

Is Agent Orange exposure associated with Waldenström's macroglobulinemia and related plasma cell disorders?

Ola Landgren, MD, PhD¹

¹Myeloma Service, Memorial Sloan Kettering Cancer Center, New York, NY

Agent Orange was used by the US Air Force personnel who conducted aerial spray missions of herbicides (Operation Ranch Hand) in the Vietnam War from 1962 to 1971. The main ingredients of Agent Orange were 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), but the human carcinogen tetrachlorodibenzo-p-dioxin (TCDD) was also present in variable amounts as a contaminant. The measurement of serum TCDD levels in the Ranch Hand personnel confirmed TCDD exposure, raising concerns regarding long-term health effects from Agent Orange and TCDD. The Air Force Health Study (AFHS) that began in 1982 included multiple myeloma and other relatively rare cancers as end points, but it lacked statistical power to assess the excess risk associated with Agent Orange/TCDD exposure in the Ranch Hand cohort. A series of reports from the Institute of Medicine (IOM) from 1994 to 2013 addressed these concerns by reviewing available literature and drawing conclusions from the overall evidence. The IOM reports identified 7 specific types of cancer for which the evidence of a positive association with Agent Orange/TCDD exposure was considered sufficient or at least limited or suggestive. Four of these were B-cell lymphoid malignant neoplasms; the evidence was sufficient for chronic lymphocytic leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma, whereas the evidence was only limited or suggestive for multiple myeloma. All 7 types of cancer were recognized by the US Department of Veterans Affairs and federal law as presumptive conditions for the purposes of health care and disability compensation.

Occupational studies have shown that other pesticides (i.e., insecticides, herbicides, fungicides) are associated with excess risk of multiple myeloma and its precursor state, monoclonal gammopathy of undetermined significance (MGUS). To examine the relationship between MGUS and exposure to Agent Orange, including its contaminant 2,3,7,8-TCDD, in Vietnam War veterans we conducted a prospective cohort study where we tested for MGUS in serum specimens collected and stored in 2002 by the Air Force Health Study (AFHS) (Landgren et al, *JAMA Oncology*. 2015 Nov;1(8):1061-8). We tested all specimens without knowledge of the exposure status. The AFHS included former US Air Force personnel who participated in

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Operation Ranch Hand (Ranch Hand veterans) and other US Air Force personnel who had similar duties in Southeast Asia during the same time period (1962 to 1971) but were not involved in herbicide spray missions (comparison veterans). In our study, we included 479 Ranch Hand veterans and 479 comparison veterans who participated in the 2002 follow-up examination of AFHS. The crude prevalence of overall MGUS was 7.1% (34 of 479) in Ranch Hand veterans and 3.1% (15 of 479) in comparison veterans. This translated into a 2.4-fold increased risk for MGUS in Ranch Hand veterans than comparison veterans (adjusted OR, 2.37; 95% CI, 1.27-4.44; P=0.007). Our work shows that Operation Ranch Hand veterans have a significantly increased risk of MGUS, supporting an association between Agent Orange exposure and multiple myeloma.