Australian Government
Repatriation Medical Authority

REPATRIATION MEDICAL AUTHORITY

STATEMENT OF REASONS

S 196B(9) *VETERANS' ENTITLEMENTS ACT 1986*

DECISION NOT TO AMEND THE CURRENT STATEMENT OF PRINCIPLES CONCERNING ACUTE MYELOID LEUKAEMIA FOLLOWING A REVIEW

Instrument No. 72 of 2015

PART I INTRODUCTION

1. The Repatriation Medical Authority (the Authority) pursuant to subsection 196B(9) of the *Veterans' Entitlements Act 1986* (the VEA), has decided not to amend Statement of Principles concerning acute myeloid leukaemia, Instrument No. 72 of 2015, following an investigation which was notified in the *Commonwealth of Australia Gazette* on 29 October 2019. The investigation related to "insecticides".

2. Having carried out the investigation as notified, the Authority concluded that the sound medical-scientific evidence available to it, including the new sound medical-scientific evidence, is sufficient to justify the inclusion of a factor relating to exposure to dieldrin or aldrin, and a factor relating to exposure to diazinon, in Statement of Principles Instrument No. 71 of 2015. However the sound medical-scientific evidence available to it, including the new sound medical-scientific evidence, is insufficient to justify inclusion of factors concerning exposure to these insecticides in Statement of Principles Instrument No. 72 of 2015

PART II BACKGROUND TO THE INVESTIGATION

3. A request dated 4 July 2019, was received from a representative of a veterans' organisation, seeking a review into the association between exposure to toxic chemicals in Nui Dat during the Vietnam War and leukaemia and other cancers. A telephone call conducted with the applicant by the Acting Principal Medical Officer clarified that the request was to review the Statements of Principles concerning four leukaemias (acute lymphoblastic leukaemia, chronic lymphocytic leukaemia/small lymphocytic lymphoma, acute myeloid leukaemia, and chronic myeloid leukaemia) with respect to exposure to pesticides, being dieldrin, chlordane, lindane, diazinon, malathion, and DDT.

4. In support of the request, the applicant provided the following:

   - Mordike J (2013). Insecticide deceit?: the truth about insecticides used at Nui Dat.
   - Denner R (2013). Rampant & uncontrolled use of insecticides in Australian Army bases in South Vietnam. The Vietnam Veterans Peacekeepers and Peacemakers Journal; pp 12-13.
   - AAP (2013). Double risk of leukaemia for Vietnam vets. 2nd September 2013. AAP (2013). Double risk of leukaemia for Vietnam vets. 2nd September 2013.
   - McBride D, Cox B, Broughton J, et al (2013). The mortality and cancer experience of New Zealand Vietnam war veterans: a cohort study. BMJ Open, 3(9): e003379.
   - Tchounwou PB, Patlolla AK, Yedjou CG, et al (2015). Environmental exposure and health effects associated with malathion toxicity. Intech Open Limited. Internet published article. https://www.intechopen.com/books/toxicity-and-hazard-of-agrochemicals/environmental-exposure-and-health-effects-associated-with-malathion-toxicity.

5. On 2 October 2019, the Authority, under s 196B(7A) of the VEA, decided to review the contents of the Statements of Principles concerning acute myeloid leukaemia, Instrument Nos. 71 and 72 of 2015, to find out if there was new information in respect of "insecticides" as a factor in acute myeloid leukaemia.

6. The investigation notice was signed by the Chairperson of the Authority on 18 October 2019 and was gazetted in accordance with s 196G of the VEA in the *Commonwealth of Australia Gazette* on 29 October 2019. Submissions were invited from persons and organisations wishing to make a submission by 19 November 2019.

PART III SUBMISSIONS RECEIVED BY THE AUTHORITY PURSUANT TO SECTION 196F

7. Following notification of its investigation, the Authority did not receive any information from persons eligible to make submissions pursuant to s 196F of the VEA.

PART IV EVIDENCE/INFORMATION AVAILABLE TO THE REPATRIATION MEDICAL AUTHORITY

8. The following information was available to the Authority:

   8.1. The information held by the Authority and obtained during its previous considerations leading to the determination of Statements of Principles concerning acute myeloid leukaemia, Instrument Nos. 71 and 72 of 2015.

   8.2. Literature searches were also conducted on the 15th October 2019 using the Ovid search engine from 2004 to current, limited to English language and humans. The search terms were: Exp Dieldrin which produced 69 articles, Exp Diazinon which produced 32 articles, Exposure Malathion which produced 41 articles, and Exp Organophosphates combined with exp Neoplasms which produced 148 articles. An additional 4 articles were selected for further study. Articles were selected based on relevance, study quality, reliability and journal authority.

   8.3. A briefing paper concerning acute myeloid leukaemia prepared for presentation to the Authority by a Medical Researcher of the Secretariat.

PART V SOUND MEDICAL-SCIENTIFIC EVIDENCE

9. The Statements of Principles are determined on the basis of the available "sound medical-scientific evidence" as defined in s 5AB(2) of the VEA which states:

"*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."

Dieldrin and aldrin

10. The International Agency for Research on Cancer (IARC) (2019), in a recent evaluation of dieldrin (and aldrin metabolised to dieldrin), concluded that it is probably carcinogenic to humans (Group 2A), with limited evidence for breast cancer, but not for leukaemia. However, this evaluation was based on incomplete evidence, with the subsequent publication of an important nested case-control study that was based on serum levels of organochlorine pesticides (Bassig et al 2019).

11. There was some consistency in the findings of three cohort or nested case-control studies, although the association was not supported by one case-control study. Of the three cohorts or nested case-control studies, all reported that exposure to aldrin or dieldrin increased the risk of acute myeloid leukaemia or leukaemia, although the association was only statistically significant in one study (Bassig et al 2019). In contrast, a case-control study from the US Midwest (Brown et al 1990) found no association between leukaemia and ever exposure to either aldrin or dieldrin.

12. The strength of the association in the positive studies was weak to moderate. In a case-control study nested in the general population of Norway, Bassig et al (2019) found that the highest tertile of serum levels of dieldrin measured on average 17 years previously, significantly increased the risk of acute myeloid leukaemia [Odds Ratio (OR) 2.7]. A retrospective cohort study of the mortality of Dutch aldrin and dieldrin production workers employed for at least one year (Van Amelsvoort et al 2009) reported a non-significant weak excess of leukaemia among all workers [Standardised Mortality Ratio (SMR) 114], increasing in workers with moderate exposure [SMR 234]. The Agricultural Health Study (AHS) (Purdue et al 2007) reported non-significant increased risks of leukaemia with ever exposure to aldrin [Relative Risk (RR) 1.4] and dieldrin [RR 1.7] respectively.

13. The correct temporal relationship has been demonstrated by the three cohort or nested case-control studies, with exposure to aldrin and dieldrin recorded prior to the development of acute myeloid leukaemia/leukaemia. Importantly, two of these studies involved measurement of dieldrin in blood prior to the onset of acute myeloid leukaemia/leukaemia.

14. There is some biological plausibility for the association, as IARC (2019) concluded that there is moderate evidence that dieldrin is genotoxic (although no positive studies in humans are mentioned), modulates receptor mediated effects (anti-estrogenic effects), induces oxidative stress, induces chronic inflammation and alters cell proliferation.

15. Some limitations were evident in each of these studies.Two of the positive studies (Bassig et al 2019, Purdue et al 2007) adjusted for smoking and body mass index. However, other occupational exposures such as other organochlorine pesticides (Bassig et al 2019), benzene or formaldehyde were not adjusted for, raising the possibility of confounding. Exposure in the AHS was based on self-report by farmers or pesticide applicators.

16. Chance may also be an alternate explanation for the observed associations, as the increased risk was not statistically significant in two of the positive studies (Van Amelsvoort et al 2009, Purdue et al 2007) and all studies performed multiple testing. Two of the three positive studies used the non-specific endpoint of leukaemia, so that the actual association in these studies might be with forms of leukaemia other than acute myeloid leukaemia.

17. Evidence for a dose-response effect was inconsistent, with one nested case-control study finding a dose-response (Bassig et al 2019), one retrospective mortality cohort unclear (Van Amelsvoort et al 2009), and no dose-response evident in the AHS or the case-control study (Brown et al 1990).

Diazinon

18. The International Agency for Research on Cancer (IARC) (2017), in a recent evaluation of the organophosphate insecticide diazinon (Group 2A), concluded that there is limited evidence for a causal association with leukaemia, non-Hodgkin lymphoma and lung cancer. Two of three studies found positive associations between diazinon and leukaemia. The AHS (Beane Freeman et al 2005) reported a significantly increased risk of leukaemia [RR 3.4] with at least 39 days of exposure to diazinon in a lifetime. A case-control study nested in a cohort of unionised farm workers (Mills et al 2005) reported that high exposure to diazinon non-significantly increased the risk of leukaemia [OR 1.32], especially granulocytic (i.e. acute or chronic myeloid) leukaemia [OR 1.94] and less so for lymphocytic [OR 1.42]. In contrast, a case-control study from the US Mid-west in farming regions (Brown et al 1990) found no significant association between leukaemia and ever exposure to diazinon.

19. The strength of the association was moderate in view of the AHS. Evidence for a dose-response was inconsistent. The AHS reported a significant positive trend with lifetime days of exposure to diazinon. However, an inverse trend was apparent in the case-control study (Brown et al 1990).

20. The correct temporal relationship has been demonstrated by the AHS and the united farm workers nested case-control study, with exposure to diazinon recorded prior to development of leukaemia. There is some biological plausibility as diazinon is considered to be genotoxic and produce oxidative stress (IARC 2017).

21. Some limitations were evident in each of these studies. Exposure assessment was based on self-report in the AHS and only farm-level exposure data were used in the united farm workers nested case-control study. No biological measurements of diazinon exposure were used. The AHS adjusted for smoking, BMI and other pesticides correlated to diazinon, although other occupational exposures to benzene or formaldehyde were not addressed, raising the possibility of confounding. Chance may also be an alternate explanation, as the AHS performed multiple testing and the association was not statistically significant in the united farm workers nested case-control study. The AHS used the non-specific endpoint of leukaemia and the united farm workers nested case-control study used granulocytic leukaemia, so that the actual association in these studies might be with forms of leukaemia other than acute myeloid leukaemia.

PART VII SUMMARY AND CONCLUSIONS

22. Overall, results of the available studies indicate that the evidence is too limited to permit a judgement of a probable or convincing causal relationship between acute myeloid leukaemia and exposure to the insecticides dieldrin, aldrin and diazinon, but supports a judgement of a possible causal relationship. An association has been observed between exposure to dieldrin, aldrin and diazinon and acute myeloid leukaemia, but the evidence is limited in quality and quantity.

23. The VEA requires that the same body of evidence be assessed according to two different standards of proof. For assessment under the reasonable hypothesis standard (s 196B(2)) the VEA requires that the sound medical-scientific evidence must indicate or point to a causal association between a risk factor related to t
and the disease in question. On the other hand, for the balance of probabilities standard (s 196B(3)), the sound medical-scientific evidence must show that it is more probable than not that there is a causal association between a risk factor related to t
and the disease. In this matter the distinction between those standards of proof is significant.

24. The available sound medical-scientific evidence indicates or points to a causal association between exposure to the insecticides dieldrin, aldrin and diazinon and acute myeloid leukaemia, such being sufficient to support a judgement of a possible causal association. The reasonable hypothesis standard is met and factors concerning exposure to dieldrin, aldrin and diazinon will be included in that Statement of Principles.

25. However, as detailed in the reasons set out above, the sound medical-scientific evidence does not show that it is more probable than not that there is a causal association between exposure to dieldrin, aldrin and diazinon and acute myeloid leukaemia. The available evidence is therefore insufficient to support a judgement of a probable causal association between exposure to dieldrin, aldrin and diazinon and acute myeloid leukaemia, and the balance of probabilities standard cannot be met. In these circumstances no factors can be included in that Statement of Principles.

PART VIII DECISION NOT TO AMEND INSTRUMENT NO. 72 OF 2015

26. At its meeting on 12 February 2020 the Authority decided not to amend the balance of probabilities Statement of Principles in respect of acute myeloid leukaemia for the purposes of subsections 196B(3) and (8) of the VEA as the Authority concluded, for the reasons set out above, that the sound medical-scientific evidence available to it, including the new sound medical-scientific evidence, is insufficient to justify the inclusion of factors relating to exposure to the insecticides dieldrin, aldrin and diazinon in the balance of probabilities Statement of Principles already determined in respect of acute myeloid leukaemia.

Professor Nicholas Saunders AO
Chairperson
Repatriation Medical Authority

28 February 2020

PART IX BIBLIOGRAPHY

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