Vietnam Veterans and Brain Cancer
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VA’s Important Mission

DEPARTMENT OF VETERANS AFFAIRS

TO CARE FOR HIM WHO SHALL HAVE BORNE THE BATTLE AND FOR HIS WIDOW, AND HIS ORPHAN
A. LINCOLN

“I CARE” Values: Integrity, Commitment, Advocacy, Respect, Excellence
Why VA Turns to the Academy?

- In response to public law: “This report is the final of the Veterans and Agent Orange series, which was required by Public Law 102-4, The Agent Orange Act of 1991, and extended by Public Law 107-103. The Secretary of Veterans Affairs was directed to contract with the National Academies to biennially conduct a comprehensive review of scientific and medical literature on health effects from exposure to herbicides used during the Vietnam War.”
  [http://www.nationalacademies.org/hmd/Activities/Veterans/AgentOrangeEleventhUpdate.aspx](http://www.nationalacademies.org/hmd/Activities/Veterans/AgentOrangeEleventhUpdate.aspx)

- The Reports help provide evidence based information for policy decisions - such as advising the Secretary on new disease presumptions. Importantly, however, in that process VA also uses newer research, and any other available information in a multi-step process of review (see VA Directive 0215).

- VA has 14 disease established presumptions with others under consideration at this time.  [https://www.publichealth.va.gov/exposures/agentorange/conditions/](https://www.publichealth.va.gov/exposures/agentorange/conditions/)
Overall Charge to this Committee

The statute directs each new NAS committee to determine, to the extent that scientific data permit:

- Whether there is a statistical association between the specific diseases and herbicide use, taking into account the strength of the scientific evidence and the appropriateness of the methods used to detect the association;

- The increased risk of disease among individuals exposed to herbicides during service in Vietnam; and

- Whether there is a plausible biologic mechanism or other evidence of a causal relationship between herbicide exposure and a disease.
In evaluating the long-term health effects of herbicide exposure among Vietnam War Veterans, the committee should look broadly for relevant information. Information sources to pursue could include, but are not limited to:

- Published peer-reviewed literature related to herbicide exposure among the Vietnam War Veteran population;

- Published peer-reviewed literature related to herbicide exposure among similar populations, such as Allied military personnel; and,

- Published peer-reviewed literature related to herbicides in other populations.
Four “Special Topic” Charges

- [The] National Academies will assess the current research available on possible generational health effects that may be the result of exposures to these chemicals—including the biologic plausibility or potential for an exposure to lead to an increased risk of birth defects or other adverse conditions in the descendants of male Veterans—and will address myeloproliferative neoplasms (MPN) as part of its consideration of the literature concerning leukemias and related diseases. (From the Statement of Work from VA to the National Academies)

- The Committee, with the consent of Dr. David Butler, has also agreed to specifically give “special” emphasis to the study of:
  - Brain Cancer, with an emphasis on Glioblastoma multiforme
  - Monoclonal Gammopathy of Undetermined Significance (MGUS)
How Have These Conditions Primarily Come to the Attention of the VA?

- Intergenerational (especially paternal) potential health effects – PL 114-315, media/press, advocacy, Congressional interest.
  - PL 114-315: *Not later than 180 days after the date of the enactment of this Act, the Secretary of Veterans Affairs shall seek to enter into an agreement with the National Academy of Medicine under which the National Academy of Medicine conducts an assessment on scientific research relating to the descendants of individuals with toxic exposure.* VA has contracted with the NAM to do this under the Gulf War and Health series and the committee’s study is underway.

- MPN – advocacy group

- Brain Cancer/Glioblastoma - media/press, advocacy (including by VSOs), Congressional interest, recent events, e.g. brain cancers - Senator John McCain & Mr. Bo Biden

- MGUS – formal petition for rule making
In Summary About Your Important Role

• VA will likely use the outcomes of committees of the Academies to help make very important policy decisions on disease conditions that affect our Nation’s Veterans.

• VA will now present some data and information on brain cancer.
Examples of what has been in the news:

- “The Agent Orange Widows Club” : After their husbands died of an aggressive brain cancer, the widows of Vietnam veterans have found one another as they fight the VA for benefits: [https://www.propublica.org/article/the-agent-orange-widows-club](https://www.propublica.org/article/the-agent-orange-widows-club)

Comparison Brain Cancer Incidence Rates (Per 100,000)

<table>
<thead>
<tr>
<th>Source</th>
<th>Years</th>
<th>Cohort</th>
<th>Crude</th>
<th>Age Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDHS</td>
<td>2014-15</td>
<td>Vietnam Deployed</td>
<td>7.6</td>
<td>5.4</td>
</tr>
<tr>
<td>PDHS</td>
<td>2014-15</td>
<td>All VHA health-care users</td>
<td>7.2</td>
<td>NA</td>
</tr>
<tr>
<td>PDHS</td>
<td>2014</td>
<td>Gulf War Deployed</td>
<td>5.0</td>
<td>4.1</td>
</tr>
<tr>
<td>SEER</td>
<td>2010-14</td>
<td>US Population</td>
<td>NA</td>
<td>6.4</td>
</tr>
<tr>
<td>CBTRUS</td>
<td>2010-14</td>
<td>US Population</td>
<td>NA</td>
<td>7.2</td>
</tr>
</tbody>
</table>

**PDHS** – Mean rates derived from the 3rd quarter 2014 - 2nd quarter 2015 rates in the PDHS, Post-Deployment Surveillance Report, Dec 2015, Uses VHA Healthcare Utilization Data


**CBTRUS** – Central Brain Tumor Registry accessed at [http://www.cbtrus.org/factsheet/factsheet.html](http://www.cbtrus.org/factsheet/factsheet.html)

(Note in CBTRUS Gliomas CR of 3.46. In the literature the age adjusted incidence rate ranges from: 0.59 to 3.69. It is controversial whether or not the rate of these tumors is increasing. Gliomas are the most common primary intracranial tumor, representing up to 81% of malignant brain tumors. Ostrum et al. Neuro Oncol. 2014 Glioblastoma Multiforme a sub-type is about 52% of malignant tumors.) [http://www.aans.org/Patients/Neurosurgical-Conditions-and-Treatments/Glioblastoma-Multiforme](http://www.aans.org/Patients/Neurosurgical-Conditions-and-Treatments/Glioblastoma-Multiforme)
Veteran Specific Studies

Past VAO committees have carefully reviewed and considered Veteran specific studies. Why?

- **Person:** Veterans - Population of Interest studied
- **Place:** Veterans deployed to geographical regions of known or likely exposure
- **Time:** Definable time period of possible/probable exposure
- **Exposure:** Service in the combat zone or where AO or other herbicides has been used as a proxy for exposure to the Chemicals of Interest (COIs). Example: Studies by Yi et al (2013-2014) analyzing Korean Veterans used an Agent Orange Exposure Opportunity Index based on the proximity of the veteran’s military unit to AO-sprayed areas (Stellman and Stellman, J Expo Ann Env. Epid. 2004).

**Note:** The following slides only consider Veteran studies; however, important and relevant findings may also be found in other occupational or environmental based literature.
Brain Cancer Studies

- **Operation Ranch Hand (ORH) Study**: ORH Veterans (1,189) who sprayed (dioxin) contaminated herbicides in Vietnam. Comparisons (1,176) served in Southeast Asia during the same period but did not spray herbicides. Expected rates in the ORH Veterans was 2.71. **Standardized Incidence Ratios vs. U.S. National Rates** were 1.8 (0.7-4.1) and 0.5 (0.1-1.8) in non-sprayers. Atkhar et al J Occup Environ Med. 2004

- **CDC Study**: Vital status and underlying cause-of-death data on the Vietnam Experience Study cohort (18,313 male US Army veterans) were retrospectively ascertained from 1965 through 2000 and compared to Non-Vietnam Veterans same time-period. **Demonstrated crude Rate Ratio** was 1.2 (0.4-3.2) for brain cancer/meninges/other CNS causes of death. Boehmer et al. Arch Int Med 2004

- **Army Chemical Corps (ACC)**: Mortality in deployed (2,872) vs. non-deployed ACC (2,737) Cypel and Kang Ann Epid 2010 – results through 2005:

<table>
<thead>
<tr>
<th>Test with 95% CI</th>
<th>Number</th>
<th>Crude Rate</th>
<th>Ratio</th>
<th>Adj RR</th>
<th>95% CI</th>
<th>SMR - 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deployed</td>
<td>4</td>
<td>0.4</td>
<td>1.9</td>
<td>1.7</td>
<td>0.3-10.2</td>
<td>0.9 (0.2-2.2)</td>
</tr>
<tr>
<td>Non-Deployed</td>
<td>2</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
<td>0.5 (0.1-2.0)</td>
</tr>
</tbody>
</table>

Crude Rate is per 10,000
Brain Cancer Studies

- **Women Vietnam War Veterans:** Analyzed the data of two cohorts of women veterans who either served in Vietnam (“Vietnam veteran” cohort, n = 4586) or served elsewhere during the Vietnam War (“non-Vietnam veteran” cohort, n = 5325). All cause and cause-specific mortality were compared between Vietnam and non-Vietnam veteran cohorts, to the U.S. population, and to earlier research. Similar analyses were performed for nurses only. (3,690 in Vietnam, 3,283 non-deployed) Two time periods were studied.

<table>
<thead>
<tr>
<th>Study</th>
<th>Time Period</th>
<th>N exp.</th>
<th>RR All</th>
<th>Women</th>
<th>RR Nurses only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cypel et al 2008</td>
<td>thru 2004</td>
<td>8</td>
<td>2.0 (0.7-5.9)</td>
<td>3.6 (0.9-14.5)</td>
<td></td>
</tr>
<tr>
<td>Kang et al 2014*</td>
<td>thru 2010</td>
<td>22</td>
<td>2.3 (0.9-5.7)</td>
<td>4.6 (1.3-16.8)</td>
<td></td>
</tr>
</tbody>
</table>

*Comment on the 2014 study by the committee for VAO 2014: ...* [the study] provides somewhat suggestive evidence of an association however, this was not in the main analysis but only in a sub-analysis. With such a large cohort and scores of comparison, the study is prone to false positives associations, further weakening the conclusions that can be drawn from a particular positive finding.
### Brain Cancer Studies

Three large Korean Veteran Studies have been published by Yi et al between 2013 and 2014 and the authors used the Spellman Exposure Opportunity Index to compare high and low exposure groups. (In the 2013 study, also added a “no exposure” group)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Type</th>
<th>Statistic</th>
<th>OR or RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yi et al 2013</td>
<td>114,562</td>
<td>Prevalence</td>
<td>Self Reported:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>high exp vs. low exp</td>
<td>1.7 (1.3-2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>high vs. no exp</td>
<td>2.7 (1.9-3.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>low vs. no exp</td>
<td>1.3 (0.9-2.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Exposure Model:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>high exp. 4 groups</td>
<td>1.2 (0.8-1.8)</td>
</tr>
<tr>
<td>Yi et al 2014</td>
<td>111,726</td>
<td>Incidence</td>
<td>OR, adjusted</td>
<td>1.0 (0.6-1.7)</td>
</tr>
<tr>
<td>Yi et al 2014</td>
<td>180,639</td>
<td>Mortality</td>
<td>HR, adjusted</td>
<td>1.0 (0.9-1.1)</td>
</tr>
</tbody>
</table>
## Brain Cancer Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>N</th>
<th>Exposed</th>
<th>Cases</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVA 2005</td>
<td>Incidence</td>
<td>59,179</td>
<td>97</td>
<td></td>
<td>1.1 (0.9-1.2)</td>
</tr>
<tr>
<td></td>
<td>1982-2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADVA 2005</td>
<td>Mortality</td>
<td>58,330</td>
<td>99</td>
<td></td>
<td>1.0 (0.8-1.1)</td>
</tr>
<tr>
<td></td>
<td>thru 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADVA Conscripted</td>
<td>Incidence</td>
<td>18,940</td>
<td>Deployed</td>
<td>23</td>
<td>1.4 (0.7-2.6)</td>
</tr>
<tr>
<td></td>
<td>1982-2000</td>
<td></td>
<td>Non-Dep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Army National Service</td>
<td>Mortality</td>
<td>24,642</td>
<td>Non-Dep</td>
<td>27</td>
<td>1.6 (0.9-3.1)</td>
</tr>
<tr>
<td>2005</td>
<td>1966-2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Current/Future Studies with Brain Cancer as a Studied Condition

- **VE-HEROeS** – A 2016-17 survey of a national sample of Vietnam era Veterans compared with age matched non-Veterans to determine current health. Response goals met: 6,735 Vietnam in-theater; 12,131 Vietnam era non-theater, 4,530 non-Veterans. Data in analysis. Results begin publication in later 2018.

- **Vietnam Veteran Mortality Study** – rates, causes, and patterns of mortality from 1979 through 2014 of all Vietnam era Veterans and determine differences between those who served in-theater vs. non-theater. This study is in development.

- **Agent Orange Registry Brain Cancer Study** – Exploratory study with a more definitive study to be planned in near future.

- **Sources of initial data:**
  - Agent Orange Registry n=693,000,
  - National Patient Care Data System Inpatient Encounter
  - Veterans Affairs Central Cancer Registry (1995 to present).

- **Goal** is to assess possible associations based on 3 levels of exposure: (self reported) and will include analysis by major brain cancer types, and select personal and military characteristics.
Potential limitations in the use of registries to draw inferences regarding the presence or strength of an association between an exposure and a health outcome:

- **Self-reporting** - may result in exaggerated or underestimated effect estimates
- **Misclassification** - can result in under or over estimate of effect
- **Recall Bias** - threatens internal validity; may distort the magnitude of estimates
- **Self-selection** - effects representativeness; findings may not be generalizable to the target population
- **Missing data** - limits strength of findings
- **Large populations** - may lead to inflated “statistical significance” but not necessarily clinical relevance
Conclusion

• Studies that examined brain cancer in Vietnam Veterans
  – Most have shown no association between brain cancer and COI
  – Two studies that reported positive associations may be subject to methodological weaknesses

• Studies have not separately reported on Glioblastoma multiforme vs. total brain cancer.

• VA seeks Committee input on this topic and a review of the evidence consistent with their charge

• VA has new studies planned or underway on the Vietnam cohort.

• **We have great empathy and respect for the Veterans and their families that have been given a diagnosis of brain cancer.**
Thank you again for serving on this very important committee

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