

REPATRIATION MEDICAL AUTHORITY

STATEMENT of REASONS

subsection 196b(9), *Veterans' Entitlements Act 1986*

Decision not to amend the Statements of Principles concerning malignant neoplasm of the BRAIN

Instrument Nos. 85 and 86 of 2016

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1. Introduction
2. On 25 March 2021, the Repatriation Medical Authority (the Authority) received a request from the applicant. The applicant sought a review, by way of an investigation, of the contents of the Statements of Principles (SOPs) concerning malignant neoplasm of the brain (Instrument Nos. 85 and 86 of 2016). The applicant requested that the Authority review the SOPs concerning malignant neoplasm of the brain (Instrument Nos. 85 and 86 of 2016) in relation to the following exposures:
	* pesticides and herbicides; and
	* non-ionising radiation.
3. The request for review was made under s 196E of the *Veterans' Entitlements Act 1986* (the VEA) by an organisation representing veterans, Australian mariners, members of the Forces, members of Peacekeeping Forces, or members within the meaning of the MRCA, or their dependants.
4. At its meeting on 5 May 2021, the Authority decided not to review the contents of the SOPs concerning malignant neoplasm of the brain in relation to herbicides generally or non-ionising radiation. A statement of reasons for this decision was issued to the applicant on 21 May 2021.
5. However, after an initial review of the available sound medical-scientific evidence (SMSE) the Authority decided to conduct a focussed review in relation to exposure to carbamate insecticides and fungicides as a factor for malignant neoplasm of the brain. A notice of investigation advertising this focussed review was published in the Government Notices Gazette on 1 June 2021.
6. Having completed the review, the Authority decided at its meeting on 4 August 2021 not to amend the SOPs concerning malignant neoplasm of the brain to include a factor in relation to exposure to carbamate insecticides and fungicides. This Statement of Reasons provides the Authority's reasons for deciding not to amend the SOPs to include such a factor.
7. Background to the Request
8. The applicant requested that the Authority consider adding the following factors to the SOPs concerning malignant neoplasm of the brain (Instrument Nos. 85 and 86 of 2016):
	* exposure to pesticides and herbicides; and
	* exposure to non-ionising radiation.

Each of these requests was supported by a single ground. However, only the information related to exposure to pesticides and herbicides is presently relevant.

**Pesticides and herbicides**

1. The applicant stated that 'I have been requested by a family member for the RMA to review this SOP as the family member believes that information coming out of the USA supports a (tenuous) link between MN of Brain and pesticide and herbicide exposure'.
2. In support of this ground, the applicant provided three papers published in academic journals[[1]](#footnote-1), and one feature article published in the online news website 'The Daily Beast'[[2]](#footnote-2). The Authority made the following observations in relation to this supporting information:
	* two of the three academic papers addressed malignant neoplasm of the brain in agricultural workers and farmers (Fallahi et al (2017) and Lee et al (2005)), while the third paper (Hagan et al (2017)) was not relevant to the topic of this request;
	* the article in The Daily Beast would not meet the definition of 'sound medical-scientific evidence' (SMSE) in subsection 5AB(2) of the VEA, and it is only SMSE on which the Authority is permitted to rely in forming any view during an investigation (subsection 196C(3), VEA).
3. Consequently, of the information provided in support of the request, the Authority had regard only to the two academic papers (Fallahi et al (2017) and Lee et al (2005)) which were relevant to the topic of the association between exposure to pesticides and herbicides and malignant neoplasm of the brain.
4. Evidence Previously Considered by the Authority
5. At the time that the SOPs concerning malignant neoplasm of the brain(Nos. 85 and 86 of 2016) were determined, the Authority had before it information including:
* briefing papers prepared in October 2016 by a Repatriation Medical Authority medical researcher; and
* an extensive number of articles published in the peer-reviewed literature.
1. New Information Considered by the Authority
2. The information provided by the applicant, identified above, was considered. A discussion paper that considered the information supplied by the applicant and other available relevant SMSE was prepared by a Repatriation Medical Authority medical researcher for the Authority's meeting held on 5 May 2021.
3. A briefing paper providing a more detailed analysis of the current SMSE was prepared by a medical researcher for the Authority's meeting held on 4 August 2021, as part of the focussed review into 'exposure to carbamate insecticides and fungicides' as a factor in malignant neoplasm of the brain.
4. Summary of New and Existing Evidence
5. Findings of the available SMSE that was considered at the last full investigation, as well as recently published reviews and other studies, are insufficient to suggest a causal association between herbicides or specific herbicides and malignant neoplasm of the brain.
6. The American case-control study by Lee et al (2005) cited by the applicant had already been considered in the previous investigation and had significant methodological limitations. Some isolated positive associations were observed in males but not females, most of the positive associations were limited to proxy respondents and the study was retrospective and subject to recall bias. The other article provided by the applicant (Fallahi et al 2017), related to farming as a risk factor without specification of herbicide use.
7. A search of the literature located one cohort study and one case-control study which found significant positive associations between glioma and use of carbamate insecticides (Piel et al 2019a)[[3]](#footnote-3) and specific carbamate insecticides (Piel et al 2019a, Lee et al 2005). One cohort study (Piel et al 2019b)[[4]](#footnote-4) found significant positive associations between glioma and use of carbamate fungicides, as well as specific carbamate fungicides. An earlier study of this cohort (Lemarchand et al 2017)[[5]](#footnote-5) reported that glioma risks were not significantly increased in any category, including those who used pesticides on crops.
8. The two French cohort studies found significant or borderline significant linear trends with duration of use for most individual carbamates. Conversely, a US case-control study (Yiin et al 2012)[[6]](#footnote-6) found no significant positive associations with glioma with cumulative years or estimated lifetime cumulative exposure of any class of farm pesticide, including carbamates.
9. While some studies have found increased risk of gliomas or brain tumours in farmers or in association with pesticide use, particular chemicals remain difficult to identify. A problem with studies of multiple chemical exposures is collinearity; some positive associations could be explained by co-exposures to other carbamates or other chemical groups such as organophosphates, organochlorines or inorganic chemicals.
10. In the French agricultural context 79% of farmers have worked on more than one farming type over their life, thus potentially being exposed to multiple chemicals of different classes and with different effects (Piel et al 2017)[[7]](#footnote-7). Other limitations of these studies are positive findings by chance due to multiple comparisons, and potential confounding from unknown risk factors, radiation exposure, other chemicals or a family history of brain cancer. There is a lack of information on specificities of use like the type of equipment, the duration of treatment days and the use of protective equipment.
11. The biological mechanism by which carbamates might cause brain cancer is not clearly established. Carbamate insecticides are not persistent in the environment and have a low potential for bioaccumulation (Piel et al 2019a). Experimental studies on effects of carbamate herbicides and fungicides in animals have not shown an increased risk of brain tumours (Piel et al 2019b).
12. Overall, the evidence showing an association between carbamate insecticides or fungicides is limited in quality and quantity (Grade 4). Longer follow up of the French cohort study with a comparison across all pesticide groups may help elucidate whether reported associations are specific to carbamates and whether effects persist beyond the initial 7 years of follow up. The authors anticipate more precise exposure metrics including probability, frequency and intensity of use.
13. Findings of Fact
14. In light of the material discussed above, the Authority made the following finding of fact:
	* The body of available SMSE does not support the existence of a causal association between exposure to carbamate insecticides or fungicides and the clinical onset or clinical worsening of malignant neoplasm of the brain. Consequently, the Authority is not satisfied that there is at least a reasonable hypothesis that being exposed to carbamate insecticides or fungicides is a factor which causes, or contributes to, the clinical onset or clinical worsening of malignant neoplasm of the brain.
15. Reasons for the Decision
16. The Authority was cognisant of the provisions of the VEA, and had particular regard to subsection 5AB(2) SMSE, s 5D injury/disease, and Part XIA.

SMSE is defined 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."*

1. The Authority noted sub-sections 196B(7), 196B(8) and 196B(9) and section 196E, which relevantly provide:

196B(7)

*If the Authority:*

*(a) is asked under section 196E to review:*

*(i) some or all of the contents of a Statement of Principles;*

*[…]*

*(b) thinks that there are grounds for such a review;[…]*

*the Authority must, subject to subsection 196C(4) and section 196CA in a case where paragraph (a) applies, carry out an investigation to find out if there is new information available about:*

*(d) how the injury may be suffered, the disease may be contracted or the death may occur; or*

*(e) the extent to which the disease, injury or death may be war-caused or defence-caused.*

196B(8)

*If, after carrying out the investigation, the Authority is of the view that there is a new body of sound medical‑scientific evidence available that, together with the sound medical‑scientific evidence previously considered by the Authority, justifies the making of a Statement of Principles, or an amendment of the Statement of Principles already determined, in respect of that kind of injury, disease or death, the Authority must:*

*(a) […]; or*

*(b) make a determination amending the Statement of Principles determined under subsection (2) or (3) in respect of that kind of injury, disease or death; or*

*(c) […];*

*as the case requires.*

196B(9)

*If, after carrying out the investigation, the Authority is of the view:*

*(a) that there is no new sound medical‑scientific evidence about that kind of injury, disease or death; or*

*(b) that the new sound medical‑scientific evidence available is not sufficient to justify the making of a Statement of Principles, or an amendment of the Statement of Principles already determined in respect of that kind of injury, disease or death;*

*the Authority must make a declaration in writing:*

*(c) stating that it does not propose to make a Statement of Principles, or amend the Statement of Principles already determined (as the case may be); and*

*(d) giving the reasons for its decision.*

196E

*(1) Any of the following:*

*(b) a person eligible to make a claim for a pension under Part II or IV;*

*(ba) a person eligible to make a claim for compensation under section 319 of the MRCA;*

*(c) an organisation representing veterans ….*

*may ask the Repatriation Medical Authority:*

*(f) to review the contents of a Statement of Principles in force under this Part.*

**Basis for commencing review of an existing SOP**

1. It is the applicant's request which prompted the Authority to commence an investigation into this particular factor under s 196B(7)(a) of the VEA.[[8]](#footnote-8)

**Basis for amending an existing SOP**

1. In forming any view during an investigation, the Authority may rely only on SMSE. Subsection 196B(8) provides that where there is a new body of sound medical-scientific evidence available that, together with the sound medical-scientific evidence previously considered by the Authority, justifies the amendment of a SOP the Authority is required to do so. On the other hand where there is no new SMSE or the new SMSE is insufficient to justify an amendment subsection 196B(9) provides that the Authority *must* make a declaration stating that it does not propose to amend the SOP and give reasons for that decision.

**Reasons for deciding not to amend an existing SOP**

1. Together with its own expert knowledge, the Authority took into consideration:
* the information provided by the applicant;
* the information held by the Authority and obtained during its previous investigations leading up to the determination of the SOPs concerning malignant neoplasm of the brain (Instrument Nos. 85 and 86 of 2016); and
* the discussion paper prepared by a medical researcher for the May 2021 meeting;
* the briefing paper prepared by a medical researcher for the August 2021 meeting.
1. As noted above, the applicant relied on the following ground for seeking a review of the contents of the SOPs concerning malignant neoplasm of the brain:
* information coming out of the USA supports a (tenuous) link between malignant neoplasm of the brain and pesticide and herbicide exposure.

*Is there new sound medical-scientific evidence?*

1. Since its previous consideration of the SMSE in relation to pesticide and herbicide exposure, new SMSE concerning exposure to these substances has been published. This new SMSE has been discussed above.

*Is the available sound medical-scientific evidence sufficient to justify amendment?*

1. The Authority is of the view that the currently available SMSE including the new SMSE was not sufficient to justify the amendment which the applicant sought. The available epidemiological studies involve subjects who have been exposed to multiple different chemicals. Some positive associations could be explained by co-exposures to other carbamates, other chemical groups such as organophosphates, organochlorines or inorganic chemicals, or other non-chemical risk factors.
2. Overall, there are significant other limitations of these studies, including positive findings by chance due to multiple comparisons, imprecise exposure assessment, and potential confounding from unknown risk factors, radiation exposure, other chemicals or a family history of brain cancer. There is a lack of information on specificities of use like the type of equipment, the duration of treatment days and the use of protective equipment. There is no established biological mechanism by which carbamates insecticides or fungicides might cause brain cancer.
3. Consequently, the evidence is too equivocal to say with any certainty whether exposure to a carbamate insecticide or fungicide plays a causal role in the clinical onset or worsening of malignant neoplasm of the brain.
4. Conclusions
5. Overall, for the reasons set out above, the available SMSE is not sufficient to justify the amendment of the SOPs concerning malignant neoplasm of the brain by including factors for exposure to carbamate insecticides or fungicides.
6. Decision
7. The Authority decided at its meeting on 4 August 2021 not to amend the SOPs concerning malignant neoplasm of the brain (Instrument Nos. 85 and 86 of 2016) as it considered that the SMSE was not sufficient to justify the amendment sought in the application.

Professor Terence Campbell AM

Chairperson

Repatriation Medical Authority

20 August 2021

1. Fallahi P, Foddis R, Cristaudo A, et al (2017). High risk of brain tumors in farmers: a mini-review of the literature, and report of the results of a case control study. Clin Ter, 168(5): e290-e292. <https://pubmed.ncbi.nlm.nih.gov/29044349/>.

Lee W, Colt J, Heineman E, et al (2005). Agricultural pesticide use and risk of glioma in Nebraska, United States. Occup Environ Med, 62(11): 786-92. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1740883/>.

Hagan K, Bhavsar S, Arunkumar R, et al (2017). Association between perioperative hyperglycemia and survival in patients with glioblastoma. 29(1): 21-9. [www.ncbi.nlm.nih.gov/pubmed/27438798](http://www.ncbi.nlm.nih.gov/pubmed/27438798). [↑](#footnote-ref-1)
2. The Daily Beast (30/03/2021). The last battle of the Vietnam War: Agent Orange and its ‘presumed diseases’. <https://www.thedailybeast.com/the-last-battle-of-the-vietnam-war-agent-orange-and-its-presumed-diseases>. [↑](#footnote-ref-2)
3. Piel C, Pouchieu C, Carles C, et al (2019). Agricultural exposures to carbamate herbicides and fungicides and central nervous system tumour incidence in the cohort AGRICAN. Environ Int, 130: 104876. [↑](#footnote-ref-3)
4. Piel C, Pouchieu C, Migault L, et al (2019). Increased risk of central nervous system tumours with carbamate insecticide use in the prospective cohort AGRICAN. Int J Epidemiol, 48(2): 512-26. [↑](#footnote-ref-4)
5. Lemarchand C, Tual S, Leveque-Morlais N et al (2017). Cancer incidence in the AGRICAN cohort study (2005-2011). Cancer Epidemiol, 49:175–85. [↑](#footnote-ref-5)
6. Yiin JH, Ruder AM, Stewart PA et al (2012). The Upper Midwest health study: a case–control study of pesticide applicators and risk of glioma. Environ Health, 11:39. [↑](#footnote-ref-6)
7. Piel C, Pouchieu C, Tual S, et al (2017). Central nervous system tumors and agricultural exposures in the prospective cohort AGRICAN. Int J Cancer, 141(9):1771-1782. [↑](#footnote-ref-7)
8. It not otherwise being an application within either subsection 196C(4) or section 196CA of the VEA. [↑](#footnote-ref-8)