



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 HYPERTENSION FOLLOWING A REVIEW**

Instrument No. 64 of 2013

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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 hypertension, Instrument No. 64 of 2013, following an investigation which was notified in the *Commonwealth of Australia Gazette* on 8 January 2019.
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 factors relating to exposure to phenoxyherbicides/dioxin (Agent Orange) in Statement of Principles Instrument No. 63 of 2013. 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 phenoxyherbicides/dioxin (Agent Orange) in Statement of Principles Instrument No. 64 of 2013.

PART II BACKGROUND TO THE INVESTIGATION

3. The Authority decided on its own initiative to notify a review of the contents of the Statements of Principles concerning hypertension, based on the recently published United States National Academies of Sciences, Engineering, and Medicines' *Veterans and Agent Orange: Update 11 (2018)*. The review was restricted to consideration of "exposure to phenoxyherbicides/dioxin (Agent Orange)" as a causal factor.
4. On 12 December 2018, the Authority, under s 196B(7A) of the VEA, decided to review the contents of the Statements of Principles, Instrument Nos. 63 and 64 of 2013, to find out if there was new information in respect of "exposure to phenoxyherbicides/dioxin (Agent Orange)" as a factor in hypertension.
5. The investigation notice was signed by the Chairperson of the Authority on 21 December 2018 and was gazetted in accordance with s 196G of the VEA in the *Commonwealth of Australia Gazette* on 8 January 2019. Submissions were invited from persons and organisations wishing to make a submission by 18 March 2019.

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

6. 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

7. The following information was available to the Authority:
 - 7.1. The information held by the Authority and obtained during its previous considerations leading to the determination of Statements of Principles concerning hypertension, Instrument Nos. 63 and 64 of 2013.

- 7.2. A PubMed search was conducted on 11 February 2019 using the search terms ("hypertension"[MeSH Terms] OR "hypertension"[All Fields]) AND ("herbicides"[Pharmacological Action] OR "herbicides"[MeSH Terms] OR "herbicides"[All Fields] OR "herbicide"[All Fields]). A total of 127 references was generated. A further PubMed search using the search terms ("hypertension"[MeSH Terms] OR "hypertension"[All Fields]) AND ("pesticides"[Pharmacological Action] OR "pesticides"[MeSH Terms] OR "pesticides"[All Fields] OR "pesticide"[All Fields]) generated a total of 989 references, while using the search terms ("dioxins"[MeSH Terms] OR "dioxins"[All Fields] OR "dioxin"[All Fields]) AND "humans"[MeSH Terms] generated a total of 21 references. Articles were selected based on relevance, study quality, reliability and journal authority. The above searches were supplemented by internet searches, manual searches of reference lists, review of citations and consideration of relevant sections of textbooks.
- 7.3. Medical or scientific publications as set out in the bibliography attached hereto (including United States National Academies of Sciences, Engineering, and Medicines' *Veterans and Agent Orange: Update 11 (2018)*).
- 7.4. A briefing paper concerning hypertension prepared for presentation to the Authority by a Medical Researcher of the Secretariat.

PART V SOUND MEDICAL-SCIENTIFIC EVIDENCE

8. 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."*

PART VI REASONS FOR THE DECISION

9. The Authority initiated an investigation into phenoxy herbicides/dioxin based on the recently published United States National Academies of Sciences, Engineering, and Medicines' *Veterans and Agent Orange: Update 11 (2018)*, the eleventh biennial update on the health effects in Vietnam veterans of exposure to herbicides. The Veterans and Agent Orange publication is considered an authoritative source of information on the association between phenoxy herbicides or dioxin and various diseases.
10. The Veterans and Agent Orange committee upgraded its classification of the evidence for the association between the herbicides of interest, including 2,3,7,8-

tetrachlorodibenzo-para-dioxin (TCDD), and hypertension from limited or suggestive evidence of an association in its 2014 update, to sufficient evidence of an association in its 2018 update. The upgrading of the association between the herbicides of interest, including TCDD, and hypertension was based largely on the recent, large cross-sectional study by Cypel et al (2016) of the US Army Chemical Corps Vietnam veterans. The study found that herbicide sprayers compared with nonsprayers had a significantly elevated risk of self-reported hypertension after adjustment for relevant potential confounders (OR 1.74, 95% CI 1.44-2.11), and some evidence of a positive dose response with likely exposure levels.

11. There were five other new studies which the Veterans and Agent Orange update considered with respect to hypertension since the previous update in 2014. The additional studies comprised two occupational studies (Cappeletti et al 2016, Yamamoto et al 2015) and three environmental exposure investigations (Lind et al 2014, Shiue et al 2014, Van Larebeke et al 2015). Each of these studies had significant study design deficiencies and would not be adequate to change the level of association individually. However, the Veterans and Agent Orange committee concluded that they corroborated an elevated risk between exposure to the compounds of interest and hypertension using a variety of study designs, populations, and measurements of exposure. The committee found that this new research, in addition to the earlier research, demonstrated a consistency in the direction and magnitude of an association between herbicides and hypertension. Additional data from animal and human cell culture models supported the hypothesis that TCDD activation of aryl hydrocarbon receptors increases the development of hypertension, providing a plausible biological mechanism for causation.
12. There are no prospective cohort studies that affirm an association of exposure to dioxin or phenoxy herbicides and the clinical onset or clinical worsening of hypertension, and the available studies are likely subject to varying degrees of exposure misclassification and confounding by other multiple chemicals. No evidence confirms a dose response relationship.
13. In a Flemish biomonitoring program, dioxin-like activity showed a positive association with risk of “hypertension”, significantly for both sexes together, and marginally significantly for men separately (Van Larebeke et al 2015). In the Canary Islands, dioxin-like PCBs were not associated with hypertension (Henríquez-Hernández et al 2014). In Uppsala, Sweden, none of dioxin-like PCBs were significantly associated with prevalent hypertension (Lind et al 2014).
14. There was no evidence of higher rates of self-reported hypertension in an environmental study of long-term health outcomes in Yusho survivors (Akahane et al. 2017), who were exposed to polychlorinated biphenyls (PCBs), dioxins (e.g., polychlorinated dibenzo-p-dioxins (PCDDs)/polychlorinated dibenzofurans (PCDFs)), and dioxin-like chemicals through the ingestion of contaminated rice bran oil. In an occupational study from Japan, Yamamoto et al (2015) found that serum levels of PCDFs and total dioxins were significantly associated with prevalence of hypertension, but analysis suggested that something other than dioxin may be contributing to increased risk for hypertension in younger population. It was likely that occupational exposure to present levels of dioxins did not contribute to health outcomes in incinerator workers. In Japan, toxic equivalent quotients of PCDDs, PCDFs, and dioxin-like-PCBs were associated with high blood

pressure and tests of trend were all statistically significant (Uemara et al 2009). Both serum dioxin-like and nondioxin-like PCBs tended to be positively associated with hypertension, mostly in men in NHANES cross-sectional study of adults, but the associations were not correlated with toxic equivalency factors (Ha et al 2009).

15. There is a very limited and inconsistent body of evidence linking dioxins and other persistent organic pollutants to the prevalence of hypertension as a component of 'metabolic' syndrome' in cross-sectional population studies (e.g., Chang et al 2010). The few available studies on non-occupationally-exposed subgroups show inconsistent results, both in the associations found and in the chemicals responsible for the observed effects in relation to prevalent and incident hypertension in relation to measures of exposure to both dioxin and non-dioxin like PCBs. Several cross-sectional studies have linked different environmental contaminants to metabolic syndrome, but mixture effects have not been investigated, and no prospective studies exist regarding environmental contaminants and metabolic syndrome or its specific components, including hypertension. Positive associations between PCBs and individual components of metabolic syndrome, including prevalence of elevated blood pressure, were reported in analyses of Anniston cohort (Goncharov et al 2010, Goncharov et al 2011; Aminov et al 2013), but there is no data specifically about the association of hypertension with potent dioxin-like PCBs. In a study in the Taiwanese population, PCDD/Fs were linked to metabolic syndrome through shared correlations with high diastolic blood pressure, but not systolic blood pressure (Chang et al 2010).
16. Previous investigations of hypertension by the Authority have examined the published cohort studies from Seveso (Italy) which have reported different health effects by sex in a population heavily accidentally exposed to 2,3,7,8-TCDD. There have not been any recent updates from this population in relation to hypertension. Only women, not men, showed a higher risk of mortality related to hypertensive diseases (Pesatori et al 1998). Sex differences in the response to TCDD have been also observed in animal studies.
17. A description of clinical status in chemical workers who were heavily exposed to dioxins in a Czech factory (Pelcl et al 2018) found that the prevalence of arterial hypertension was 87.5% in the exposed group and 71.8% in the unexposed population. The patient with the highest TCDD burden showed multiple signs of metabolic impairment, more severe than patients with lower TCDD levels. Pelcl et al suggested that TCDD played a role in the development of metabolic impairment and vascular changes in exposed subjects, although the nature of the study precluded a causal interpretation of the data.

PART VII SUMMARY AND CONCLUSIONS

18. 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 hypertension and exposure to dioxins and dioxin-contaminated compounds, including phenoxy herbicides, but supports a judgement of a possible causal relationship. An association has been observed between exposure to these chemicals and hypertension, but the evidence is limited in quality or quantity. This conclusion is based primarily on the finding of a significantly increased relative risk by the high quality cross-sectional study by Cypel et al (2016), with no obvious biases or confounding, and some suggestion of a dose

response. Other descriptive and analytical studies provided some signals of an association, but with evidence of bias or confounding, and a lack of specificity for dioxins.

19. 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.
20. The available sound medical-scientific evidence indicates or points to a causal association between "exposure to phenoxyherbicides/dioxin (Agent Orange)" and hypertension, such being sufficient to support a judgement of a possible causal association. The reasonable hypothesis standard is met and factors will be included in that Statement of Principles.
21. 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 phenoxyherbicides/dioxin (Agent Orange)" and hypertension. The available evidence is therefore insufficient to support a judgement of a probable causal association between "exposure to phenoxyherbicides/dioxin (Agent Orange)" and hypertension, 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. 64 OF 2013

22. At its meeting on 7 August 2019 the Authority decided not to amend the balance of probabilities Statement of Principles in respect of hypertension 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 phenoxyherbicides/dioxin (Agent Orange) in the balance of probabilities Statement of Principles already determined in respect of hypertension.



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