Environmental Exposures

Agent Orange exposure and risk of death in Korean Vietnam veterans: Korean Veterans Health Study

Sang-Wook Yi,1 So-Yeon Ryu,2* Heechoul Ohrr3 and Jae-Seok Hong4

1Department of Preventive Medicine and Public Health, Kwandong University College of Medicine, Gangneung, Republic of Korea, 2Department of Preventive Medicine, Chosun University Medical School, Gwangju, Republic of Korea, 3Department of Preventive Medicine and Public Health, Yonsei University College of Medicine, Seoul, Republic of Korea and 4Health Insurance Review and Assessment Service, Seoul, Republic of Korea

*Corresponding author. Department of Preventive Medicine, Chosun University Medical School, 309 Pilmundae-ro, Dong-gu, Gwangju, 501–759, Republic of Korea. E-mail: canrsy@chosun.ac.kr

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Abstract

Background: Agent Orange (AO) was a mixture of phenoxy herbicides, containing several dioxin impurities including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Various military herbicides, including AO, were sprayed by the US military and allied forces for military purposes during the Vietnam War. This study was performed to identify the associations between the AO exposure and mortality in Korean Vietnam veterans.

Methods: From 1 January 1992 to 31 December 2005, 180,639 Korean Vietnam veterans were followed up for vital status and cause of death. The AO exposure index was based on the proximity of the veteran’s unit to AO-sprayed areas, using a geographical information system-based model. The adjusted hazard ratios and 95% confidence intervals were calculated by Cox’s proportional hazard model.

Results: The mortality from all causes of death was elevated with AO exposure. The deaths due to all sites of cancers combined and some specific cancers, including cancers of the stomach, small intestine, liver, larynx, lung, bladder and thyroid gland, as well as chronic myeloid leukaemia, were positively associated with AO exposure. The deaths from angina pectoris, chronic obstructive pulmonary disease and liver disease including liver cirrhosis were also increased with an increasing AO exposure.

Conclusions: Overall, this study suggests that AO/TCDD exposure may account for mortality from various diseases even several decades after exposure. Further research is needed to better understand the long-term effects of AO/TCDD exposure on human health.

Key words: Agent Orange, cohort studies, dioxins, herbicides, Korea, mortality, veterans
Introduction

From 1961 to 1971, the United States and allied military forces sprayed around 77 million litres of herbicides over the former South Vietnam; Agent Orange (AO) was the best known and the most used herbicide.1 AO was a mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), which contained dioxin contaminants including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).2 Despite numerous studies on the environmental and health effects of AO, the effects of the chemicals have not been fully explained.3–11

From 1964 to 1973, around 320 000 military personnel from the Republic of Korea (ROK) were sent to Vietnam.12 Since the mid 1990s, AO-related health issues have been investigated in Korean Vietnam veterans; the relationship between AO and veterans’ health, however, remains inconclusive.12,13 All-cause mortality in Korean Vietnam veterans was lower than expected from the general population,14 and this was explained by a ‘healthy-soldier effect’, in that Vietnam veterans were more fit and healthier than the general population or even than non-Vietnam veterans.3,4,11,14 In populations with a strong healthy-worker effect, the mortality and morbidity of AO exposure among Vietnam veterans should be explored by comparisons between people with high exposure and veterans with low exposure, rather than using the general population. Several studies in Korean Vietnam veterans assessed the exposure to AO based on subjective self-report or crude military information such as the Corps Tactical Zone in which the veterans’ unit had been stationed.13,15 Therefore, some limitations have been noted.12,13

AO exposure has been assessed primarily by the experience of Vietnam service, and the association between potential AO exposure and mortality has been examined in Australian, New Zealand and US Vietnam veterans.3–11 Since the association between AO and morbidity in Vietnam veterans might vary by ethnicity or geographical area,7 exploring the association in Korean Vietnam veterans would be helpful to elucidate this. We constructed the AO exposure index using a geographical information system (GIS)-based model,16,17 which enabled us to estimate potential AO exposure at an individual level and to compare mortality within Vietnam veterans by exposure, rather than using a Vietnam experience-based index.

The aim of this cohort study was to evaluate the association between AO exposure and the risk of death from all causes as well as specific causes of death among Korean Vietnam veterans.

Methods

Study population

The Korean Veterans Health Study (KVHS) was established to evaluate primarily the association between Vietnam War experience and AO exposure, and the morbidities and mortalities from various diseases. In the KVHS study, from November 1999 to April 2000 the authors identified 187 897 veterans and were assured of their official residential status as of March 2000 and June 2004. Since the administrative database of resident registration could not provide complete information on those deceased before 1992, and deaths before 1992 were unidentifiable in the death records of the National Statistical Office, the study cohort was considered to be established as of 1 January 1992. After excluding 7258 individuals who were deceased, had emigrated to another country or had an unknown residence before 1992, or whose exposure to AO was not calculated because of lack of necessary information, finally 180 639 veterans were selected to be followed up for death.

Follow-up and ascertainment of deaths

The deaths of Korean Vietnam veterans and underlying causes of their deaths were ascertained by the 1992–2005 death records of the National Statistical Office. Until 31 December 2005, when veterans died the reported date of death was considered the end of follow-up. When veterans had emigrated to another country or their residential status was unknown during 1992–2005, the changed date of the residential status was considered the date of loss to
follow-up. A complete follow-up was achieved for 177,899 veterans (98.5%). This study was ethically approved by the Institutional Review Board of Kwandong University.

**Classification of causes of death**

The causes of death were classified according to the International Classification of Diseases 10th revision (ICD-10), and we categorized all-causes of death, 15 chapter diseases, 23 specific cancers and 36 specific causes of death other than cancer. Except for congenital malformations and skin diseases, generally, causes of death with 10 or more cases were analysed. Subcategories of leukaemia with five or more cases were segmented by four-character ICD-10 code and included.

**AO exposure assessment**

The AO exposure index was based on the proximity of the veteran’s military unit to AO-sprayed areas, using GIS-based exposure opportunity model E4. Researchers identified the coordinates of the ROK military unit’s post location and tactical area of responsibility during the Vietnam War. The veteran’s deployed unit information was obtained from the Ministry of Defence for the division or brigade level. Each unit’s post location was collected by point coordinates. Each coordinate representing 1 km by 1 km within the units’ tactical area of responsibility was obtained. The coordinate information was sent to Stellman’s team in the USA, and they constructed E4 scores based on the dates and coordinates. Unit-level E4 scores by calendar day were constructed for the Vietnam War period. An individual E4 score was obtained from the unit in which the veteran served and the period of deployment. After adding 1 to each E4 score, the common log-transformed E4 score (Log10E4) was used as the individual’s AO exposure index. The veterans were categorized into two groups, low (Log10E4 < 4.0) and high exposure (Log10E4 ≥ 4.0). The exposure index and group classification are described elsewhere in more detail.

**Statistical analysis**

A Cox proportional hazard regression analysis, controlling for age at cohort entry (as of 1 January 1992) and military rank, was implemented. The hazard ratio (HR) for mortality was calculated using AO exposure as a continuous variable (Log10E4) or by comparing the high-exposure group with the low-exposure group. The military rank was included in the model since it could be a partial reflection of veterans’ socioeconomic status and a confounder for evaluating Korean veterans’ health. Since this veterans’ cohort is a cohort of survivors as of 1992, additional analyses were done in all of the participants with follow-up until 1998, and in survivors as of 1999 with follow-up until 2005, with or without stratification by age at enrolment, to evaluate whether the association of AO exposure differed by follow-up period and age. The P-value was calculated with two-sided tests. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

**Results**

The total follow-up person-years summed to 2,403,799, and 17,529 veterans died during 1992–2005. The average age (SD) for Vietnam veterans was 46.3(3.5) years as of 1 January 1992. The average age in the low- and high-exposure groups was 45.3(3.6) years and 47.5(3.1) years, respectively. The high-exposure group included more combat units and fewer support units, and had fewer officers than the low-exposure group. All veterans deployed in Vietnam from 1971 belonged to the low-exposure group (Table 1).

The risk of all-cause mortality was elevated with AO exposure (Table 2). As for ICD-10 chapter diseases, the risks of deaths from neoplasms, circulatory diseases, digestive diseases and external causes were elevated with an increase of Log10E4, as well as in the high-exposure group compared to the low-exposure group. The risk of death from respiratory disease in the high-exposure group was higher than in the low-exposure group [1.24, 95% confidence interval (CI) = 1.02–1.50] (Table 2).

As for specific cancers, adjusted HRs (aHRs) of stomach cancer, liver cancer, thyroid cancer and chronic myeloid leukaemia increased as the Log10E4 increased, and these were also higher in the high-exposure group than in the low-exposure group (P < 0.05) (Table 3). The aHR of larynx cancer was elevated with an incremental Log10E4, and the aHRs of lung cancer (1.15, 95% CI = 1.02–1.30) and bladder cancer (2.04, 95% CI = 1.17–3.55) were higher in the high-exposure group than in the low-exposure group (Table 3).

In specific causes of death other than cancers, the risks of deaths from angina pectoris, chronic obstructive pulmonary disease (COPD), liver disease, alcoholic liver disease, liver cirrhosis and transport accidents increased with an increasing Log10E4, and these were also higher in high-exposure group compared with the low-exposure group (P < 0.01) (Table 4).

The associations of AO exposure with mortality were generally stronger during the earlier period [aHR for all-cause (1.16) and cancer mortality (1.20)] of follow-up than during the later period [aHR for all-cause (1.06) and...
Table 1. Age and Vietnam service characteristics by Agent Orange exposure among Vietnam veterans (n=180,639)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Classification</th>
<th>n</th>
<th>%</th>
<th>Low exposure</th>
<th>High exposure</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age as of 1 January 1992 (years)</td>
<td>&lt;45</td>
<td>71,014</td>
<td>39.3</td>
<td>59,710</td>
<td>63.1</td>
<td>11,304</td>
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<td></td>
<td>45–49</td>
<td>90,631</td>
<td>50.2</td>
<td>27,144</td>
<td>28.7</td>
<td>63,487</td>
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<tr>
<td></td>
<td>50–54</td>
<td>12,471</td>
<td>6.9</td>
<td>4,446</td>
<td>4.7</td>
<td>8,025</td>
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<tr>
<td></td>
<td>≥55</td>
<td>6,523</td>
<td>3.6</td>
<td>3,319</td>
<td>3.5</td>
<td>3,204</td>
</tr>
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<td>Deployed unit</td>
<td>Capital Division</td>
<td>65,550</td>
<td>36.3</td>
<td>29,906</td>
<td>31.6</td>
<td>35,644</td>
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<td></td>
<td>9th Division</td>
<td>61,209</td>
<td>33.9</td>
<td>31,031</td>
<td>32.8</td>
<td>30,178</td>
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<td>Marine 2nd Brigade</td>
<td>56,080</td>
<td>3.1</td>
<td>27,457</td>
<td>2.9</td>
<td>28,623</td>
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<td></td>
<td>ROK Army Headquarters</td>
<td>51,242</td>
<td>2.8</td>
<td>51,242</td>
<td>5.4</td>
<td>0</td>
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<tr>
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<td>Construction Support Group</td>
<td>9,762</td>
<td>5.4</td>
<td>6,677</td>
<td>7.1</td>
<td>3,085</td>
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<td>Naval Transport Group</td>
<td>56,5</td>
<td>0.3</td>
<td>50,4</td>
<td>0.5</td>
<td>6,1</td>
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<td></td>
<td>100th Logistic Command</td>
<td>31,939</td>
<td>17.7</td>
<td>18,152</td>
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<td></td>
<td>Unknown</td>
<td>882</td>
<td>0.5</td>
<td>480</td>
<td>0.5</td>
<td>402</td>
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<tr>
<td>Military rank</td>
<td>Enlisted</td>
<td>140,480</td>
<td>77.8</td>
<td>73,816</td>
<td>78.0</td>
<td>66,664</td>
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<td></td>
<td>Noncommissioned officer</td>
<td>25,806</td>
<td>14.0</td>
<td>12,460</td>
<td>13.2</td>
<td>12,746</td>
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<td>Company officer</td>
<td>12,209</td>
<td>6.8</td>
<td>6,698</td>
<td>7.1</td>
<td>5,511</td>
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<td>Field officer or general</td>
<td>2,661</td>
<td>1.5</td>
<td>1,645</td>
<td>1.7</td>
<td>1,099</td>
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<tr>
<td>Year first deployed to Vietnam</td>
<td>– 1966</td>
<td>31,427</td>
<td>17.4</td>
<td>10,324</td>
<td>10.9</td>
<td>21,103</td>
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<td></td>
<td>1967–68</td>
<td>49,181</td>
<td>27.2</td>
<td>6,166</td>
<td>6.5</td>
<td>43,015</td>
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<td>1969–70</td>
<td>55,725</td>
<td>30.8</td>
<td>33,823</td>
<td>35.7</td>
<td>21,902</td>
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<tr>
<td></td>
<td>1971–</td>
<td>44,306</td>
<td>24.5</td>
<td>44,306</td>
<td>46.8</td>
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</table>

ROK, Republic of Korea.

Table 2. Numbers of deaths and adjusted hazard ratios for major causes of death according to Agent Orange exposure

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>ICD-10</th>
<th>Total deaths</th>
<th>Log_{10}E4</th>
<th>95% CI</th>
<th>P-value</th>
<th>Low exposure Deaths</th>
<th>High exposure Deaths</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes of death</td>
<td>A00–R99, V01–Y89</td>
<td>17,529</td>
<td>1.03</td>
<td>1.02–1.04</td>
<td>&lt;0.001</td>
<td>7,973</td>
<td>9,556</td>
<td>1.10–1.14</td>
</tr>
<tr>
<td>Infectious and parasitic diseases</td>
<td>A00-B99</td>
<td>377</td>
<td>1.00</td>
<td>0.95–1.05</td>
<td>0.894</td>
<td>181</td>
<td>196</td>
<td>0.84–1.29</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>C00-D48</td>
<td>6,282</td>
<td>1.03</td>
<td>1.02–1.04</td>
<td>&lt;0.001</td>
<td>2,803</td>
<td>3,479</td>
<td>1.13–1.19</td>
</tr>
<tr>
<td>Diseases of the blood and blood-forming organs</td>
<td>D50-D89</td>
<td>24</td>
<td>1.13</td>
<td>0.91–1.39</td>
<td>0.266</td>
<td>10</td>
<td>14</td>
<td>0.56–2.95</td>
</tr>
<tr>
<td>Endocrine diseases</td>
<td>E00-E88</td>
<td>746</td>
<td>1.02</td>
<td>0.98–1.06</td>
<td>0.287</td>
<td>347</td>
<td>399</td>
<td>0.86–1.16</td>
</tr>
<tr>
<td>Mental disorders</td>
<td>F01-F99</td>
<td>237</td>
<td>1.03</td>
<td>0.96–1.10</td>
<td>0.434</td>
<td>113</td>
<td>124</td>
<td>0.82–1.40</td>
</tr>
<tr>
<td>Diseases of the nervous system</td>
<td>G00-G98</td>
<td>140</td>
<td>0.98</td>
<td>0.91–1.07</td>
<td>0.709</td>
<td>68</td>
<td>72</td>
<td>0.68–1.34</td>
</tr>
<tr>
<td>Diseases of the circulatory system</td>
<td>I00-I99</td>
<td>3,180</td>
<td>1.02</td>
<td>1.00–1.04</td>
<td>0.028</td>
<td>1,464</td>
<td>1,716</td>
<td>0.97–1.12</td>
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<td>Diseases of the respiratory system</td>
<td>J00-J99</td>
<td>446</td>
<td>1.04</td>
<td>0.99–1.09</td>
<td>0.084</td>
<td>180</td>
<td>266</td>
<td>1.24–1.50</td>
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<tr>
<td>Diseases of the digestive system</td>
<td>K00-K92</td>
<td>2,222</td>
<td>1.05</td>
<td>1.03–1.08</td>
<td>&lt;0.001</td>
<td>1,005</td>
<td>1,207</td>
<td>1.18–1.29</td>
</tr>
<tr>
<td>Diseases of the skin</td>
<td>L00-L98</td>
<td>9</td>
<td>1.03</td>
<td>0.74–1.44</td>
<td>0.842</td>
<td>4</td>
<td>5</td>
<td>1.21–3.48</td>
</tr>
<tr>
<td>Diseases of the musculoskeletal system</td>
<td>M00-M99</td>
<td>38</td>
<td>0.89</td>
<td>0.76–1.03</td>
<td>0.108</td>
<td>22</td>
<td>16</td>
<td>0.30–1.09</td>
</tr>
<tr>
<td>Diseases of the genitourinary system</td>
<td>N00-N98</td>
<td>190</td>
<td>0.98</td>
<td>0.92–1.05</td>
<td>0.590</td>
<td>92</td>
<td>98</td>
<td>0.71–1.27</td>
</tr>
<tr>
<td>Congenital malformations</td>
<td>Q00-Q99</td>
<td>1</td>
<td>0.78</td>
<td>0.29–2.09</td>
<td>0.617</td>
<td>1</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Symptoms, not elsewhere classified</td>
<td>R00-R99</td>
<td>430</td>
<td>1.04</td>
<td>1.00–1.09</td>
<td>0.077</td>
<td>210</td>
<td>240</td>
<td>1.09–1.33</td>
</tr>
<tr>
<td>External causes of morbidity</td>
<td>V01-Y89</td>
<td>3,197</td>
<td>1.04</td>
<td>1.02–1.06</td>
<td>&lt;0.001</td>
<td>1,473</td>
<td>1,724</td>
<td>1.18–1.27</td>
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</tbody>
</table>

CI, confidence interval; HR, hazard ratio; ICD-10, 10th revision of the International Classification of Diseases.

*AAdjusted for age at cohort entry (as of 1 January 1992) and military rank during service in Vietnam.

Log_{10}E4 is the common log-transformed E4 score which was constructed using a geographical information system-based model grounded in the proximity of the veteran’s military unit to an Agent Orange-sprayed area.

Hazard ratio as 1-point increase in Log_{10}E4.

Compared with the low-exposure group (2-group analysis).
cancer mortality (1.09) when comparing high-exposure group with low-exposure group, and the associations also were generally stronger at younger age (below 45 years) than they were at older age (Supplementary Tables 1–3, available as Supplementary data at IJE online).

**Discussion**

**All causes of death and all cancers combined**

The results showed that a higher AO exposure modestly elevated the risk of all-cause death. Some studies, in which Vietnam veterans were compared with general population, have clearly shown the well-known ‘healthy-soldier effect’, that Vietnam veterans had a lower all-cause mortality than general population.7,11,14 The present study, by comparing the mortality of veterans with that of comparable controls according to AO exposure, may have provided evidence of the toxic effects of AO in accord with studies in US veterans.4,6,10

TCDD has been classified as a carcinogen to humans for all sites of cancer by the International Agency for Research on Cancer (IARC).19 This study showed that the mortality from all cancers combined was increased with TCDD-contaminated AO exposure, which was in line with previous studies regarding occupationally TCDD-exposed workers.20–23

**Gastrointestinal cancers**

Gastrointestinal cancers rarely have been associated with AO/TCDD exposure in previous cohort studies,24 but
### Table 4. Numbers of deaths and adjusted hazard ratios for specific causes of death according to Agent Orange exposure

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</thead>
<tbody>
<tr>
<td>number of deaths n</td>
<td>227 1.00 0.94–1.07 0.974 105</td>
<td>71 1.01 0.90–1.13 0.877 36</td>
<td>58 0.99 0.87–1.13 0.860 31</td>
<td>703 1.02 0.98–1.05 0.414 327</td>
<td>203 1.03 0.96–1.11 0.388 97</td>
<td>192 1.06 0.99–1.14 0.108 82</td>
<td>843 0.99 0.96–1.03 0.729 406</td>
<td>24 1.01 0.98–1.04 0.757 12</td>
<td>332 0.99 0.93–1.03 0.979 12</td>
<td>17 0.94 0.74–1.18 0.591 9</td>
<td>25 1.01 0.83–1.22 0.947 12</td>
<td>6 0.87 0.60–1.35 0.838 3</td>
<td>23 1.14 0.91–1.41 0.255 10</td>
<td>1618 1.01 0.99–1.04 0.353 739</td>
<td>117 1.02 0.93–1.12 0.677 37</td>
<td>82 0.97 0.85–1.08 0.585 41</td>
<td>439 1.07 1.02–1.12 0.007 207</td>
<td>1618 1.01 0.99–1.04 0.353 739</td>
<td>117 1.02 0.93–1.12 0.677 37</td>
<td>82 0.97 0.85–1.08 0.585 41</td>
<td>439 1.07 1.02–1.12 0.007 207</td>
<td>1618 1.01 0.99–1.04 0.353 739</td>
<td>117 1.02 0.93–1.12 0.677 37</td>
<td>82 0.97 0.85–1.08 0.585 41</td>
<td>439 1.07 1.02–1.12 0.007 207</td>
<td>1618 1.01 0.99–1.04 0.353 739</td>
</tr>
<tr>
<td>Log10E4b</td>
<td>1.00 0.94–1.07</td>
<td>1.00 0.94–1.07</td>
<td>0.99 0.96–1.03</td>
<td>1.00 0.99–1.15</td>
<td>1.00 0.99–1.15</td>
<td>1.00 0.99–1.15</td>
<td>1.00 0.99–1.15</td>
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<tr>
<td>Low exposure deaths HRd</td>
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<td>1.00 0.94–1.07</td>
<td>0.99 0.96–1.03</td>
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<td>Low exposure deaths 95% CI</td>
<td>0.974 105</td>
<td>0.877 36</td>
<td>0.860 31</td>
<td>0.414 327</td>
<td>0.388 97</td>
<td>0.108 82</td>
<td>0.729 406</td>
<td>0.757 12</td>
<td>0.979 12</td>
<td>0.99 0.96–1.03</td>
<td>0.877 36</td>
<td>0.860 31</td>
<td>0.388 97</td>
<td>0.108 82</td>
<td>0.353 739</td>
<td>0.677 37</td>
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<td>P-value</td>
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<td>0.877 36</td>
<td>0.860 31</td>
<td>0.414 327</td>
<td>0.388 97</td>
<td>0.108 82</td>
<td>0.729 406</td>
<td>0.757 12</td>
<td>0.979 12</td>
<td>0.99 0.96–1.03</td>
<td>0.877 36</td>
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CI, confidence interval; HR, hazard ratio; ICD-10, 10th revision of the International Classification of Diseases.

*Adjusted for age at cohort entry (as of 1 January 1992) and military rank during service in Vietnam.

*Log10E4 is the common log-transformed E4 score which was constructed using a geographical information system-based model grounded in the proximity of the veteran’s military unit to an Agent Orange-sprayed area.

**Hazard ratio as 1-point increase in Log10E4.

*dCompared with the low-exposure group (2-group analysis).
several case-control studies have reported a positive association mainly with stomach cancer.\textsuperscript{25} The association of stomach cancer in Western populations has been controversial. However, the carcinogenic effects of AO/TCDD exposure on the stomach may be more apparent in the Korean population where stomach cancer is the most common cancer. As shown in the present study, previous research among Korean rural populations also found that high exposure to herbicides (and pesticides) increased cancer incidence of the digestive organs (aHR = 1.5, 95% CI = 1.0–2.3) including stomach (aHR = 1.6, 95% CI = 0.9–2.8) and liver (aHR = 2.0, 95% CI = 0.7–5.9) cancer.\textsuperscript{26} However, the possibility that the low excess risk of stomach cancer in the present study might be accounted for uncontrolled confounding by important risk factors such as \textit{Helicobacter pylori}, smoking and diet should not be overlooked. Meanwhile, the present study showed that the death rate from small intestine cancer was higher in the high-exposure group (aHR = 2.88, 95% CI = 1.00–8.28); the association of small intestine cancer has rarely been examined in previous studies.\textsuperscript{20,27}

Liver cancer and liver diseases

Few studies have reported the positive association between AO/TCDD exposure and hepatobiliary cancers in Vietnam veterans or among occupational cohorts,\textsuperscript{28,29} whereas TCDD is an established carcinogen in animal models.\textsuperscript{30} Inconsistent hepatotoxicity in previous human studies has been explained by various reasons such as the lack of good measures of exposure, a small number of subjects or not applying dose-response types of analysis.\textsuperscript{31} However, the present study revealed a meaningful association between AO exposure and deaths from liver cancer, in line with another Korean study,\textsuperscript{26} based in part on a large number of deaths from liver cancer\textsuperscript{32} and a dose-response analysis of individual exposure assessment.

The hepatotoxicity of TCDD is manifested by hypertrophy, necrosis, fatty degeneration, inflammation, hepatic lipid peroxidation and porphyria of liver cells.\textsuperscript{31,33–36} The prevalence of liver diseases including liver cirrhosis has been associated with possible AO exposure in Vietnam veterans,\textsuperscript{2,37} whereas mortality from liver diseases has rarely been associated with AO.\textsuperscript{4,6,24} The current study showed that the risk of deaths from liver diseases including alcoholic liver diseases and liver cirrhosis was elevated with AO exposure. The prevalences of chronic hepatic viral infection including hepatitis B and C and alcohol drinking, known risk factors of hepatocellular carcinoma and liver cirrhosis, are much higher in Korea than in Western countries.\textsuperscript{38} The hepatotoxicity of AO/TCDD might be confounded by chronic hepatic infection and alcohol drinking, which were not adjusted for in the present study. Further research may reveal the mechanism of hepatotoxic effects of AO in more detail.

Other sites of cancer

Our study found a modestly higher mortality from lung cancer with AO exposure, in accordance with previous research,\textsuperscript{19} whereas our results did not find association between potential TCDD exposure and soft tissue sarcoma (ICD-10, C47 + C49: aHR = 0.96, 95% CI = 0.33–2.80 in high-exposure group compared to low-exposure group) that was suggested in previous studies.\textsuperscript{19,24}

The risk of death from bladder cancer in the high-exposure group was higher than in the low-exposure group in this study. Even though bladder cancer is the most common genitourinary cancer, the relationship between occupational and environmental exposure to dioxin-related chemicals and bladder cancer has not been fully elucidated.\textsuperscript{29,39–41} Meanwhile cacodylic acid, which was one of the organo-arsenic compounds in military herbicides, has been known to induce bladder tumours in animal experiments,\textsuperscript{42} and exposure to arsenic has been linked with bladder cancer.\textsuperscript{43}

This study found that a greater exposure to AO was significantly related to a greater mortality from thyroid cancer. The more the TCDD contamination in the residential area, the higher the incidence of thyroid cancer was in Seveso residents ($P > 0.05$).\textsuperscript{41} In animal experiments, 2,4-D and 2,4,5-T were suggested to be mutagenic or carcinogenic to the thyroid,\textsuperscript{44–46} but conclusive evidence of AO/TCDD as a carcinogen to the human thyroid has been lacking. Further research into the histological type of thyroid cancer may elucidate the effects of AO-related chemicals on the thyroid gland.

Non-Hodgkin lymphoma (NHL) has been tentatively associated with TCDD exposure.\textsuperscript{19} In the present study, the mortality from NHL was modestly higher in the high-exposure group (aHR = 1.2, 95% CI = 0.8–1.8) than in the low-exposure group, whereas the mortality from chronic myeloid leukaemia was strongly elevated with AO exposure (aHR = 7.9, 95% CI = 1.7–37.5 in the high-exposure group). Few prospective studies have examined the association between AO/TCDD exposure and leukaemia and the results have been inconclusive.\textsuperscript{24} Our results may indicate new grounds for suggesting carcinogenic effects of AO/TCDD exposure on myeloid leukaemia. Further research is needed to confirm this association.

Non-cancerous causes of death other than liver diseases

In this study, the mortality from angina and other heart diseases was associated with AO exposure but deaths from
hypothesis and myocardial infarction were not associated with AO exposure. A few studies have reported significant associations between AO-related chemicals and circulatory diseases, including hypertension and ischaemic heart disease, but the association remains unclear. Therefore further investigation is needed.

The risk of death from chronic obstructive pulmonary disease (COPD) had a positive relationship with AO exposure (aHR = 1.73, 95% CI = 1.16–2.60 in the high-exposure group compared with the low-exposure group). The association between environmental and occupational exposure to AO/TCDD and non-malignant respiratory diseases has been reported in previous research, but the findings have not been consistent in Vietnam veterans. However, the present study did not adjust for smoking, an important risk factor for COPD. Our results, nevertheless, could provide valuable evidence of the harmful effects of AO/TCDD to lung tissue. Mortality from asthma, however, was not associated with AO exposure. The different inflammatory processes affecting COPD and asthma might result in different associations with AO exposure.

An incremental exposure to AO led to an increased risk of death from external causes, especially transport accidents and falls. Vietnam veterans, compared with non-Vietnam veterans or general population, had higher mortality from some external causes such as transport accidents, intoxication and suicide. This can be explained by the illegal use of drugs and posttraumatic stress disorder (PTSD), both of which were related to the war experience. However, current research could not confirm whether high-exposure group had more severe war experience, PTSD or drug addiction than the low-exposure group.

Limitations and strengths of the study

This study, however, has some limitations. First, our cohort was constructed among survivors as of 1 January 1992, when at least 19 years had passed since the veterans had returned from Vietnam. Our results showed that HRs of AO exposure were generally higher during the earlier period of follow-up than during the later period, and they also were generally higher in veterans aged below 45 years than in those aged 45 and above at enrolment (Supplementary Tables 1–3, available as Supplementary data at IJE online). Furthermore, among younger veterans less than 45 years old, aHRs for leukaemia and NHL, two cancers with short latency, were higher in [2.4 (95% CI = 1.1–5.4) and 1.8 (95% CI = 0.8–4.4), respectively] the high-exposure group relative to the low-exposure group; whereas among veterans aged 45 years or above as of 1992, they were not higher [1.04 (95% CI = 0.6–1.7) and 0.96 (95% CI = 0.6–1.6), respectively]. Therefore, there is a possibility that vulnerable veterans with high AO exposure and subsequent consequences may have died before 1992, at a young age. In such cases, the risk of AO exposure may be underestimated in this study, especially for diseases with short latency and high fatality such as lymphohaematopoietic malignancies.

Second, the present assessment of AO exposure has some limitations in accuracy and precision, especially compared with other studies in which exposure was validated with levels of target chemicals in human tissue. However, we believe that this GIS-based exposure index is more valid and reliable than assessments based on subjective self-report or Vietnam experience. On the other hand, non-differential misclassification of the exposure index was possible in this exposure assessment, which may have biased the estimation of the hazard ratios toward the null.

Third, some important risk factors of death, such as smoking (e.g. for lung cancer and COPD), drinking (e.g. for liver cancer and liver diseases) and obesity (e.g. for cardiovascular diseases and diabetes) were not adjusted for. However neither smoking, alcohol drinking nor obesity were prevalent in the high-exposure group compared with the low-exposure group in Korean Vietnam veterans, and we believe that not adjusting for those variables in this study would not overestimate the effects of the AO exposure. Nonetheless, not adjusting for those variables as well as other specific risk factors for some causes of death (e.g. H. pylori infection for stomach cancer, and infection with chronic hepatitis virus and liver fluke for liver cancer) is a potential limitation of the study.

Fourth, information on occupational or environmental exposure to herbicides/TCDD, such as use of herbicides and food consumption, was not controlled for.

Fifth, as a mortality study, our results may be different from those of incidence or prevalence studies, especially in diseases with low severity and long survival time, since the severity of diseases and treatment-related factors may affect the estimated risk of death from some diseases.

Despite these limitations, this study has several strengths, including a large-sized cohort, a nearly complete follow-up over a long period and the use of an internal comparison group by exposure level rather than with the general population. Therefore, our results may provide meaningful evidence for the effects of AO/TCDD exposure on human health, such as deaths from various cancers, angina, COPD and liver diseases, some of which have rarely been examined.

Conclusion

This study showed that the mortality from all cancers combined was positively associated with AO exposure, which
generally supports TCDD as a human carcinogen. The mortality from cancers of the stomach, liver, larynx, lung, bladder and thyroid gland, and chronic myeloid leukaemia, was also positively associated with AO exposure. An elevated mortality from COPD with an increasing AO exposure was found and generally concurs with the potential effect of TCDD on lung tissue. A subtle excess mortality from liver cirrhosis, as well as the aforementioned liver cancer with AO exposure, was observed. However, the clear interpretation of some results may be limited for the various reasons that readers should note. Further research is needed to better understand the long-term effects of AO/TCDD exposure on human health.

**Supplementary Data**

Supplementary data are available at IJE online.

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**Specific author contributions**

Drafting the manuscript (including checking the references) and guarantor for the paper: S.Y and S.R.; performing statistical analysis and interpretation of the results: S.Y.; reviewing the literature and revising the manuscript critically: H.O.; reviewing the literatures, interpreting the results and editing the manuscripts: J.H.; all the authors approved the final draft.

**Conflict of interest:** None declared.

**References**


