



Australian Government

Repatriation Medical Authority

REPATRIATION MEDICAL AUTHORITY

STATEMENT OF REASONS

S196B(9) *VETERANS' ENTITLEMENTS ACT 1986*

**DECISION NOT TO AMEND THE CURRENT STATEMENTS OF PRINCIPLES
CONCERNING MALIGNANT NEOPLASM OF THE BLADDER
FOLLOWING A REVIEW**

Statements of Principles Instrument Nos. 96 & 97 of 2011

Part I	INTRODUCTION	3
Part II	Background to the Investigation	3
Part III	Submissions received by the Authority pursuant to section 196F	4
Part IV	Evidence/Information Available to the Repatriation Medical Authority	4
Part V	Sound medical-scientific evidence	4
Part VI	Reasons for the decision	5
Part VII	Decision	8
Part VIII	Bibliography	9

PART I INTRODUCTION

1. The Repatriation Medical Authority (the Authority) has decided not to amend the Statements of Principles concerning malignant neoplasm of the bladder Instrument Nos. 96 & 97 of 2011, under subsection 196B(9) of the *Veterans' Entitlements Act* 1986 (the Act), following an investigation which was notified in the *Commonwealth of Australia Gazette* on 3 May 2016.
2. The Authority concluded that there is insufficient new sound medical-scientific evidence to justify an amendment to Statements of Principles Instrument Nos. 96 and 97 of 2011, already determined in respect of malignant neoplasm of the bladder.

PART II BACKGROUND TO THE INVESTIGATION

3. On 6 April 2016, the Authority decided to initiate a review, under subsection 196B(7A) of the Act, in respect of phenoxyherbicides/dioxin (Agent Orange) as a factor in malignant neoplasm of the bladder.
4. In support of the review, the Authority considered the following:
 - Bonneterre V, Mathern G, Pelen O, Balthazard AL, Delafosse P, Mitton N, Colonna M. (2012) Cancer incidence in a chlorochemical plant in Isère, France: an occupational cohort study, 1979-2002. *Am J Ind Med.* Sep;55(9):756-67.
 - IARC Working Group (2012). 2,3,7,8-tetrachlorodibenzo-para-dioxin, 2,3,4,7,8-pentachlorodibenzofuran, and 3,3',4,4',5-pentachlorobiphenyl. Vol 100F- 339-78. IARC Press, Lyon.
 - Di Lorenzo G, Federico P, De Placido S, Buonerba C. (2015) Increased risk of bladder cancer in critical areas at high pressure of pollution of the Campania region in Italy: A systematic review. *Crit Rev Oncol Hematol.* Dec;96(3):534-41.
 - National Academies of Sciences, Engineering, and Medicine (2016) *Veterans and Agent Orange: Update 2014*. Washington, DC: The National Academies Press, pp. 514-529.
 - Yi SW, Ohrr H. (2014) Agent Orange exposure and cancer incidence in Korean Vietnam veterans: a prospective cohort study. *Cancer.* Dec 1;120(23):3699-706.
 - Yi SW, Ryu SY, Ohrr H, Hong JS. (2014) Agent Orange exposure and risk of death in Korean Vietnam veterans: Korean Veterans Health Study. *Int J Epidemiol.* Dec;43(6):1825-34.
5. The investigation notice was signed by the Chairperson of the Authority on 22 April 2016 and was gazetted in accordance with section 196G of the Act in the *Commonwealth of Australia Gazette* on 3 May 2016. Submissions were invited from persons and organisations wishing to make a submission by 15 July 2016.

6. Statements of Principles Instrument Nos. 96 and 97 of 2011 concerning malignant neoplasm of the bladder do not have any factors relating to "phenoxyherbicides/dioxin (Agent Orange)".

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 section 196F of the Act.

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 malignant neoplasm of the bladder, Instrument Nos. 96 and 97 of 2011.
 - 8.2. Literature searches using the Ovid search engine from 1996 to July Week 1 2016, limited to English language. The search terms were: Urinary bladder neoplasms AND 2,4-dichlorophenoxyacetic acid/ or herbicides/ or phenoxyherbicides.mp OR dioxins. Articles were selected based on relevance, study quality, reliability and journal authority. The above search was supplemented by a PubMed search, internet searches, manual searches of reference lists and extracts from relevant sections of textbooks, particularly the Veterans and Agent Orange (VAO) series.
 - 8.3. Medical or scientific publications as set out in the bibliography attached hereto.
9. A briefing paper concerning malignant neoplasm of the bladder prepared for presentation to the Authority by a Medical Researcher of the Secretariat.

PART V SOUND MEDICAL-SCIENTIFIC EVIDENCE

10. The Statements of Principles are determined on the basis of the available "sound medical-scientific evidence" as defined in section 5AB(2) of the Act 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

11. The International Agency for Research on Cancer (IARC) classifies TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxin, or “dioxin”) as a group 1 carcinogen, based on the risk of all cancers combined, but only sporadic reports of associations with bladder cancer. The most recent update of Veterans and Agent Orange has reclassified the evidence for the association between bladder cancer and the compounds of interest (TCDD, the phenoxyherbicides 2,4,5-T and 2,4-D, picloram and cacodylic acid) from “insufficient” to “limited or suggestive”. This assessment was made on the basis of a new Korean Vietnam Veterans study (Yi et al 2014), which found an increase in risk of mortality from bladder cancer in veterans at higher versus lower risk of dioxin exposure, as well as previous evidence of a non-significantly elevated mortality risk in the IARC phenoxyherbicide industrial cohort and significant elevations in two subcohorts.
12. However, while some studies have found positive associations between dioxin-contaminated compounds and bladder cancer, the majority of studies report null or negative associations, and chance, bias or confounding could account for some of the positive associations.
13. An important limitation of the Korean Vietnam Veterans studies was the accuracy of the measurement of exposure to phenoxyherbicides. Exposure was estimated using an exposure opportunity index (EOI) model, developed by Stellman and Stellman (2003). The exposure index was based on the proximity of the veteran's unit to Agent Orange-sprayed areas, using a geographical information system-based model. Given the lag time since herbicide exposures in Vietnam took place and the lack of direct exposure measurements from that era, it is not possible to fully validate the EOI model, or to ascertain the accuracy and precision of estimates from the model.
14. Biological studies do not support an adverse effect of dioxins on risk of bladder cancer. No studies have reported an increased incidence of urinary bladder cancer in TCDD- or 2,4-D-treated animals. Two studies suggest a protective effect of aryl hydrocarbon receptor signalling on bladder cancer.
15. Evidence of a clear dose-response effect is lacking. Dose-response analyses were only reported for six studies listed in the VAO 2014 report. The IARC phenoxyherbicide cohort (Kogevinas et al 1997) appeared to show a possible dose-response effect, with risks being lower in those not exposed to highly chlorinated dioxins (SMR 0.7, 95% CI 0.3-1.2) than those with such exposure (SMR 1.4, 95% CI 0.9-2.1), though a gradient is uncertain due to overlapping confidence intervals. Of the other five studies, four did not demonstrate a dose-response effect (Boers et al 2012, Ott and Zober 1996, McLean et al 2006, Samanic et al 2006) and one (Hansen et al 2007) was equivocal due to overlapping confidence intervals and crude exposure assessment (assessed by period of employment).
16. Null or non-significant associations were observed in the most informative study of Vietnam Veterans (the US Air Force “Ranch Hand” Health Study), most studies of industrially exposed production workers, all studies of herbicide sprayers, and in the Seveso industrial accident study (incidence and mortality). Many of these studies were limited by small numbers of bladder cancer cases. In the Korean Vietnam Veterans study,

findings were also null for incidence of bladder cancer (Yi and Ohrr 2014). Studies of bladder cancer incidence were fewer than studies of bladder cancer mortality, but tended to be closer to the null.

- This overall lack of positive associations in most studies is demonstrated in the figures below, one showing studies that reported bladder cancer mortality and the other showing studies that reported bladder cancer incidence. The data for these figures is taken from VAO 2014, using the estimates from the most recent updates of each cohort. In these figures the squares represent the calculated relative risk and the lines represent the 95% confidence intervals, that is, the range of values that is 95% likely to include the true value. A shorter line indicates that the calculated relative risk is more precise. A relative risk of one indicates that there is no difference in risk of disease between the exposed group and the unexposed group. If the confidence interval crosses the value of one, the relative risk is not statistically significant.

FIGURE 1 DIOXIN AND PHENOXYHERBICIDE EXPOSURE AND BLADDER CANCER MORTALITY

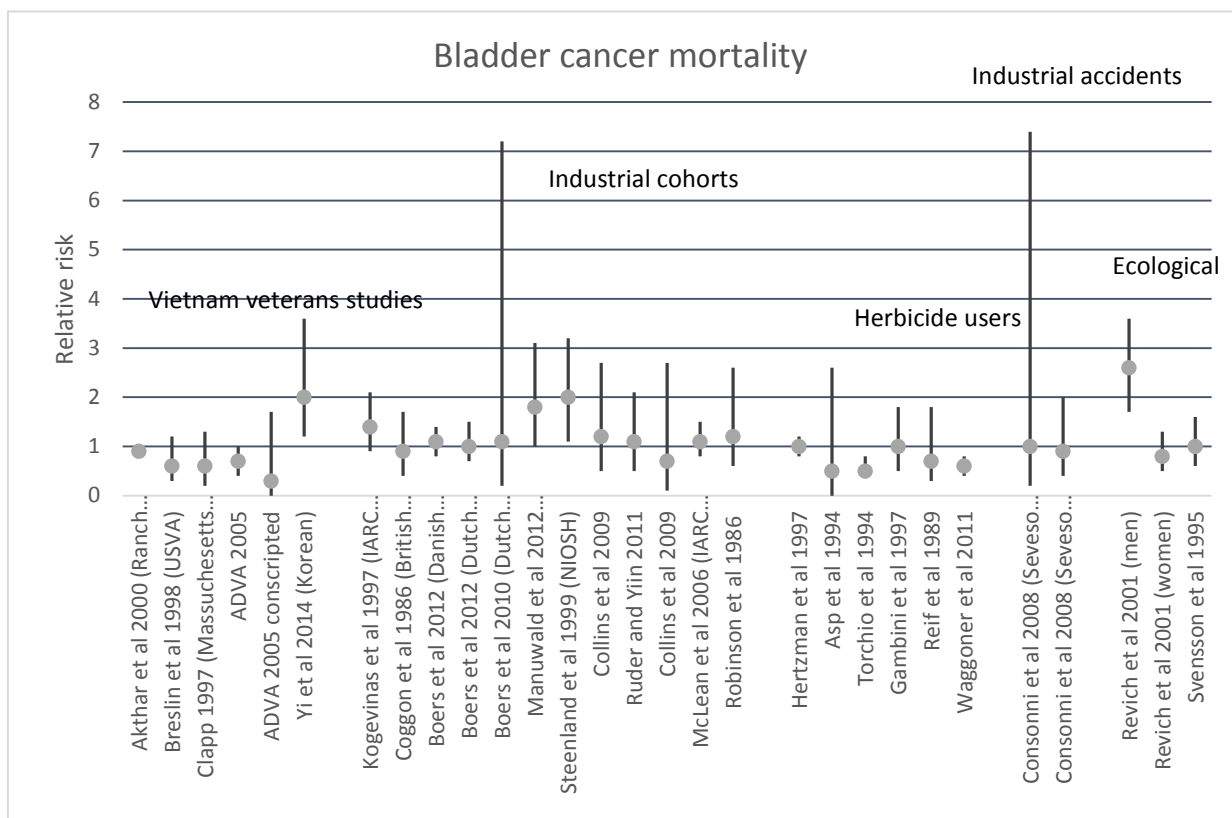
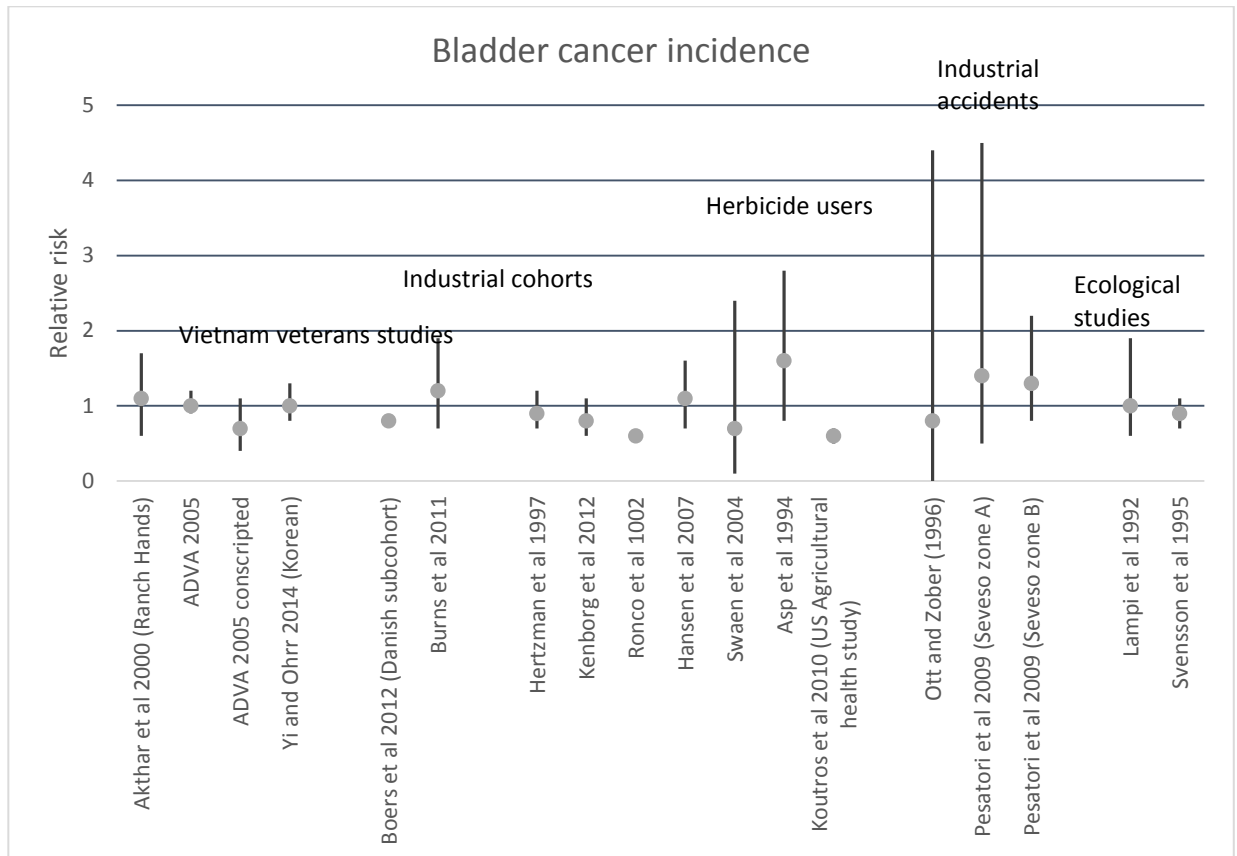


FIGURE 2 DIOXIN AND PHENOXYHERBICIDE EXPOSURE AND BLADDER CANCER INCIDENCE



18. Two additional studies that were not part of the VAO 2014 review did not change the weight of evidence. A systematic review (Di Lorenzo et al 2015) of ecological studies in a polluted area of Italy found that the average values of polychlorinated dibenzo(p)dioxins and furans (PCDD/F) and polychlorinated biphenyls (PCBs) reported in blood serum and human milk of the area population were not elevated compared to national levels. A cohort study of workers in a major French chlorine chemical plant (Bonnetterre et al 2012) found a non-significant elevated risk for bladder cancer. The association was significant for workers employed before 1964. However, all of the 20 cases with bladder cancer were smokers, there was no significant elevation in those exposed to polychlorophenols and there was also confounding by multiple chemical exposures.
19. Overall, the evidence in support of phenoxyherbicides or dioxins as a cause of malignant neoplasm of the bladder is very limited, with null associations in most studies, no clear dose-response effects and lack of supporting biological plausibility. The new Korean studies are not of sufficient quality to tip the balance of the overall assessment to the extent of suggesting a reasonable hypothesis of a causal association between dioxin/phenoxyherbicides and risk of bladder cancer.

PART VII DECISION

20. At its meeting on 2 August 2016 the Authority decided not to amend the Statements of Principles in respect of malignant neoplasm of the bladder for the purposes of subsections 196B(2), (3) and (8) of the Act as the Authority concluded, for the reasons set out above, that there is insufficient new sound medical-scientific evidence to justify an amendment to the Statements of Principles already determined in respect of malignant neoplasm of the bladder.



Professor Nicholas Saunders AO
Chairperson
Repatriation Medical Authority

26 August 2016

PART VIII BIBLIOGRAPHY

Bonneterre V, Mathern G, Pelen O, Balthazard AL, Delafosse P, Mitton N, Colonna M. (2012) Cancer incidence in a chlorochemical plant in Isère, France: an occupational cohort study, 1979-2002. *Am J Ind Med.* Sep;55(9):756-67.

IARC Working Group (2012). 2,3,7,8-tetrachlorodibenzo-para-dioxin, 2,3,4,7,8-pentachlorodibenzofuran, and 3,3',4,4',5-pentachlorobiphenyl. Vol 100F- 339-78. IARC Press, Lyon.

Di Lorenzo G, Federico P, De Placido S, Buonerba C. (2015) Increased risk of bladder cancer in critical areas at high pressure of pollution of the Campania region in Italy: A systematic review. *Crit Rev Oncol Hematol.* Dec;96(3):534-41.

National Academies of Sciences, Engineering, and Medicine (2016) Veterans and Agent Orange: Update 2014. Washington, DC: The National Academies Press, pp. 514-529.

Yi SW, Ohrr H. (2014) Agent Orange exposure and cancer incidence in Korean Vietnam veterans: a prospective cohort study. *Cancer.* Dec 1;120(23):3699-706.

Yi SW, Ryu SY, Ohrr H, Hong JS. (2014) Agent Orange exposure and risk of death in Korean Vietnam veterans: Korean Veterans Health Study. *Int J Epidemiol.* Dec;43(6):1825-34.