidence.

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

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

10. The SMSE relevant to this application (the relevant SMSE) is listed in **Table 2 of Appendix A.**

11. The information to which the Applicant referred, being information which the RMA advised was new information, that is, information which was not available to the RMA at the relevant times, was not considered by the Council in reaching its review decision is listed in **Table 3 of Appendix A**.

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

13. **Appendix C** provides a list of abbreviations used in these reasons.

SCOPE OF THIS REVIEW

14. In her application, the Applicant sought review of the contents of **SoPs No. 28 as amended by No. 57 of 2014 and No. 86 of 2014; and SoPs No. 29 of 2010 as amended by No. 87 of 2014.** The Applicant contended that there was SMSE on which the RMA could have relied to amend either or

---

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

3 Relevant service in balance of probabilities statements of principles refers to non-operational service having regard to the various definitions applying to types of 'service' as defined in the VEA and the *Military Rehabilitation and Compensation Act 2004* (MRCA).

both of the Statements of Principles in respect to exposure to ionising radiation.

15. The Council wrote to both the Applicant and the Commissions advising its preliminary decision on the proposed scope of the review and inviting comment. No comments were received on the proposed scope of the review and therefore the Council has decided that it will have particular regard to whether there was SMSE on which the RMA could have relied to amend either or both of the SoPs in any or all of the following ways:

- the possible inclusion of a factor or factors in **SoPs No. 28 of 2010** as amended by **SoPs No. 57 of 2014 and No. 86 of 2014**, as contended, for exposure to ionising radiation; and
- the possible inclusion of a factor or factors in **SoPs No. 29 of 2010** as amended by **SoPs No. 87 of 2014** as contended, for exposure to ionising radiation.

COUNCIL'S EVALUATION OF THE SMSE

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

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

18. For ease of reference, the Bradford Hill criteria (noting that these are not exhaustive) are:

- strength of association
- consistency across investigation
- specificity of the association
- temporal relationship of the association
- biological gradient
- biological plausibility
- coherence
- experiment
- analogy

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

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

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

- did not provide data that the Council could draw conclusions on about ionising radiation and non-Hodgkin's lymphoma.

Council's decisions on the relevant SMSE

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

22. The Council wrote to both the Applicant and the Commissions advising of its preliminary decisions on the SMSE identified for the purpose of conducting the review and inviting comment. No comments were received.

23. The Council's final decision on the SMSE for the review was that it should comprise the information listed in **Table 2 at Appendix A**.

WRITTEN AND ORAL SUBMISSIONS

24. The Council took into account the written and oral submissions made to it.

Applicant's Submission

25. Through her representative, the Applicant advised the Council that the information provided with her application incorporated her written submission. Her son represented the Applicant at the Council's hearing of submissions held on 28 January 2014, but elected not to make an oral submission.

26. The Applicant contended that there are available studies that support an association between exposure to ionising radiation and non-Hodgkin's lymphoma.

27. In support of her contention, the Applicant cited Richardson et al. (2009)[4]; and UNSCEAR 2013[5] paragraph B275[6] which she submitted reported:

---

[4] Richardson, D. B., Sugiyama, H., Wing, S., Sakata, R., Grant, E., Shimizu, Y., Nishi, N., Geyer, S., Soda, M., Suyama, A., Kasagi, F., & Kodama, K. (2009). Positive association between ionising radiation and lymphoma mortality among men. American Journal of Epidemiology, 169(8), 969-976. (RMA ID 068828)

"…an elevated risk of non-Hodgkin's lymphoma for males exposed to radiation."

28. The Applicant also referred to paragraph B276[7] of UNSCEAR 2013 which concerns the effects of radiation exposure on children which she said:

"…found an excess of non-Hodgkin's lymphoma however it was determined to be non-significant."

29. The Applicant also cited Cardis et al. (2007)[8] which she submitted:

"…found an elevated non-significant non-Hodgkin's lymphoma association…"

The Applicant noted however that, "higher dose workers were excluded" from the study.

30. The Applicant also cited Kim et al. (2013)[9] which she said:

"…found an increased risk of non-Hodgkin's lymphoma following radiotherapy".

Commissions' Submission

31. The Repatriation Commission and the Military Rehabilitation and Compensation Commission (The Commissions) made a written submission to the Council dated November 2014 and a Medical Officer representing the Commissions made an oral submission complementing the Commissions' written submission at the Council's meeting on 28 January 2015.

---

5 UNSCEAR 2013 REPORT Vol. II SOURCES, EFFECTS AND RISKS OF IONISING RADIATION, United Nations Scientific Committee on the Effects of Atomic Radiation, Volume II: Scientific Annex B: Effects of radiation exposure of children. (RMA ID 071213)

6 B275. An earlier analysis by Preston et al.(1994) of non-Hodgkin's lymphoma incidence in the LSS found no excess for females, but an estimated EAR for males of 0.56 (10 PY Sv)' (95% CI: 0.08, 1.39) [P47]. No age-at-exposure effect was found (p> 0.5). A recent analysis by Hsu et al. suggested the possibility of risk among men, with an ERR Gy' of 0.46 (95% CI: -0.08, 1.3) and an EAR (104PY Sv)' of 0.54 (95% CI: 0.09, 1.32), but both the ERR and EAR were essentially zero among women [H70]. The male EAR did not vary with age at exposure (p = 0.15).

7 B276. A study of tuberculosis patients who received multiple fluoroscopic examinations in monitoring pneumothorax treatments found a non-significant excess of non-Hodgkin's lymphoma (RR = 1.3, 95% CI: 0.5, 3.5) and did not examine age at exposure [D15].

8 Cardis E., Vrijheid, M., Blettner, M., Gilbert, E., Hakama, M., Hill, C., Howe, G., Kaldor, J., Muirhead, C. R., Schubauer-Berigan, M., Yoshimura, T., Bermann, F., Cowper, G., Fix, J., Hacker, C., Heinmiller, B., Marshall, M., Thierry-Chef, I., Utterback, D., Ahn, Y. O., Amoros, E., Ashmore, P., Auvinen, A., Bae, J. M., Bernar, J., Biau, A., Combalot, E., Deboodt, P., Diez Sacristan, A., Eklöf, M., Engels, H., Engholm, G., Gulis, G., Habib, R. R., Holan, K., Hyvonen, H., Kerekes, A., Kurtinaitis, J., Malker, H., Martuzzi, M., Mastauskas, A., Monnet, A., Moser, M., Pearce, M. S., Richardson, D. B., Rodriguez-Artalejo, F., Rogel, A., Tardy, H., Telle-Lamberton, M., Turai, I., Usel, M., & Veress, K (2007). The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. Radiation Research, 167(4), 396-416. (RMA ID 043945)

9 Kim, C. J., Freedman, D. M., Curtis, R. E., Berrington de Gonzalez, A., & Morton, L. M. (2013). Risk of non-Hodgkin lymphoma after radiotherapy for solid cancers. Leukemia & Lymphoma, 54(8), 1691-1697. (RMA ID 069996)

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

- atomic bomb survivors in Japan
- radiotherapy
- thorotrast studies
- nuclear industry
- Chernobyl studies
- nuclear test veterans
- people exposed to high background radiation levels.

33. The Commissions submitted that the series of studies by the International Agency for Research on Cancer (IARC)[10] and by the United Nations[11] along with a number of reviewers,

> "are in general agreement that non-Hodgkin's lymphoma is not one of the cancers that is clearly linked to the ionising radiation"

adding that,

> "these authors note that there's some limited evidence in support of an association."

34. The Commissions submitted that evidence from the Life Span series of studies regarding the cohort of atomic bomb survivors in Japan is the "most important evidence on ionising radiation and cancer generally".

35. Of the Life Span Study cohort, the Commissions submitted that it:

> "…is effectively the gold standard for assessing risk from ionising radiation and the lack of an overall association and a dose-response in that cohort is an important finding against the posited relationship. However, the non-significant excess of non-Hodgkin's lymphoma in males, particularly for subjects of young age when exposed, is somewhat supportive. The study also gave an indication of a decline in risk with time since exposure, with risk approaching zero by attained age of 40 (the study has a built in 5 year latency, with follow-up commencing in late 1950)."

36. Of Cardis et al. (2007)[12], a 15-country international collaborative mortality study of 407 391 nuclear industry workers, the Commissions submitted that

---

10 IARC Working Group (2012). x- and y-radiation. IARC Monographs - A Review of Human Carcinogens, Vol. 100 Part D, Radiation: 131-132. IARC Press, Lyon. (RMA ID 065039)

11 UNSCEAR (2006). Non-Hodgkin's lymphoma. United Nations Scientific Committee on the Effects of Atomic Radiation, Vol 1: 108-110, 209-212. United Nations Publications, New York. (RMA ID 055814)

12 Cardis et al. (2007). The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. Radiation Research, 167(4), 396-416. (RMA ID 043945)

the authors found an excess relative risk, but that this did not reach statistical significance.

37. The Commissions referred to the paper by Richardson et al.(2009)[13] as an "outlier study":

> "…with findings on mortality in a sub-cohort of the LSS at odds with those from the incidence study of the whole cohort and with findings on nuclear industry workers inconsistent with those from other sites. The strong association reported in this study for the Savannah River site workers has not been replicated elsewhere.

38. In his oral submission the Commissions' representative said of Richardson that for both cohorts studied (mortality in the lifespan study cohort and also a cohort from the Savannah River industrial site) the authors found:

> "… elevated risks at higher doses a long time after exposure…"

and added that this is:

> "…the strongest evidence of a positive association, but it has some findings that are a bit in conflict with other studies about the strength of the association, about the timing of the association.

In terms of the quality of the study, he concluded that it:

> "…seemed reasonably well-conducted," and "there didn't seem to be any major confounding issues".

39. In his oral submission the Commissions representative referred to a study by Kim et al. (2013)[14] on exposure to radiotherapy, which he said provided "some weakly positive evidence" in support of the association.

40. The Commissions submitted that the Weiss et al. (1994)[15] study on cancer mortality in 14,556 ankylosing spondylitis patients treated with X-ray concluded that for non-Hodgkin's lymphoma there was a significantly increased risk (RR 2.83, $p < 0.001$) in the irradiated patients in the 5 to 25 years since first treatment, but not thereafter (RR 1.06).

41. In conclusion, the Commissions submitted that on the basis of its assessment of the sound medical scientific evidence:

---

13 Richardson et al. (2009). Positive association between ionising radiation and lymphoma mortality among men. American Journal of Epidemiology, 169(8), 969-976. (RMA ID 068828)

14 Kim et al. (2013). Risk of non-Hodgkin lymphoma after radiotherapy for solid cancers. Leukemia & Lymphoma, 54(8), 1691-1697. (RMA ID 069996)

15 Weiss, H.A., Darby, S.C., & Doll, R. (1994). Cancer mortality following x-ray treatment for ankylosing spondylitis. International Journal of Cancer, 59(3), 327-338. (RMA ID 025044)

- At the balance of probabilities standard of proof, the available sound medical scientific evidence is insufficient to justify the inclusion of a new factor for ionising radiation in **instrument 29 of 2010 (as amended by 87 of 2014**).

- At the reasonable hypothesis standard of proof there is available evidence of an association that may be sufficient to warrant a new factor, particularly for a higher level of exposure than has been included in other SOPs with ionising radiation factors.

42. The Commissions concluded that, "…if the Council was to conclude that the inclusion of an RH factor was warranted, the Commissions suggest that the following might be suitable.

> "…having received a cumulative equivalent dose of at least 0.2 sievert of ionising radiation to the bone marrow at least five years before the clinical onset of non-Hodgkin's lymphoma,""

COUNCIL'S CONCLUSIONS ON THE RELEVANT SMSE

43. There were a large number of published studies on the relationship between exposures to ionising radiation as a factor in non-Hodgkin's lymphoma. The relevant studies are grouped by exposure type:

- Japanese atomic bomb survivors
- Military testing of nuclear weapons
- Occupational exposure to ionising radiation
- Communities residing near sources of ionising radiation
- Accident recovery workers at Chernobyl nuclear power station
- Patients administered radiation
- Other relevant studies

Studies of Japanese Atomic Bomb Survivors

44. The Council examined a number of studies of people exposed to radiation during the atomic bomb explosions in Hiroshima and Nagasaki in Japan in August, 1945. Primarily gamma rays and neutrons were emitted simultaneously with the bomb explosions, exposing people in Hiroshima and Nagasaki to a large acute dose of radiation over a relatively short period.

45. All studies considered by the Council analysed data from the Life Span Study, a long term prospective cohort study, which began in 1950 with a five year lag. The cohort includes survivors who were residents of Hiroshima or Nagasaki, and were present within 10 kilometres of the hypocentres at the time of the bombings. The study also includes data of residents who were not in either city at the time of the bombings.

46. The most recent and comprehensive analysis of the Life Span Study was conducted by **Hsu et al. (2013)[16] [RMA ID: 072597]** who analysed the radiation effects on the incidence of leukaemia, lymphoma, and multiple myeloma. A total of 113,011 cohort members were included, almost 60% were women and 41% were less than 20 years old at the time of the bombings, although exact figures were not provided. There was a total of 3.6 million person-years of follow-up from late 1950 to December 2001, and 43% were still alive at the end of follow-up. The exact numbers of age at exposure and attained age of cohort members were not provided by the authors, although the cohort included individuals aged 5 years and older. A total of 402 non-Hodgkin's lymphoma cases were identified. The majority of non-Hodgkin's lymphoma cases (*n* = 226) were exposed to radiation doses < 0.005 Gray (Gy), and the other 176 non-Hodgkin's lymphoma cases were exposed to 0.1 Gy (*n* = 99), 0.2 Gy (*n* = 21), 0.5 Gy (*n* = 28), 1.0-2.0 Gy (*n* = 27) and ≥2Gy (*n* = 1).

47. A risk analysis for radiation dose response was conducted to assess if there was an excess risk of the incidence of non-Hodgkin's lymphoma at any given level of radiation exposure. Dose response is the relationship between the quantity of the exposure to radiation (dose) and its overall effect (response) on an individual. The incremental change per unit of additional radiation on the individual is important to measure the relationship between the frequency and occurrence of a disease as the exposure of radiation increases. Excess relative risk (ERR) and excess absolute rate (EAR) models per Gy of exposure were calculated adjusting for age at exposure, and either age attained or time since exposure.

48. Background rates for non-Hodgkin's lymphoma increased rapidly with attained age, there was also a complex non-linear birth cohort effect ($p > 0.001$) with the highest age-specific rates for cohort members born around 1940 (around 5 years of age at exposure) and lower age specific rates for people born in earlier or later years.

49. The ERR in a simple linear dose response model showed an increased effect in males (ERR/Gy = 0.46; 95% confidence interval (CI): -0.08, 1.29; $p = 0.11$), but no indication of an increased effect for females (ERR/Gy = 0.02; 95% CI: <-0.44, 0.64; $p > 0.5$). At younger ages of exposure the ERR/Gy for males was large although this effect declined markedly with age (and thus time since exposure) and approached zero by age 40. The excess rate peaked around age 20 and there was little excess after age 30, which also implies that the radiation effects were seen primarily among those exposed as children or young adults. Additionally, as non-Hodgkin's lymphoma increased rapidly with attained age, the baseline rates are highly variable as the estimates for younger age are based on lower numbers.

[16] Hsu, W. L., Preston, D. L., Soda, M., Sugiyama, H., Funamoto, S., Kodama, K., Kimura, A., Kamada, N., Dohy, H., Tomonaga, M., Iwanaga, M., Miyazaki, Y., Cullings, H. M., Suyama, A., Ozasa, K., Shore, R. E., & Mabuchi, K. (2013). The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001. Radiation Research, 179(4), 361-382. (RMA ID 072597)

50. In an EAR model, there was a statistically significant increased effect in males (EAR/Gy = 0.54; 95% CI: 0.09, 1.32; p = 0.003) although no increased effect for females (EAR/Gy = 0.0; 95% CI: -0.02, 0.31; p > 0.5). Additionally, the EAR did not change with attained age (p = 0.3), time since exposure (p = 0.46), or age at exposure (p = 0.15). Therefore, the EAR showed a risk of 0.54 cases per 10 000 person-years (PY) at 1 Gy.

51. An incidence analysis of the Life Span Study from 1950 to1987 conducted by **Preston et al. (1994)[17] [RMA ID: 003046]** found similar results. For the 170 non-Hodgkin's lymphoma cases, a weak association of an increased risk of non-Hodgkin's lymphoma for males exposed to low dose ionising radiation (0 - 4 Gy) was reported.

52. An earlier analysis of Life Span Study from 1945 to1965 of the relationship between malignant lymphoma and exposure to ionising radiation was conducted by **Nishiyanma et al. (1973)[18] [RMA ID: 054444].** The cohort included residents of Hiroshima (n = 61 974) and Nagasaki (n = 20 348), and 38 malignant lymphomas were identified (Hiroshima = 26; Nagasaki = 12). Non-Hodgkin's lymphoma was not separately examined.

53. For Hiroshima survivors, there was an increased risk of malignant lymphoma for the eight survivors exposed to 100 rad (1 Gy) or more. The unit rad is equivalent to 0.01 Gy. In Hiroshima, for the period of 1945 to 1965 by dose estimate, there was a crude prevalence rate of 25.49 per 10,000 population, which slightly increased when adjusted to the standardised population, with an adjusted prevalence rate of 27.91. The relative risk (calculated from the adjusted prevalence with less than 1 rad (0.01 Gy) exposure category assigned a value of 1.0) was 8.0 (although confidence intervals were not provided).

54. This increased risk was not seen in the Nagasaki survivors. Excess risk of malignant lymphoma was apparent in both Hiroshima males and females exposed to 100 rad (1 Gy) or more. However, this difference was statistically significant only for males. The authors concluded that there was an increased risk of malignant lymphoma among survivors of the Hiroshima atomic bomb exposed to a 100 or more rad (1 Gy) but the risk was not evident in Nagasaki.

---

17 Preston, D. L., Kusumi, S., Tomonaga, M., Izumi, S., Ron, E., & Kuramoto, A. (1994). Cancer incidencein atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987 + Errata. Radiation Research, 137(Suppl 2), S68–S97. (RMA ID 003046)

18 Nishiyanma, H., Anderson, R. E., Ishimaru, T., Ishida, K., It, Y., & Okabe, N. (1973). The incidence of malignant lymphoma and multiple myeloma in Hiroshima and Nagasaki atomic bomb survivors, 1945-1965. Cancer, 32(6), 1301-1309. (RMA ID 054444)

55. Mortality in the Life Span Study from 1950 to 1990 was evaluated by **Pierce et al. (1996)[19] [RMA ID: 016850]**, and included 86,572 subjects. There were 162 malignant lymphoma deaths (males = 74; females = 88), although non-Hodgkin's lymphoma was not separately analysed. There was a non-significant association with the number of deaths from malignant lymphoma and radiation dose effect (p = 0.449, one sided). A time-constant ERR model was fitted to mortality and followed-up through 1990, a non-significant positive association with radiation dose among males (ERR/ units of Sievert (Sv) = 0.27; 90% CI; ND, 1.49) and a non-significant association among females (ERR/Sv = -0.17; 90% CI: ND, 0.30) was shown. The radiation dose response for both sexes combined was also non-significant (ERR/Gy = 0.02; 90%CI: NA, 0.33; p = 0.90).

56. **Richardson et al. (2009)**[20] **[RMA ID: 068828]** examined the association between ionising radiation and lymphoma mortality among men in two cohorts; the Life Span Study and the Savannah River Site (a nuclear reservation in the United States). Cohort one included 20,940 men in the Life Span Study, aged 15-64 years at time of the bombings in Hiroshima and Nagasaki, prospectively followed from 1950 to 2000. There were 84 non-Hodgkin's lymphoma deaths (Hiroshima = 58, Nagasaki = 26) and the majority (n = 69) were aged 60 years or over.

57. Estimates of non-Hodgkin's lymphoma mortality and ionising radiation dose for under 5 year and 10 years exposure lags showed a significant association with both a 5 year lag (ERR/ Sv = 0.86; 90% CI: 0.13, 2.03; p = 0.04) and a 10 year lag (ERR/Sv = 1.12; 90% CI: 0.26, 2.51; p = 0.02). There was no evidence of an association between radiation dose and non-Hodgkin's lymphoma mortality during the period of 5-35 years after irradiation, however, there was a statistically significant dose-response seen greater than 35 years after exposure (36-45 years: n = 16, ERR/Sv = 2.23; 90% CI: 0.09, 6.91; p = 0.08 and 46-55 years: n = 23, ERR/Sv = 1.70; 90% CI: 0.16, 5.36; p = 0.05).

58. Table 1 shows the observed and expected numbers of malignant lymphoma deaths by dose category of under 5 years and 10 year lag.

[19] Pierce, D. A., Shimizu, Y., Preston, D. L., Vaeth, M., & Mabuchi, K. (1996). Studies of the mortality of atomic bomb survivors. Report 12. Part 1. Cancer: 1950-1990. Radiation Research, 146(1), 1-27. (RMA ID 016850)

[20] Richardson et al. (2009). Positive association between ionising radiation and lymphoma mortality among men. American Journal of Epidemiology, 169(8), 969-976. (RMA ID 068828)

TABLE 1. OBSERVED AND EXPECTED DEATHS DUE TO MALIGNANT LYMPHOMA AMONG MALE ATOMIC BOMB SURVIVORS (1950-2000), BY RADIATION DOSE CATEGORY UNDER 5 YEAR AND 10 YEAR LAG

Assumed Lag and Cohort	Radiation Dose, Sv						
	<0.005	0.005–<0.10	0.10–<0.20	0.20–<0.50	0.50–<1	1–<2	≥2
5-year lag							
Atomic bomb survivors[b]							
No. of deaths observed	32	29	8	11	3	5	2
Obs/Exp ratio[c]	0.80	0.97	1.33	1.61	0.72	2.04	2.60
Mean dose, Sv	0.001	0.032	0.141	0.322	0.721	1.340	2.392
Person-years of follow-up	260,641	195,354	38,255	45,932	28,566	16,674	5,937
10-year lag							
Atomic bomb survivors							
No. of deaths observed	27	27	8	11	3	5	2
Obs/Exp ratio	0.73	0.97	1.44	1.73	0.78	2.19	2.73
Mean dose, Sv	0.001	0.032	0.141	0.322	0.722	1.338	2.392
Person-years of follow-up	213,808	160,274	31,330	37,840	23,545	13,827	4,926

Abbreviations: Exp, expected; Obs, observed.
[a] Because of rounding, some column totals for person-time differ slightly from the sums of rows.
[b] Japanese males who were aged 15–64 years and present in Hiroshima or Nagasaki at the time of the bombings.
[c] Ratio of the number of deaths observed to the number of deaths expected.

(Source: Richardson et al. (2009). Positive association between ionising radiation and lymphoma mortality among men. *American Journal of Epidemiology*, 169(8), p. 974).

59. This finding provided evidence of an association between increasing ionising radiation dose and malignant lymphoma mortality (84 of 90 malignant lymphomas in the study were non-Hodgkin's lymphoma). While there is no evidence of a risk below 0.10 Sv of the observed and expected numbers of deaths due to malignant lymphoma for men, an increased risk for men exposed to 0.10 Sv or more was evident. When the data were analysed by ionising radiation dose there appeared to be a trend, though p values for trend and confidence intervals were not provided.

Council's Conclusions on Studies of Japanese Atomic Bomb Survivors

60. The Council considered that the two most informative papers were **Hsu et al. (2013)**[21] and **Richardson et al. (2009)**[22]. **Hsu et al. (2013)**[23] found that younger men were significantly at risk and this effect declined markedly with age and thus time since exposure and the risk effect was not evident by age 40.

61. In contrast, **Richardson et al. (2009)**[24] found that the risk (of mortality) manifested much later. After 35 years following exposure, an increased risk

21 Hsu et al. (2013). The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001. Radiation Research, 179(4), 361-382. (RMA ID 072597)

22 Richardson et al. (2009). Positive association between ionising radiation and lymphoma mortality among men. American Journal of Epidemiology, 169(8), 969-976. (RMA ID 068828)

23 Hsu et al. (2013). *ibid.*

24 Richardson et al. (2009). *ibid.*

was seen at > 0.10 Sv. The largest risk of malignant lymphoma was associated with radiation dose for those men exposed to greater than 1 Sv (at both a 5 year 1-<2 Sv: Standardised Mortality Ratio (SMR) = 2.04, ≥2 Sv: SMR = 2.60; and 10 year lag 1-<2 Sv: SMR = 2.19, ≥2 Sv: SMR = 2.73).

62. However, there were a number of differences between the two studies. First, **Hsu et al. (2013)**[25] conducted an incidence analysis whereas, **Richardson et al. (2009)**[26] examined mortality**.** Secondly, Richardson used a subset of the Life Span Study (males aged between 15 and 64 years at the time of the bombings). Therefore excluding those people exposed to the radiation at a young age that were shown to be at increased risk in **Hsu et al. (2013)**[27]**.** Thirdly, the statistical analysis methods and presentation of the results between the two papers made direct comparisons difficult.

Studies of Military Testing of Nuclear Weapons

63. A number of studies have reported the effects of the atmospheric nuclear weapons tests in the Pacific islands. The Council focused on four studies by **Pearce et al. (1997)**[28] **[RMA ID: 017372], Darby et al. (1993)**[29] **[RMA ID: 026537], Darby et al. (1988)**[30] **[RMA ID: 006753],** and **Watanabe et al. (1993)**[31] **[RMA ID: 007499],** all of which found no association between exposure to ionising radiation during atmospheric nuclear weapons tests and non-Hodgkin's lymphoma.

64. In a study by **Pearce et al. (1997)**[32] **[RMA ID: 017372]** only two non-Hodgkin's lymphoma cases were identified, so there were too few cases to make any inferences of a relationship between ionising radiation exposure of personnel involved on nuclear weapons testing and non-Hodgkin's lymphoma. **Darby et al. (1993)**[33] **[RMA ID: 026537]** and an earlier study by

---

25 Hsu et al. (2013). *ibid*.

26 Richardson et al. (2009). *ibid.*

27 Hsu et al. (2013). *ibid.*

28 Pearce, N., Winkelmann, R., Kennedy, J., Lewis, S., Purdie, G., Slater, T., Prior, I., & Fraser, J (1997). Further follow-up of New Zealand participants in United Kingdom atmospheric nuclear weapons tests in the Pacific. Cancer Causes and Control, 8(1), 139-145. (RMA ID 017372)

29 Darby, S., Kendall, G., Fell, T., Doll, R., Goodill, A. A., Conquest, A. J., Jackson, D. A., & Haylock, R. G. E.. (1993). Further follow up of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapons tests and experimental programmes. British Medical Journal, 307(6918), 1530-1535. (RMA ID 026537)

30 Darby, S. C., Kendall, G. M., Fell, T. P., O'Hagan, J. A., Muirhead, C. R., Ennis, J. R., Ball, A. M., Dennis, J. A., & Doll, R. (1988). A summary of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapon tests and experimental programmes. British Medical Journal, 296(6618), 332-338. (RMA ID 006753)

31 Watanabe, K. K., Kang, H. K., & Dalager, N. A. (1995). Cancer mortality risk among military participants of a 1958 atmospheric nuclear weapons test. American Journal of Public Health, 85(4), 523-526. (RMA ID 007499)

32 Pearce et al. (1997). *ibid.*

33 Darby et al. (1993). *ibid.*

Darby et al. (1988)[34] **[RMA ID: 006753]** showed participation in nuclear weapon tests had no detectable effect on non-Hodgkin's lymphoma mortality or clinical onset of non-Hodgkin's lymphoma.

65. The risk of cancer mortality for Navy veterans who participated in the United States atmospheric nuclear weapon tests in the Pacific was examined by **Watanabe et al. (1993)**[35] **[RMA ID: 007499].** The Navy veterans received a median radiation dose of 388 millirem (mrem) (0.00388 Sv). The unit rem is equivalent to 0.01 Sv. There were six observed non-Hodgkin's lymphoma deaths, and the radiation doses veterans were exposed to were generally less than 500 mrem (0.005 Sv), although there were too few non-Hodgkin's lymphoma deaths to make any firm conclusions.

Council's Conclusions on Studies of Military Testing of Nuclear Weapons

66. The Council concluded that each of the four studies reviewed provided no evidence of an association between exposure to ionising radiation during atmospheric nuclear weapons tests and non-Hodgkin's lymphoma. The one study that estimated exposure considered it to be less than 0.005 Sv, although there were a small number of non-Hodgkin's lymphoma deaths.

Studies of Occupational Radiation Exposure

67. The Council considered a large number of studies reporting the effects of exposure to ionising radiation on nuclear industry workers.

Radiation Workers at Nuclear Production and Research Facilities

68. One of the largest comprehensive epidemiological studies involves a 15-Country collaborative retrospective cohort examining direct estimates of cancer risk following protracted low doses of ionising radiation conducted by **Cardis et al. (2007)**[36] **[RMA ID: 043945].** Analysis of mortality data among nuclear industry workforces from studies in three countries was also conducted by **Cardis et al. (1995)**[37] **[RMA ID: 005770]**. Table 2 provides an overview both of these studies. The risk estimates mainly reflect risks in men as there were few exposed women in the cohort.

---

34 Darby et al. (1988). *ibid.*

35 Watanabe et al. (1995). Cancer mortality risk among military participants of a 1958 atmospheric nuclear weapons test. American Journal of Public Health, 85(4), 523-526. (RMA ID 007499)

36 Cardis et al. (2007). The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. Radiation Research, 167(4), 396-416. (RMA ID 043945)

37 Cardis, E., Gilbert, E. S., Carpenter, L., Howe, G. R., Kato, I., Armstrong, B. K., Beral, V., Cowper, G., Douglas, A., Fix, J., Fry, S. A., Kaldor, J., Lave, C., Salmon, P. G., Smith, P. G., Voelz, G. L., & Wiggs, L. D. (1995). Effects of low doses and low dose rates of external ionising radiation: Cancer mortality among nuclear industry workers in three countries. Radiation Research, 142(2), 117-132. (RMA ID 005770)

69. **Cardis et al. (2007)**[38] **[RMA ID: 043945]** followed up 598,068 workers from 154 facilities. There was a skewed distribution of recorded doses with 90% of workers having cumulative doses below 50 mSv (0.05 Sv) and less than 0.1% receiving cumulative doses greater than 500 mSv (0.5 Sv). Of the 248 non-Hodgkin's lymphoma deaths, 243 had a cumulative radiation dose of less than 100 mSv (0.1 Sv). No dose-response trend was seen. The relative risk at 100 mSv (0.1 Sv) was 1.04, and non-significant. Similar results were seen in **Cardis et al. (1995)**[39] **[RMA ID: 005770].** For the 135 non-Hodgkin's lymphoma deaths, no association for dose response for non-Hodgkin's lymphoma was seen.

Table 2. Combined Analysis of the 15-Country Collaborative and the 3-Country Collaborative of Nuclear Industry Workers

Study	Counties	Cohort	non-Hodgkin's lymphoma	Exposure	Outcome
Cardis et al. (2007)[40]	Australia Belgium Canada Finland France Hungary Japan Korea Lithuania Slovakia Spain Sweden Switzerland UK, USA	407 391; 90% men	248 non-Hodgkin's lymphoma deaths	243 non-Hodgkin's lymphoma = < 100 mSv cumulative radiation dose	Negative association RR/100mSv = 1.04 Non Significant No dose response trend
Cardis et al. (1995)[41]	UK USA Canada	95 673; 85.4% men	135 non-Hodgkin's lymphoma deaths	126 non-Hodgkin's lymphoma = < 100 mSv cumulative radiation dose	Negative association Trend -0.25 (p =0.600) No dose response trend

70. Of the studies included in the 15-Country collaborative by **Cardis et al. (2007)**[42] **[RMA ID: 043945],** 14 studies were considered by the Council in this review. The studies included **Cardis et al. (1995)**[43] **[RMA ID: 005770], Gilbert et al. (1993)**[44] **[RMA ID: 016572], Polednak & Frome (1981)**[45]

38 Cardis et al. (2007). *ibid.*

39 Cardis et al. (1995). Effects of low doses and low dose rates of external ionising radiation: Cancer mortality among nuclear industry workers in three countries. Radiation Research, 142(2), 117-132. (RMA ID 005770)

40 Cardis et al. (2007). The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. Radiation Research, 167(4), 396-416. (RMA ID 043945)

41 Cardis et al. (1995). *ibid*

42 Cardis et al. (2007). *ibid*

43 Cardis et al. (1995). *ibid.*

44 Gilbert, E. S., Omohundro, E., Buchanan, J. A., & Holter, N. A. (1993). Mortality of workers at the Hanford Site: 1945-1986. Health Physics, 64(6), 577-590. (RMA ID 016572)

45 Polednak, A. P., & Frome, E. L. (1981). Mortality among men employed between 1943 and 1947 at a uranium-processing plant. Journal of Occupational Medicine, 23(3), 169-178. (RMA ID 020359)

[RMA ID: 020359], Checkoway et al. (1985)[46] [RMA ID: 020354], Ritz et al. (1999)[47] [RMA ID: 015538], Wiggs et al. (1991)[48] [RMA ID: 023575] , Cragle et al. (1988)[49] [RMA ID: 006813], Gribbin et al. (1993)[50] [RMA ID: 029478], Smith & Douglas (1986)[51] [RMA ID: 016952], Douglas et al. (1994)[52] [RMA ID: 015937], Beral et al. (1985)[53][RMA ID: 009570], Fraser et al. (1993)[54] [RMA ID: 005214], Muirhead et al. (1999)[55] [RMA ID: 017201] , and **Kendall et al. (1992)[56] [RMA ID: 014621]** and are shown in Table 3.

Table 3. All Studies Included in the 15 Country Collaborative Reviewed by the Council

Study	Site	Cohort	non-Hodgkin's lymphoma	Exposure	Outcome
USA					
Gilbert et al. (1993)[57]	Hanford	44 154; 71.3% men	59 non-Hodgkin's lymphoma deaths	54 non-Hodgkin's lymphoma = cumulative radiation dose < 10 mSv	Negative association trend test = -0.85 (10 year lag), -1.1 4(2 year lag)
Polednak & Frome (1981)[58]	Oak Ridge	18 869; 100% men	17 lymphosarcoma reticulosarcoma deaths	Exposed to high average air levels of uranium dust	Negative association SMR = 0.67

46 Checkoway, H., Mathew, R. M., Shy, C. M., Watson, J. E., Tankersley, W. G., Wolf, S. H., Smith, J. C., & Fry, S. A. (1985). Radiation, work experience, and cause specific mortality among workers at an energy research laboratory. British Journal of Industrial Medicine, 42(8), 525-533. (RMA ID 020354)

47 Ritz, B., Morgenstern, H., Froines, J., & Young, B. B. (1999). Effects of exposure to external ionising radiation of cancer mortality in nuclear workers monitored for radiation at Rocketdyne/Atomics International. American Journal of Industrial Medicine, 35(1), 21-31. (RMA ID 015538)

48 Wiggs, L. D., Cox-deVore, C. A., Wilkinson, G. S., & Reyes, M. (1991). Mortality among workers exposed to external ionising radiation at a nuclear facility in Ohio. Journal of Occupational Medicine, 33(5), 632-637. (RMA ID 023575)

49 Cragle, D. L., McLain, R. W., Qualters, J., Hickey, J. L. S., Wilkinson, G. S., Tankersley, W. G., & Lushbaugh, C. C. (1988). Mortality among workers at a nuclear fuels production facility. American Journal of Industrial Medicine, 14(4), 379-401. (RMA ID 006813)

50 Gribbin, M. A., Weeks, J. L., & Howe, G. R. (1993). Cancer mortality (1956-1985) among male employees of atomic energy of Canada limited with respect to occupational exposure to external low-linear-energy-transfer ionising radiation. Radiation Research, 133(3), 375-380. (RMA ID 029478)

51 Smith, P. P., & Douglas, A. J. (1986). Mortality of workers at the Sellafield plant of British nuclear fuels. British Medical Journal (Clinical Research Edition), 293(6551), 845-854. (RMA ID 016952)

52 Douglas, A. J., Omar, R. Z., & Smith, P. G. (1994). Cancer mortality and morbidity among workers at the Sellafield plant of British nuclear fuels. British Journal of Cancer, 70(6), 1232-1243. (RMA ID 015937)

53 Beral, V., Inskip, H., Fraser, P., Booth, M., Coleman, D., & Rose, G. (1985). Mortality of employees of the United Kingdom Atomic Energy Authority, 1946-1979. British Medical Journal, 291(6493), 440-447. (RMA ID 009570)

54 Fraser, P., Carpenter, L., Maconochie, N., Higgins, C., Booth, M., & Beral, V. (1993). Cancer mortality and morbidity in employees of the United Kingdom Atomic Energy Authority, 1946-86. British Journal of Cancer, 67(3), 615-624. (RMA ID 005214)

55 Muirhead, C. R., Goodill, A. A., Haylock, R. G. E., Vokes, J., Little, M. P., Jackson, D. A., … & Berridge, G. L. C. (1999). Occupational radiation exposure and mortality: second analysis of the National Registry for radiation workers. Journal of Radiological Protection, 19(1), 3-26. (RMA ID 017201)

56 Kendall, G., Muirhead, C. R., MacGibbon, B. H., O'Hagan, J. A., Conquest, A. J., Goodil, A. A., Butland, B. K., Fell, T. P., Jackson, D. A., Webb, M. A., Haylock, R. G. E., Thomas, J. M., & Silk, T. J. (1992). Mortality and occupational exposure to radiation: first analysis of the national registry for radiation workers. British Medical Journal, 304(6821), 220-225. (RMA ID 014621)

57 Gilbert, et al. (1993). Mortality of workers at the Hanford Site: 1945-1986. Health Physics, 64(6), 577-590. (RMA ID 016572)

Study	Site	Cohort	non-Hodgkin's lymphoma	Exposure	Outcome
Checkoway et al. (1985)[59]	Oak Ridge	8375; 100% men	5 lymphosarcoma reticulosarcoma deaths	Dose response rates were not done for non-Hodgkin's lymphoma	Negative association SMR = 0.80
Ritz et al. (1999)[60]	Rocketdyne Atomics International	4563; 94% men	2 lymphosarcoma reticulosarcoma deaths	Radiation exposure was not done for lymphosarcoma reticulosarcoma	Negative association SMR = 0.54
Wiggs et al. (1991)[61]	Mound Facility	4182; 100% men	2 lymphosarcoma deaths	Exposure 1 =≥10mSv compared to 1 => 10mSv RR = 2.22 95%CI 0.07-58.48	SMR = 1.06. Exposure 1 =10mSv compared to 1 => 10mSv RR = 2.22 95%CI 0.07-58.48
Cragle et al. (1988)[62]	Rocky Flats nuclear plant	9860; 100% men	2 lymphosarcoma reticulosarcoma deaths	Radiation exposure not done for lymphosarcoma reticulosarcoma deaths	Workers death = 1, SMR 0.21; salaried workers death = 1, SMR = 0.43
Canada					
Gribbin et al. (1993)[63]	Atomic Energy of Canada Limited	4260; 100% men	7 non-Hodgkin's lymphoma deaths	Mean cumulative equivalent dose = 52.1 mSv. No exposure = 4 non-Hodgkin's lymphoma deaths (SMR = 0.89); ≥50 mSv = 3 non-Hodgkin's lymphoma deaths (SMR = 2.51)	SMR = 0.84; 95% CI: 0.34, 1.73 no linear trend associated with non-Hodgkin's lymphoma p trend for positive association was non-significant (p = 0.38).
Sont et al (2001)[64]	Canadian National Dose Registry and the Canadian Cancer Database	3737; 56% men	133 non-Hodgkin's lymphoma cases	average radiation dose of the entire cohort was 6.64 mSv, males = 11.50 mSv females = 1.75 mSv	SIR = 0.71; 90% CI: 0.61, 0.82. Non-significant excess relative risks of non-Hodgkin's lymphoma for males (n = 92, ERR = 7.3; 90%CI: <0, 31.8) For males and females combined (n = 133, ERR = 6.6; 90%CI: <0, 28.3)
UK					
Muirhead et al. (1999)[65]	UK National Registry for Radiation Workers	124 743; 91% men	103 non-Hodgkin's lymphoma deaths (unlagged analysis) 84 non-Hodgkin's lymphoma deaths	Average lifetime radiation dose higher for males than females (males mSv=33.0, n=113 112; females mSv = 6.4, n = 11 631). For the 90 =non-Hodgkin's	Unlagged SMR = 100; 95% CI: 81,121; lagged: SMR = 105; 95% CI: 83, 130 no dose-response trend was seen, with a non-

58 Polednak, A. P., & Frome, E. L. (1981). Mortality among men employed between 1943 and 1947 at a uranium-processing plant. Journal of Occupational Medicine, 23(3), 169-178. (RMA ID 020359)

59 Checkoway et al. (1985). Radiation, work experience, and cause specific mortality among workers at an energy research laboratory. British Journal of Industrial Medicine, 42(8), 525-533. (RMA ID 020354)

60 Ritz et al. (1999). Effects of exposure to external ionising radiation of cancer mortality in nuclear workers monitored for radiation at Rocketdyne/Atomics International. American Journal of Industrial Medicine, 35(1), 21-31. (RMA ID 015538)

61 Wiggs et al. (1991). Mortality among workers exposed to external ionising radiation at a nuclear facility in Ohio. Journal of Occupational Medicine, 33(5), 632-637. (RMA ID 023575)

62 Cragle et al. (1988). Mortality among workers at a nuclear fuels production facility. American Journal of Industrial Medicine, 14(4), 379-401. (RMA ID 006813)

63 Gribbin et al. (1993). Cancer mortality (1956-1985) among male employees of atomic energy of Canada limited with respect to occupational exposure to external low-linear-energy-transfer ionising radiation. Radiation Research, 133(3), 375-380. (RMA ID 029478)

64 Sont, et al. (2001). First analysis of cancer incidence and occupational radiation exposure based on the national dose registry of Canada. American Journal of Epidemiology, 153(4), 309-318. (RMA ID 026169)

65 Muirhead et al. (1999). Occupational radiation exposure and mortality: second analysis of the National Registry for radiation workers. *Journal of Radiological Protection*, 19(1), 3-26. (RMA ID 017201)

Study	Site	Cohort	non-Hodgkin's lymphoma	Exposure	Outcome
			(10 year lag)	lymphoma deaths radiation doses, 70 non-Hodgkin's lymphoma had ≤20mSV lower than expected	significant excess risk (ERR/Sv = 0.03)
Kendall et al. (1992)[66]	UK National Registry for Radiation Workers	95 217; 92% men	47 non-Hodgkin's lymphoma deaths (unlagged analysis) 37 non-Hodgkin's lymphoma deaths (10 year lag)	For the 38=non-Hodgkin's lymphoma deaths radiation doses, 29 non-Hodgkin's lymphoma had ≤20mSV and all were lower than expected	unlagged SMR = 100) 10 year lag a non-significant slight excess SMR = 117 Radiation exposure dose negative (-0.57, p = 0.61) and the ERR/Sv = -1.21(90% CI: -1.95, 3.00).
Smith & Douglas (1986)[67]	Sellafield plant of British Nuclear Fuels	14 327; 81% men	9 non-Hodgkin's lymphoma deaths (radiation worker) 1 non-Hodgkin's lymphoma death (other workers)	For 9 =non-Hodgkin's lymphoma deaths (radiation) 6 non-Hodgkin's lymphoma had ≤20mSV and all were lower than expected	For radiation workers SMR = 114. z test for trend = -0.64(no lag) -0.54 (2 year lag) , -0.22 (15 year lag non-significant
Douglas et al. (1994)[68]	Sellafield plant of British Nuclear Fuels	14 282; 81% men	13 non-Hodgkin's lymphoma deaths (radiation worker) 2 non-Hodgkin's lymphoma death (other workers)	For 13 =non-Hodgkin's lymphoma deaths (radiation) 8 non-Hodgkin's lymphoma had <20mSV	For radiation workers SMR = 107 non-Hodgkin's lymphoma Deaths lower than expected overall SMR = 101 z test for trend = -0.90(no lag) -0.80 (2 year lag) , -0.75 (10 year lag non-significant
Beral et al. (1985)[69]	Atomic Energy Authority	39 546; 20 383 (radiation record);	20 non-Hodgkin's lymphoma deaths	13=non-Hodgkin's lymphoma deaths radiation doses 6 non-Hodgkin's lymphoma had <10mSV	SMR = 1.07 non-significant Test linear trend *p* =0.2 (+)
Fraser et al. (1993)[70]	Atomic Energy Authority	39 718; 73% men 19 760 (radiation record); 92% men	38 non-Hodgkin's lymphoma deaths	non-significant excess 27 non-Hodgkin's lymphoma deaths (SMR = 1.35) 11 non-Hodgkin's lymphoma deaths (SMR = 0.75)	SMR = 1.09 The rate ratio for workers with a radiation record compared with other workers for no lag (RR = 1.57; 95% CI: 0.7, 3.50) and for a 10-year lag (RR = 1.74; 95%CI: 0.80, 3.79) were both elevated but non-significant

71. All studies showed no association and no dose trend between exposure to ionising radiation (below 0.1Sv) and non-Hodgkin's lymphoma. Despite the

66 Kendall, et al. (1992). Mortality and occupational exposure to radiation: first analysis of the national registry for radiation workers. British Medical Journal, 304(6821), 220-225. (RMA ID 014621)

67 Smith, P. P., & Douglas, A. J. (1986). Mortality of workers at the Sellafield plant of British nuclear fuels. British Medical Journal (Clinical Research Edition), 293(6551), 845-854. (RMA ID 016952)

68 Douglas et al. (1994). Cancer mortality and morbidity among workers at the Sellafield plant of British nuclear fuels. British Journal of Cancer, 70(6), 1232-1243. (RMA ID 015937)

69 Beral et al. (1985). Mortality of employees of the United Kingdom Atomic Energy Authority, 1946-1979. British Medical Journal, 291(6493), 440-447. (RMA ID 009570)

70 Fraser et al. (1993). Cancer mortality and morbidity in employees of the United Kingdom Atomic Energy Authority, 1946-86. British Journal of Cancer, 67(3), 615-624. [RMA ID: 005214]

large number of exposed nuclear industry workers there were small numbers of non-Hodgkin's lymphoma in each individual study.

72. Similar results were seen in all occupational exposure studies reviewed by the Council (shown in TABLE 4), except for one study by McGeoghegan & Binks (2000) (RMA ID 021774), which showed an association for cancer registrations (but not mortality) due to non-Hodgkin's lymphoma, based on very small numbers for the highest radiation dose groups.

Table 4. Occupational Studies of Radiation Exposure and Nuclear Industry Workers

Study	Site	Cohort	Non-Hodgkin's Lymphoma	Exposure	Outcome
Gilbert et al. (1993)[71]	Hanford Site Oak Ridge National Laboratory and Rocky Flats Weapons Plant	Hanford Site = 32432 (76% men) Oak Ridge National Laboratory = 6348 men Rocky Flats Weapons Plant = 5952 men	72 non-Hodgkin's lymphoma deaths	Average cumulative doses for all three populations < 50 mSv, and there were no workers with doses exceeding I Sv.	No dose trend for non-Hodgkin's lymphoma was shown (Trend test statistic 10 year lag = -0.90)
Gilbert et al. (1989)[72]	Hanford Site Oak Ridge National Laboratory and Rocky Flats Weapons Plant	Hanford Site = 23704 (men Oak Ridge National Laboratory = 6332 men Rocky Flats Weapons Plant = 5897 men	49 lymphoma deaths	Average cumulative doses for Hanford Site =32.3 mSv Oak Ridge National Laboratory = 20.9 mSv Rocky Flats Weapons Plant =40.8 mSv	No dose trend for lymphoma was shown. Hanford Site Trend test statistic =0.03 (41 lymphoma deaths) Oak Ridge National Laboratory Trend test statistic =0.36 (6 lymphoma deaths) Rocky Flats Weapons Plant Trend test statistic = -0.17 (2 lymphoma deaths) Combined Trend test static = -0.17(49 lymphoma deaths)
Gilbert & Marks (1979)[73]	Hanford Site	20 842 men Exposure analysis subset of 12 522 men	19 Lymphosarcoma and reticulosarcoma deaths	For 12 522 men mean exposure = 4.75 rem (median 1.47 rem) Duration of exposure ≥2 years	No association between radiation exposure and lymphosarcoma and reticulosarcoma Length of employment <2 years SMR = 0.71 and ≥ 2years SMR = 1.05
Frome et al. (1997)[74]	Oak Ridge	106 020 workers Subset	109 lymphosarcoma	For 28 347 men	Death rates lower than expected for men (SMR = 0.92) and

71 Gilbert, E. S., Cragle, D. L., & Wiggs, L. D. (1993). Updated analyses of combined mortality data for workers at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats Weapons Plant. Radiation Research, 136(2), 408-421. (RMA ID 007183)

72 Gilbert, E. S., Fry, S. A., Wiggs, L. D., Voelz, G. L., Cragle, D. L., & Petersen, G. R. (1989). Analyses of combined mortality data on workers at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats Nuclear Weapons Plant. Radiation Research, 120, 19-35. (RMA ID 007188)

73 Gilbert, E. S., & Marks, S. (1979). An analysis of the mortality of workers in a nuclear facility. Radiation Research, 79(1), 122-148. (RMA ID 014543)

Study	Site	Cohort	Non-Hodgkin's Lymphoma	Exposure	Outcome
		of 27 982 deaths Exposure analysis subset 28 347 men	and reticulosarcoma deaths (84 = men, women = 25)	collective recorded dose equivalent was 376 Sv	slightly higher for women (SMR = 1.15) No association between radiation exposure and lymphosarcoma and reticulosarcoma
Loomis & Wolf (1996)[75]	Oak Ridge	6591 men	4 Lymphosarcoma and reticulosarcoma deaths	Not reported	No association between radiation exposure and lymphosarcoma and reticulosarcoma Death rates lower than expected for men SMR = 0.55
Ritz (1999)[76]	Uranium-processing workers at Fernald Feed Materials Production Centre Ohio	4014 men	8 Lymphosarcoma and reticulosarcoma deaths	Most monitored workers (68.9%) received cumulative external radiation doses of less than 10 mSv, only 2.6% had doses > 100 mSv, and none >300 mSv	A non-significant excess mortality rate compared to the expected death rate of 4.79 (SMR = 1.67, 95% CI: 0.72, 3.29)
Carpenter et al. (1998)[77]	United Kingdom Atomic Energy Authority, the Atomic Weapons Establishment, and the Sellafield plant of British Nuclear Fuels	75 006 Exposure analysis subset of 40 761 monitored workers with dose records (92% men)	65 non-Hodgkin's lymphoma deaths	Not reported	Workers not monitored for any radionuclide: 29 non-Hodgkin's lymphoma deaths (SMR = 1.09). Workers monitored for tritium: 7 non-Hodgkin's lymphoma deaths (SMR = 1.67, RR = 1.90; 95% CI: 0.74, 4.30). Workers monitored for plutonium: 17 non-Hodgkin's lymphoma deaths (SMR = 1.29, RR = 1.48; 95% CI: 0.76, 2.83) Workers monitored for other radionuclides:12 non-Hodgkin's lymphoma deaths (SMR = 1.20, RR = 1.48; 95% CI: 0.76, 2.83) A non-significant association of non-Hodgkin's lymphoma deaths

74 Frome, E. L., Cragle, D. L., Watkins, J. P., Wing, S., Shy, C. M., Tankersley, W. G., & West, C. M. (1997). A mortality study of employees of the nuclear industry in Oak Ridge, Tennessee. Radiation Research, 148, 64-80. (RMA ID 016856)

75 Loomis, D. P., & Wolf, S. H. (1996). Mortality of workers at a nuclear materials production plant at Oak Ridge, Tennessee, 1947-1990. American Journal of Industrial Medicine, 29(2), 131-141. (RMA ID 011771)

76 Ritz, B. (1999). Radiation exposure and cancer mortality in uranium processing workers. Epidemiology, 10(5), 531-538. (RMA ID 017998)

77 Carpenter, L. M., Higgins, C. D., Douglas, A. J., Maconochie, N. E. S., Omar, R. Z., Fraser, P., Beral, V., & Smith, P. G. (1998). Cancer mortality in relation to monitoring for radionuclide exposure in three UK nuclear industry workforces. British Journal of Cancer, 78(9), 1224-1232. (RMA ID 016797)

Study	Site	Cohort	Non-Hodgkin's Lymphoma	Exposure	Outcome
					in radiation workers in three United Kingdom nuclear facilities according to their radionuclide monitoring status.
Carpenter et al. (1994)[78]	United Kingdom Atomic Energy Authority, the Atomic Weapons Establishment and the Sellafield plant of British Nuclear Fuels	75 006 (75% men) Exposure analysis subset of 40 761 monitored workers with dose records	79 non-Hodgkin's lymphoma deaths	collective external radiation dose was 2303 Sv Average final cumulative dose of 56.5 mSv per monitored worker	79 non-Hodgkin's lymphoma deaths were lower than the expected (expected = 83.4; SMR = 0.95. Monitored workers: 50 non-Hodgkin's lymphoma deaths (expected = 45.5; SMR = 1.10) Non-monitored workers : 29 non-Hodgkin's lymphoma deaths (expected = 38.0; SMR = 0.95), A non-significant relative risk of non-Hodgkin's lymphoma mortality in monitored workers compared to other workers of 1.37 (95% CI: 0.81, 2.31). No association was found with accumulated radiation dose and non-Hodgkin's lymphoma mortality.
McGeoghegan & Binks (2000)[79]	Springfields, a uranium production facility of British Nuclear Fuels	19 454 workers Subset of 13 960 radiation workers	21 non-Hodgkin's lymphoma deaths for all workers combined 20 non-Hodgkin's lymphoma registrations	Average individual cumulative external whole body dose was 22.8 mSv The maximum cumulative dose was 769.3 mSv, the median 9.3 rnSv and 95% of all individual cumulative doses were < 89.4 mSv	Non-radiation workers: 6 non-Hodgkin's lymphoma deaths (expected = 7.62, SMR = 0.79), Radiation workers: 15 non-Hodgkin's lymphoma deaths (expected = 23.78, SMR = 0.63) All workers: 21 non-Hodgkin's lymphoma deaths (expected = 31.40, SMR = 0.67) Comparing mortality rates of radiation workers with the non-radiation workers there was a non-significant risk of 1.36. Non-Hodgkin's lymphoma registrations shows significant trend statistics, p < 0.0002 for radiation dose, when the dose was lagged by 0 years (trend statistic = 4.486; p <0001), 2 years (trend statistic = 4.513; p = <0001), 10 years (trend statistics = 3.667; p <0001), 15 years (trend statistic = 3.508; p = <0001) and 20 years (trend statistic = 3.630; p <0001). An excess was seen at 20-50mSv (6/3.87), 100-200mSv (2/0.53) and 400+ mSv (1/0.01)

73. **Richardson et al. (2009)**[80] **[RMA ID: 068828]** examined the association between ionising radiation and lymphoma mortality among men in two

[78] Carpenter, L., Higgins, C., Douglas, A., Fraser, P., Beral, V., & Smith, P. (1994). Combined analysis of mortality in three United Kingdom nuclear industry workforces, 1946-1988. Radiation Research, 138(2), 224-238. (RMA ID 016570)

[79] McGeoghegan, D., & Binks, K. (2000). The mortality and cancer morbidity experience of workers at the Springfields uranium production facility, 1946-95. Journal of Radiological Protection, 20(2), 111-137. (RMA ID 021774)

cohorts; Life Span Study and Savannah River Site. Cohort two included 15, 264 men employed at Savannah River Site in South Carolina, United States as nuclear weapons workers between 1950 and 1986 prospectively followed from 1950 to 2002. In the Savannah River Site workers cohort there were 51 non-Hodgkin's lymphoma deaths.

74. Estimates of mortality and ionising radiation dose for under 5 year and 10 years exposure lags showed an increased association for 5 year lag (ERR/Sv = 6.45; 90% CI: 0.48,17.95; p = 0.07) and 10 year lag (ERR/Sv = 7.62; 90% CI: 0.93, 20.77; p = 0.05). There was a strong association between radiation dose and non-Hodgkin's lymphoma mortality during the period of 36–52 years after irradiation (ERR/Sv = 38.35; 90% CI: 7.02, 121.57; p = 0.02).

75. Table 5 shows the observed and expected numbers of malignant lymphoma deaths by dose category under 5 year and 10 year lag for the Savannah River Site workers cohort.

Table 5. Observed Numbers of Deaths Due To Malignant Lymphoma Among Male Workers at the Savannah River Site (1950-2002), by Radiation Dose Category Under 5 Year and 10 Year Lag

Assumed Lag and Cohort	Radiation Dose, Sv						
	<0.005	0.005–<0.10	0.10–<0.20	0.20–<0.50	0.50–<1	1–<2	≥2
5-year lag							
Savannah River Site workers							
No. of deaths observed	20	24	7	5	0	0	0
Obs/Exp ratio	0.77	1.01	1.78	2.14			
Mean dose, Sv	0.001	0.028	0.142	0.266			
Person-years of follow-up	305,131	181,767	25,961	12,830	0	0	0
10-year lag							
Savannah River Site workers							
No. of deaths observed	21	24	6	5	0	0	0
Obs/Exp ratio	0.77	1.05	1.60	2.35			
Mean dose, Sv	0.001	0.028	0.141	0.264			
Person-years of follow-up	344,948	149,706	21,197	9,840	0	0	0

Abbreviations: Exp, expected; Obs, observed.

[a] Because of rounding, some column totals for person-time differ slightly from the sums of rows.

[b] Japanese males who were aged 15–64 years and present in Hiroshima or Nagasaki at the time of the bombings.

[c] Ratio of the number of deaths observed to the number of deaths expected.

(Source: Richardson et al. (2009). Positive association between ionising radiation and lymphoma mortality among men. *American Journal of Epidemiology*, 169(8), p. 974).

[80] Richardson et al. (2009). Positive association between ionising radiation and lymphoma mortality among men. American Journal of Epidemiology, 169(8), 969-976. (RMA ID 068828)

76. The risk estimate associated with radiation dose for Savannah River Site workers exposed to 0.20 Sv to <0.50 Sv at a 5 year lag was SMR = 2.14 and at a 10 year lag the SMR = 2.35. There was no increased risk shown for workers exposed to <0.10 Sv, however there was an increased risk at both a 5 year lag and a 10 year lag for those exposed to ≥0.10 Sv although there were only a small number of workers exposed to radiation doses of 0.10 Sv or more. The study showed a significant association between ionising radiation dose and lymphoma mortality among male Savannah River Site workers exposed to ≥1.0 Sv.

Council's Conclusions on Occupational Exposure

77. The majority of the studies reviewed showed no association between non-Hodgkin's lymphoma and ionising radiation exposure, nor was there any dose response trend, providing little evidence of a relationship. For most studies, the small number of deaths from non-Hodgkin's lymphoma among those exposed to occupational radiation was a major limitation. The pooled analyses by **Cardis et al. (2007)[81] [RMA ID 043945]** study, with 248 deaths, showed no association. Doses for nuclear industry workers in most of the studies were below 0.1 Sv. Additionally, errors in measuring radiation exposures or outcomes, healthy worker selection biases, residual confounding due to unmeasured factors such as smoking and chemical exposures, and different distributions of effect were also potential limitations.

78. The findings of **Richardson et al. (2009)[82] [RMA ID: 068828]** were inconsistent with the rest of the literature on occupational exposure showing an association between radiation dose and non-Hodgkin's lymphoma mortality during the period of 36–52 years after irradiation for male nuclear weapons workers at Savannah River Site in South Carolina. There was no increased risk shown for workers exposed to <0.10 Sv, but there was an increased risk at both a 5 year lag and a 10 year lag for those exposed to 0.10 Sv or more although there were only a small number of workers exposed to radiation doses of 0.10 Sv or more.

Studies of Communities Residing Near Sources of Ionising Radiation

79. Two studies examining the association between cancer and environmental exposure to ionising radiation from living in communities close to sources of radiation exposure were considered**.** In particular, concerns regarding the possible contamination of groundwater and vegetation, and increased levels of indoor radon on the health effects of people who reside near

81 Cardis et al. (2007). The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. Radiation Research, 167(4), 396-416. (RMA ID 043945)

82 Richardson et al. (2009). Positive association between ionising radiation and lymphoma mortality among men. American Journal of Epidemiology, 169(8), 969-976. (RMA ID 068828)

uranium mines. However, both studies found no increased cancer risk could be attributed to living near sources of radiation exposure.

80. **Boice et al. (2007)[83] [RMA ID: 050299]** investigated the impact mining and milling of uranium in Montrose County, Colorado had on the health of communities living on the Colorado Plateau. During 1950 to 2000 there were 75 non-Hodgkin's lymphoma deaths (United States expected deaths = 76.4; SMR = 0.98; Colorado expected deaths = 72.6; SMR = 1.03). There were no significant differences seen between Montrose County and the comparison counties (relative risk (RR) = 1.05; 95% CI: 0.82, 1.34). Similar findings were reported in a study by **Boice et al. (2003)[84] [RMA ID: 050298]** of cancer incidence of living near the Apollo-Parks nuclear processing materials plants in Pennsylvania for the years 1993 to 1997, or nearly 40 years after the plants had begun operation in 1957 and 1960, respectively. There were 23 non-Hodgkin's lymphoma cases (expected = 20.9; Standardised Incidence Ratio (SIR) = 1.10; 95% CI: 0.70, 1.65).

Council's Conclusions on Studies of Communities Residing Near Sources of Ionising Radiation

81. The Council concluded that no increased cancer risk could be attributed to living near the two former nuclear materials processing facilities.

Studies of Accident Recovery Workers at Chernobyl Nuclear Power Station

82. The Council examined two studies of people exposed to radiation as a result of an accident at Chernobyl Nuclear Power Plant in Ukraine in April, 1986. As a result of the nuclear accident, the explosion and fire released large quantities of radioactive particles into the atmosphere, which largely spread over Belarus, Russia, and Ukraine, exposing millions of people to varying degrees of radiation. The majority of people were exposed to relative low doses of radiation. In response to the accident approximately 600,000 recovery workers were involved in the cleanup of the Chernobyl site.

83. **Kesminiene et al. (2008)**[85] **[RMA ID: 052044]** assessed the effects of protracted radiation exposure and incidence of malignancies of Chernobyl accident site workers from Belarus, Russia and Baltic countries. The study was a nested case control study within cohorts of cleaners who had worked around the Chernobyl plant during 1986-1987. Most subjects received

---

83 Boice, J. D., Mumma, M. T., & Blot, W. J. (2007). Cancer and noncancer mortality in populations living near uranium and vanadium mining and milling operations in Montrose County, Colorado, 1950-2000. Radiation Research, 167(6), 711-726. (RMA ID 050299)

84 Boice, J. D., Bigbee, W. L., Mumma, M. T., & Blot, W. J. (2003). Cancer incidence in municipalities near two former nuclear materials processing facilities in Pennsylvania. Health Physics, 85(6), 678-690. (RMA ID 050298)

85 Kesminiene, A., Evrard, A.-S., Ivanov, V. K., & Malakhova, I. V. (2008). Risk of hematological malignancies among Chernobyl liquidators. Radiation Research, 170(6), 721-735. (RMA ID 052044)

median ionising radiation dose of 13 mGy (0.013 Gy). There were 20 non-Hodgkin's lymphoma cases.

84. The linear ERR model for non-Hodgkin's lymphoma (cases = 20, controls = 80) was statistically significant with the ERR/100 mGy of 2.81 (90% CI: 0.09, 24.3) corresponding to a RR at 100 mGy (0.1 Gy) of 3.81. A significant increased risk was seen overall at doses of 200 mGy (0.2 Gy) or above, however, non-Hodgkin's lymphoma was not analysed separately. The study was limited by too few non-Hodgkin's lymphoma cases and a number of inconsistencies of the estimated risk.

85. **Rahu et al. (1997)[86] [RMA ID: 011024]** conducted a cohort study of the incidence of cancer and mortality of 4,742 males from Estonia who worked as cleaners at Chernobyl accident site between 1986 and 1991, and followed through to 1993. The workers were exposed to low doses of ionising radiation and were officially allowed to accumulate up to 0.25 Gy before being sent home. Although the authors suggested that the accumulated ionising radiation dose workers absorbed may have well exceeded 0.25 Gy.

86. For the three non-Hodgkin's lymphoma cases (expected = 0.66), a non-significant excess of non-Hodgkin's lymphoma SIR = 4.52; 95% CI: 0.93, 13.20) was shown. The study was limited by the small number of cases of non-Hodgkin's lymphoma and the fact that the authors did not quantify radiation exposure of the recovery workers or their length of exposure.

Council's Conclusions on Studies of Accident Recovery Workers at Chernobyl Nuclear Power Station

87. The Council concluded that there was no evidence of an increased risk of non-Hodgkin's lymphoma for accident recovery workers at Chernobyl nuclear power station.

Studies of Patients Administered Radiation

Patients Administered Thorotrast

88. The Council reviewed studies of individual's exposure to Thorotrast, a contrast containing particles of the radioactive compound thorium dioxide (ThO2), used for radiography during 1930 to 1950. Thorotrast is radioactive and is retained in the body, resulting in lifelong storage of thorium dioxide with consequent chronic alpha-particle irradiation. Thorotrast was mostly stored in the organs of the reticuloendothelial system, *i.e*. spleen, lymph nodes, and bone marrow.

---

86 Rahu, M., Tekkel, M., T., V., Pukkala, E., Hakulinen, T., Auvinen, A., Rytomaa, T., Inskip, P. D., & Boice, J. D. J. (1997). The Estonian study of Chernobyl cleanup workers: II. Incidence of cancer and mortality. Radiation Research, 147(5), 653-657. (RMA ID 011024)

89. **van Kaick et al. (1999)[87] [RMA ID: 024771]** conducted the German Thorotrast study, a case-control study of 2,326 patients who received Thorotrast for cerebral angiography or arteriography of the upper and lower limbs and 1890 controls. There were 20 non-Hodgkin's lymphoma deaths (Thorotrast patients = 15; controls = 5) and a non-significant relative risk (RR = 2.5; $p > 0.05$) was shown.

90. The Danish Thorotrast Study began in 1949 to follow neurosurgical patients who had received Thorotrast for cerebral arteriography during 1930 to 1940, the study ceased in 1982. The Danish Thorotrast Study was re-analysed by **Visfeldt & Andersson (1995)[88] [RMA ID: 001258]** and included 1,003 Thorotrast patients. There were four non-Hodgkin's lymphoma cases (expected = 1.5), although higher than expected, no further information regarding non-Hodgkin's lymphoma was provided, other than stating the findings were similar to those published by **van Kaick et al. (1999)[89] [RMA ID: 024771].**

Patients Administered Radiotherapy

91. A number of studies have reported the adverse health effects associated with treatment using radiotherapy and cancer. Radiotherapy is used to destroy or damage cancer cells using ionising radiation such as x-rays, gamma rays, and charged particles. As radiotherapy damages cancer cells in the region being treated, damage can sometimes occur to normal healthy cells. While these healthy damaged cells can often repair themselves, sometimes they cannot, and radiotherapy has been associated with secondary malignancies in people treated with radiotherapy for malignant cancers. Additionally, radiotherapy has also been used for treatment of benign conditions such as pain management for degenerative and inflammatory conditions.

92. **Weiss et al. (1994)**[90] **[RMA ID: 025044]** analysed the mortality of ankylosing spondylitis patients diagnosed during 1935 to 1957 in the United Kingdom who received x-ray treatment. The study included 14,109 irradiated patients and 885 unirradiated patients. Of the irradiated patients, 11,776 (83.5%) were male and 13,135 (93.1%) were aged between 20 and 60 at first treatment. There were 37 non-Hodgkin's lymphoma deaths.

---

87 van Kaick, G., Dalheimer, A., Hornik, S., Kaul, A., Liebermann, D., Luhrs, H., Spiethoff, A., Wegener, K., & Wesch, H. (1999). The German Thorotrast study: recent results and assessment of risks. Radiation Research, 152(Suppl 6), S64-S71. (RMA ID 024771)

88 Visfeldt, J., & Andersson, M. (1995). Pathoanatomical aspects of malignant haematological disorders among Danish patients exposed to thorium dioxide. APMIS (Acta Pathologica, Microbiologica et Immunologica Scandinavica), 103(1-6), 29-36. (RMA ID 001258)

89 van Kaick et al. (1999). *ibid.*

90 Weiss, H. A., Darby, S. C., & Doll, R. (1994). Cancer mortality following x-ray treatment for ankylosing spondylitis. International Journal of Cancer, 59(3), 327-338. (RMA ID 025044)

93. Most irradiated patients received several courses of treatment within a five-year period, based on a one in 15 random sample; the mean total body dose received in this period was 2.64 Gy (equivalent to 2.96 Sv), with the heaviest dose to the vertebrae. Men and women received similar treatment doses, however, those who were older at first treatment tended to receive lower doses than younger patients (aged under 25 at first treatment = 2.96 Gy; aged over 55 = 2.25 Gy).

94. The study demonstrated a significant excess of non-Hodgkin's lymphoma mortality 5 years or more since first treatment (RR = 1.74; 95% CI: 1.23, 2.36; $p < 0.01$) and the period 5 - 24.9 years after first treatment (RR = 2.83; $p < 0.001$) and the risk decreased significantly with time and was no longer present by 25 or more years.

95. **Kim et al. (2013)[91] [RMA ID: 069996]** compared second primary non-Hodgkin's lymphoma incidence among patients aged 20 to 84 years who receive initial therapeutic radiation treatment for a first primary solid malignancy between 1981 to 2007 to those that did not receive radiotherapy. No dose effect analysis was conducted but therapeutic radiotherapy typically involves doses of exposure greater than 1 Gy (1.0 Sv). Data was derived from nine Surveillance, Epidemiology, and End Results population-based cancer registries in the United States. The study identified 5,590 second non-Hodgkin's lymphoma cases among a total of 8,833,038 person-years at risk.

96. The risk of non-Hodgkin's lymphoma increased significantly after initial radiotherapy for all solid cancers combined after adjusting by sex, age, stage and chemotherapy (RR = 1.13; 95% CI: 1.06, 1.20) when compared with those not treated with radiotherapy. For second primary non-Hodgkin's lymphoma, the highest significant risks were observed more than five years after prostate cancer (RR = 1.30, 95% CI: 1.13, 1.50) and decreased to below one among 10 or more year survivors ($p_{\text{trend}} = 0.017$). Although non-Hodgkin's lymphoma risks were not elevated in any individual latency period, there were significant trends with latency after both female breast cancer ($p_{\text{trend}} = 0.002$) and non-small cell lung cancer ($p_{\text{trend}} = 0.003$). There was no clear non-Hodgkin's lymphoma risk pattern by non-Hodgkin's lymphoma subtype, gender or age.

97. **Damber et al. (1995)[92] [RMA ID: 007436]** analysed a cohort of 20,024 patients treated with x-ray therapy during 1950 to1964 at two hospitals in northern Sweden. X-ray treatment was used for treating painful benign degenerative and inflammatory changes in joints and adjacent structures

91 Kim et al. (2013). Risk of non-Hodgkin lymphoma after radiotherapy for solid cancers. Leukemia Lymphoma Journal, 54(8), 1691-1697. (RMA ID 069996)

92 Damber, L., Larsson, L.-G., Johansson, L., & Norin, T. (1995). A cohort study with regard to the risk of haematological malignancies in patients treated with x-rays for benign lesions in the locomotor system. Acta Oncologica, 34(6), 714-720. (RMA ID 007436)

and also for pain management for patients with rheumatoid arthritis and ankylosing spondylitis. Gender and age were reasonably distributed and most patients were 40 to 69 years of age when first treated. A total of 81 non-Hodgkin's lymphoma cases and 50 non-Hodgkin's lymphoma deaths were identified.

98. The incidence analysis identified 81 non-Hodgkin's lymphoma cases (expected = 80.28; SIR = 1.01; 95% CI: 0.80, 1.25), with a non-significant excess of non-Hodgkin's lymphoma observed at dose levels 0.20-0.50 Gy (observed = 25, expected = 21.74) and > 0.50 Gy (observed = 31, expected = 22.21).

99. In the mortality analysis, the number of non-Hodgkin's lymphoma deaths was lower than expected (non-Hodgkin's lymphoma = 50, expected = 56.87; SMR = 0.88; 95% CI: 0.65, 1.16). The observed number of deaths for the three levels of radiation exposure was below the number of expected death in the general population. It was concluded that there was no association between x-ray therapy for management of degenerative and inflammatory conditions and non-Hodgkin's lymphoma. Latency times were not conducted as many patients received two or more courses of radiotherapy often separated by several years, making it difficult to assess.

100. **Inskip et al. (1993)**[93] **[RMA ID: 003087]** conducted a prospective cohort study of 12,955 women treated for benign gynaecological conditions at 17 hospitals in United States and followed for an average of 25 years. A total of 9,770 women (irradiated patients) were treated by radiation (intracavitary radium-226, external-beam x- rays), while 3,185 were treated by other methods such as medication and surgery (unirradiated patients). The average age at treatment was 46.5 years, and the mean dose to active bone marrow among irradiated women was 1.19 Gy. There were 53 non-Hodgkin's lymphoma deaths (irradiated = 40, unirradiated = 13). There was little evidence of effects attributable to radiotherapy for non-Hodgkin's lymphoma (RR = 0.9; 90% CI: 0.6, 1.6). There were no differences in risk of non-Hodgkin's lymphoma mortality between irradiated and unirradiated women.

Council's Conclusions on Studies of Patients Administered Radiation

101. Doses of ionising radiation in these studies were much higher than in other studied groups. There were small numbers of non-Hodgkin's lymphoma although there was reasonable consistency of the finding of increased risks of non-Hodgkin's lymphoma after exposure to ionising radiation for medical purposes.

---

93 Inskip, P. D., Kleinerman, R. A., Stovall, M., Cookfair, D. L., Hadjimichael, O., Moloney, W. C., Monson, R. R., Thompson, W. D., Wactawski-Wende, J., Wagoner, J. K., & & Boice, J. D. J. (1993). Leukemia, lymphoma and multpiple myeloma after pelvic radiotherapy for benign disease. Radiation Research, 135(1), 108-124. (RMA ID 003087)

Other Relevant Studies

102. **Alexander et al. (2007)[94] [RMA ID: 050309]** conducted a narrative epidemiologic review of the literature on non-Hodgkin's lymphoma, and specifically reviewed the relationship between non-Hodgkin's lymphoma and radiation exposure. The authors concluded that wartime and occupational exposure to ionising radiation does not have a causal association with non-Hodgkin's lymphoma. A number of studies have found no associations with therapeutic or diagnostic radiation exposure, but results are inconsistent and dose-response associations have not been observed. Furthermore, there were no trends in non-Hodgkin's lymphoma risk based on cumulative radiation dose.

103. The review concluded that other studies have reported no significant associations among United States military workers who participated in atmospheric nuclear weapons tests, participants in the United Kingdom atmospheric nuclear weapons tests, communities living near sources of ionising radiation, uranium miners, and radiology workers. A lack of a consistent association between ionising radiation and non-Hodgkin's lymphoma could indicate that there is no actual association between the two, and any associations that are seen may be due to bias or deficiencies in measurement of exposure, classification of cases, duration of follow-up, or a combination of these factors.

104. **International Agency for Research on Cancer (IARC) Working Group on the Evaluation of Carcinogenic Risks to Humans. (2000)** [95] **[RMA ID: 021776]** 2000 monograph on cancer risk and ionising radiation. There was evidence for the increased risk of several different cancers. However, for non-Hodgkin's lymphoma, the IARC noted that "some positive associations had been observed, but assessed the evidence as being limited as the results are either of borderline statistical significance or those for incidence and mortality conflict".

105. The **United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (2006)[96] [RMA ID: 055814]** reported on epidemiological studies of radiation and cancer, and stated findings from recent studies do not alter the assessment made by the Committee in previous reports. Overall the results from studies evaluating risk of non-Hodgkin's lymphoma among groups exposed to external low- linear energy

---

94 Alexander, D. D., Mink, P. J., Adami, H.-O., Chang, E. T., Cole, P., Mandel, J. S., & Trichupoulos, D. (2007). The non-Hodgkin lymphomas: a review of the epidemiologic literature. International Journal of Cancer, 120(S12), 1-39. (RMA ID 050309)

95 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. (2000). IARC Monographs on the evaluation of carcinogenic risks to humans: Ionising Radiation, Part 1: X- and Gamma (γ)-Radiation, and Neutrons. IARC Monographs, Vol 75, World Health Organisation. (RMA ID 021776)

96 UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). (2006). Non-Hodgkin's lymphoma. UNSCEAR. (RMA ID 055814)

transfer radiation are mixed, with little evidence of an association overall. There is limited information on risk of non-Hodgkin's lymphoma to either high- linear energy transfer radiation (external or internal) exposure or internal low- linear energy transfer radiation exposure and interpretation of the data is difficult, providing little evidence of an association overall.

106. The **United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) United Nations (2008)[97] [RMA ID: 071214]** report included table 41, which is a summary of epidemiological studies of radiation and cancer. The table shows the risk estimates for non-Hodgkin's lymphoma incidence and mortality from studies of radiation exposure, which quantitative estimates of risk could be made. This table was relied on by the applicant; however the summary of epidemiological studies did not provide any further information considered important to this review.

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE FACTOR(S) FOR EXPOSURE TO IONISING RADIATION

107. The Applicant contended that the Statements of Principles should be expanded to include exposure to ionising radiation as a factor for the clinical onset of non-Hodgkin's lymphoma.

108. The council found that there was evidence of an association between ionising radiation and non-Hodgkin's lymphoma in studies of medical radiation where doses are relatively high. Weiss et al. (1994) found an increased risk of non-Hodgkin's lymphoma mortality 5-24.9 years after first radiation treatment for ankylosing spondylosis patients (83.5% men). The mean total body dose received was 2.64 Gy, with the heaviest dose to the vertebrae. Kim et al. (2013) found that the risk of non-Hodgkin's lymphoma increased significantly after initial radiotherapy for all solid cancers combined after adjusting by sex, age, stage and chemotherapy when compared with those not treated with radiotherapy. Radiation doses were not provided in this paper but radiotherapy doses are traditionally above 1 Gy.

109. The Council also found that there was no evidence of an association between ionising radiation exposure and non-Hodgkin's lymphoma where the dose was below 0.1 Sv. This was demonstrated by the studies of occupational exposure, veterans involved in military testing of nuclear weapons, communities residing near sources of ionising radiation, and accident recovery workers at Chernobyl nuclear power station.

110. Evidence regarding the dose of ionising radiation which is associated with non-Hodgkin's lymphoma comes from the two analyses of the Life Span

[97] UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). (2008). Non-Hodgkin's lymphoma. Table 41 risk estimates for cancer incidence and mortality from studies of radiation exposure: non-Hodgkin's lymphoma. UNSCEAR. (RMA ID 071214)

Study (Hsu et al. (2013) [98] [RMA ID: 072597] and Richardson et al. (2009)[99] [RMA ID: 068828], and the analysis of the Savannah River cohort (Richardson).

111. Hsu et al. (2013)[100] found that both the ERR in a simple linear dose response model and the linear EAR model showed an association between ionising radiation dose and risk of non-Hodgkin's lymphoma in males, but not in females. The majority of non-Hodgkin's lymphoma cases (n = 226) were exposed to radiation doses less than 0.005 Gy and 176 cases were reported for doses ranging from 0.1 Gy to greater than 2 Gy.

112. In his analyses of the Life Span Study and the Savannah River nuclear worker cohort, Richardson et al. (2009)[101] found that the risk of mortality from malignant lymphoma was increased for those men exposed to greater than 0.10 Sv, although the studies were limited by the small number of cases at the higher doses.

113. Given the strength of these studies, the Council was satisfied that the SMSE that was available to the RMA is sufficient to justify an amendment by adding a factor for ionising radiation at exposure levels above 0.10 Sv in reasonable hypothesis Statement of Principles No. 28 of 2010 as amended by Statement of Principles No. 57 of 2014 and No. 86 of 2014.

114. The Council considered that the SMSE evidence fell short of supporting an association on the balance of probabilities due to methodological limitations, lack of statistical significance and the variation seen in the results of different studies.

115. Accordingly, the Council decided that the SMSE available to the RMA at the relevant times was insufficient to justify an amendment to the balance of probabilities Statement of Principles No. 29 of 2010 as amended by Statement of Principles No. 87 of 2014.

116. As most exposure was either total body, (in the life span studies) or vertebral bodies (in the studies of therapeutic radiation for ankylosing spondylitis) the use of bone marrow exposure is a suitable surrogate to cover these different scenarios.

117. For the reasons set out above, the Council considered that the SMSE is sufficient to justify setting a cumulative equivalent dose of at least 0.1

---

98 Hsu et al. (2013). The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001. Radiation Research, 179(4), 361-382. (RMA ID 072597)

99 Richardson et al. (2009). Positive association between ionising radiation and lymphoma mortality among men. American Journal of Epidemiology, 169(8), 969-976. (RMA ID 068828)

100 Hsu et al. (2013). The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001. Radiation Research, 179(4), 361-382. (RMA ID 072597)

101 Richardson et al. (2009). Positive association between ionising radiation and lymphoma mortality among men. American Journal of Epidemiology, 169(8), 969-976. (RMA ID 068828)

sievert of ionising radiation to the bone marrow at least five years before the clinical onset of Non-Hodgkin's Lymphoma.

DECISION

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