



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 MALIGNANT NEOPLASM OF THE PANCREAS
FOLLOWING A REVIEW**

Instrument No. 74 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 malignant neoplasm of the pancreas, Instrument No. 74 of 2013, following an investigation which was notified in the *Commonwealth of Australia Gazette* on 9 January 2018.
2. Having carried out the investigation as notified, the Authority concluded that the new sound medical-scientific evidence available to it is sufficient to justify an amendment to the factor concerning exposure to dichlorodiphenyltrichloroethane (DDT) in Statement of Principles Instrument No. 73 of 2013, to clarify the meaning of the factor. However the new sound medical-scientific evidence available to it is insufficient to justify inclusion of a factor concerning exposure to DDT in Statement of Principles Instrument No. 74 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 malignant neoplasm of the pancreas, restricted to consideration of "exposure to DDT" as a causal factor.
4. Factor 6(e) relating to exposure to DDT is included in the reasonable hypothesis Statement of Principles concerning malignant neoplasm of the pancreas, Instrument No. 73 of 2013, determined under subsection 196B(2) of the VEA. The balance of probabilities Statement of Principles concerning malignant neoplasm of the pancreas, Instrument No. 74 of 2013, determined under subsection 196B(3) of the VEA, does not include a factor relating to exposure to DDT.
5. On 6 December 2017, the Authority, under subsection 196B(7A) of the VEA, decided to review the contents of the Statements of Principles, Instrument Nos. 73 and 74 of 2013, to find out if there was new information in respect of "exposure to DDT" as a factor in malignant neoplasm of the pancreas.
6. The review was conducted for the following purposes:
 - a) To determine if the new sound medical-scientific evidence available is sufficient to justify the inclusion of a factor relating to exposure to DDT in the balance of probabilities Statement of Principles, Instrument No. 74 of 2013, already determined concerning malignant neoplasm of the pancreas; and
 - b) To examine the wording of current factor 6(e) relating to exposure to DDT in the reasonable hypothesis Statement of Principles Instrument No. 73 of 2013 to clarify the meaning of that factor.
7. The investigation notice was signed by the Chairperson of the Authority on 22 December 2017 and was gazetted in accordance with section 196G of the VEA in the *Commonwealth of Australia Gazette* on 9 January 2018. Submissions were invited from persons and organisations wishing to make a submission by 19 March 2018.

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

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

PART IV EVIDENCE/INFORMATION AVAILABLE TO THE REPATRIATION MEDICAL AUTHORITY

9. The following information was available to the Authority:
 - 9.1. 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 pancreas, Instrument Nos. 73 and 74 of 2013.
 - 9.2. Literature searches were conducted using the Ovid search engine from 1996 to March Week 3 2018, limited to English language. The search terms were: Exp pancreatic neoplasms AND DDT or DDE.mp or Dichlorodiphenyl Dichloroethylene/. Articles were selected based on relevance, study quality, reliability and journal authority. The above search was supplemented by PubMed searches for pancreatic cancer and DDT or DDE, internet searches, manual searches of reference lists and extracts from relevant sections of textbooks or International Agency for Research on Cancer (IARC) reports.
 - 9.3. Medical or scientific publications as set out in the bibliography attached hereto.
 - 9.4. A briefing paper concerning malignant neoplasm of the pancreas 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 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

11. DDT was introduced for the control of insect-borne diseases during the Second World War and was later applied widely to eradicate malaria and in agriculture. Although most

uses of DDT were banned from the 1970s, DDT and its breakdown products are highly persistent and can be found in the environment and in animal and human tissues throughout the world. Exposure to DDT still occurs, mainly through diet (IARC 2015). DDT has a long half-life in humans, and the DDT metabolite DDE (dichlorodiphenyl dichloroethylene) is a good indicator of past exposure (Beard et al 2003).

12. Loomis et al (2017) concluded that there is strong evidence that DDT affects several mechanisms that can operate in humans, including immunosuppression, increased oxidative stress, oestrogenic effects and androgen-receptor antagonism. However, evidence of sex-hormone disruption in exposed men and women was unclear. IARC has evaluated DDT as probably carcinogenic to humans (Group 2A), based on sufficient evidence that DDT causes cancer in experimental animals and limited evidence of its carcinogenicity in humans (IARC, 2017). Epidemiological studies found positive associations between exposure to DDT and non-Hodgkin's lymphoma, testicular cancer, and liver cancer, but it was concluded that there was no evidence for an association between pancreatic cancer and exposure to DDT.
13. There were nine comparative studies concerning the association between DDT or DDE exposure and risk of pancreatic cancer, with only one new study (Louis et al 2017) available since the last review.
14. Five of these studies were cohort studies which assessed risks of pancreatic cancer in subjects exposed to DDT through spraying pesticides (Andreotti et al 2009, Cocco et al 2005), being a spouse of a pesticide applicator (Louis et al 2017), using cattle dip (Beard et al 2003) and working in a chemical factory (Garabrant et al 1992). In the studies of agricultural workers (Louis et al 2017, Andreotti et al 2009) exposure to pesticides was assessed by self-report.
15. Of these cohort studies, two found significantly increased risks of pancreatic cancer (Beard et al 2003, Garabrant et al 1992), one found a non-significant decrease in risk (Cocco et al 2005), one found a significant decrease in risk (Andreotti et al 2009) and one was unable to calculate risks as there was only one case of pancreatic cancer (Louis et al 2017). In the study of outdoor cattle dip workers in Australia (Beard et al 2003), risks of pancreatic cancer were significantly increased in those with less than three years of exposure but not in those with 3 or more years of exposure.
16. Four case-control studies concerning the relationship between DDT or DDE exposure and risk of pancreatic cancer measured blood organochlorine levels (Hardell et al 2007, Porta et al 2008, Fryzek et al 1997, Hoppin et al 2000). Two found significant positive associations for DDT or DDE and two found non-significant positive associations. Most of the studies that measured organochlorine levels adjusted for serum lipid levels, as weight loss can cause bioconcentration of analytes, although the necessity and validity of this practice is uncertain (Lopez et al 2014).
17. Of the four studies which examined a dose-response effect (Cocco et al 2005, Hoppin et al 2000, Fryzek et al 1997, Garabrant et al 1992), only one cohort study found such an effect (Garabrant et al 1992).

18. The available evidence had a number of methodological limitations. All of the studies were limited by lack of control for smoking, a known cause of pancreatic cancer, and confounding by simultaneous exposure to multiple chemicals. Another concern was the risk of significant findings occurring by chance due to multiple comparisons of various outcomes and exposure groups. Exposure assessment was imprecise in the cohort studies, especially in the Agricultural Cohort study (Andreotti et al 2009) which relied on self-report. A recent study found that levels of DDT and DDE were not associated with years working in agriculture (Bosch de Basea et al 2011). Porta et al (2008) found that higher concentrations of DDT and other organochlorines were related to lower social class, although the contribution of confounding by this variable was small. Both education and social class influence diet, household conditions and exposure to chemicals in the workplace and in the general environment, which are all known to affect the body burden of persistent organic pollutants.

PART VII SUMMARY AND CONCLUSIONS

19. Overall, results of the available studies are mixed, with four studies showing significant positive associations, three finding non-significant associations and one showing a significant negative association between DDT and risk of pancreatic cancer. The strength of the evidence for causation is reduced by lack of a dose response effect in three of the four studies that assessed this, and concerns about bias and confounding in all of the studies. IARC (2017) does not list pancreatic cancer as one of the cancers contributing to the limited evidence for carcinogenicity in humans. Although there are several mechanisms by which DDT could cause some cancers, the mechanism by which DDT might cause pancreatic cancer in particular is unclear.
20. 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 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 and the disease. In this matter the distinction between those standards of proof is significant.
21. The available sound medical-scientific evidence indicates or points to a causal association between "exposure to DDT" and malignant neoplasm of the pancreas, such being sufficient to support a judgement of a possible causal association. The reasonable hypothesis standard is met and an amended factor will be included in that Statement of Principles.
22. 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 DDT" and malignant neoplasm of the pancreas. The available evidence is therefore insufficient to support a judgement of a probable causal association between "exposure to DDT" and malignant neoplasm of the pancreas, and the balance of probabilities standard cannot be met. In these circumstances no factor can be included in that Statement of Principles.

23. With regard to the wording of factor 6(e) concerning exposure to DDT in the reasonable hypothesis Statement of Principles, Instrument No. 73 of 2013, the Authority decided to amend the wording to express exposure to DDT in terms of the cumulative number of hours of exposure. Expressed in this way, the factor is more flexible with regard to the circumstances of a person's exposure to DDT, and is less open to misinterpretation.

PART VIII DECISION NOT TO AMEND INSTRUMENT NO. 74 OF 2013

24. At its meeting on 11 April 2018 the Authority decided not to amend the balance of probabilities Statement of Principles in respect of malignant neoplasm of the pancreas for the purposes of subsections 196B(3) and (8) of the VEA as the Authority concluded, for the reasons set out above, that the new sound medical-scientific evidence available to it is insufficient to justify the inclusion of a factor relating to exposure to DDT in the balance of probabilities Statement of Principles already determined in respect of malignant neoplasm of the pancreas.



Professor Nicholas Saunders AO
Chairperson
Repatriation Medical Authority

27 April 2018

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