

THE USE OF AGENT ORANGE IN VIETNAM : ASSESSMENT OF IMPACT ON VETERANS

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This Session on Agent Orange continues the dialogue on the potential impact of Agent Orange on veterans who served in Vietnam during the Vietnam Conflict. The session is timely because more than 30 years has elapsed since the last mission of spraying Agent Orange in Vietnam, and more than 20 years has elapsed since the topic was first discussed at DIOXIN 1981. In the intervening years, hundreds of human-health studies have been conducted on the phenoxy herbicides, dioxins, and related compounds. Much of this research has been large epidemiological studies of Vietnam veterans. Comprehensive reviews and discussion of key studies and health issues as they apply to veterans are appropriate.

The first presentation in this Session will be given by Dr. Alvin Young. He will discuss the **“Operational Use of Herbicides in Vietnam 1962-1971”**. Dr. Young will discuss the available literature on the type of herbicide, pattern of use, dates and location of spraying, aircraft or ground equipment used, the approval process for deployment of aircraft and herbicides, and the use of insecticides. Photographs of various operational activities will provide a perspective of how and where Agent Orange was used. The use of herbicides in the Republic of Vietnam removed foliage along thoroughfares, defoliated areas surrounding bases and communication routes, improved visibility in heavily canopied jungle, and destroyed enemy subsistence crops. The chemicals of choice were the phenoxy and arsenical herbicides. In January 1965, the military herbicide code-named “Orange”, subsequently known as “Agent Orange” was introduced into the Conflict. Orange was a 50:50 mixture of the n-butyl esters of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The 2, 4,5-T manufacturing process generates small quantities of 2,3,7,8-tetrachloro-dibenzo-p-dioxin as an unwanted but unavoidable byproduct. From January 1965 to April 1970, more than 42 million liters of Agent Orange were sprayed in military operations on over a million hectares in South Vietnam. During this same period, several nations provided combat troops to support the Army of Vietnam. Australia and New Zealand deployed 46,852 combat troops. The Republic of Korea deployed 312,853 combat troops, and the United States deployed 2.64 million military personnel. The number of combat troops engaged in the war from the Republic of Vietnam, the National Liberation Front of South Vietnam and from the Democratic Republic of Vietnam is not known, but was likely in the multi-millions. Subsequent analysis of Agent Orange returned from Vietnam in 1972 and from surplus inventory stored in the United States, showed levels of TCDD varying from 0.02 to 47 ppm.

The second presentation will be given by Professor Michael Newton from Oregon State University. He will discuss **“The Vietnam Defoliation Environment and Opportunity for Human**

Exposure". Dr. Newton provided his expertise in forestry and exposure to herbicides to the United States' National Academy of Sciences study of "The Effects of Herbicides in South Vietnam. Dr. Newton will discuss the varieties of forests and vegetation in Vietnam, the efficacy of herbicides as defoliants in Vietnam, and numerous additional specific factors affecting the potential exposure of military units/personnel.

Dr. Newton will also discuss the various potential routes of exposure to herbicides used in Vietnam. Dr. Newton concludes that opportunities for potential exposure of military personnel in the field to Agent Orange were very limited. This conclusion is consistent with studies reporting that military troops who served in Vietnam have normal background levels of TCDD comparable to those seen in veterans not involved in the spraying or handling of Agent Orange.

The third presentation will be given by Dr. Joel E. Michalek from the United States Air Force Research Laboratory, Brooks Air Force Base, San Antonio, Texas. He will present "**The Air Force Health Study: A Summary of Results**". To address concerns of veterans regarding the consequences of exposure to Agent Orange and its TCDD contaminant, the Air Force Health Study was initiated in 1978 to evaluate the health, survival and reproductive experience of veterans of Operation RANCH HAND, the unit responsible for the aerial spraying of herbicides in Vietnam from 1962 to 1971. The study includes periodic analyses of post-service mortality, physical examinations, in-person interviews, medical record retrievals, and psychological testing. Physical examinations were administered to the 1,000 RANCH HAND veterans and 1,300 Comparison veterans in 1982, 1985, 1987, 1992 and 1997. A final examination is planned for 2002, a potential latency period of 40 years from the first aerial mission of Operation RANCH HAND in Vietnam.

Ninety-nine percent of the RANCH HAND serum dioxin levels in 1987 were less than 200 parts-per-trillion (ppt), while 99 percent of the Comparison group had levels less than 13 ppt. Mortality data published in 1998 confirmed that as a group RANCH HAND veterans were not experiencing an increased risk of death. Morbidity studies have provided evidence of a potential adverse relation between dioxin and diabetes. No consistent or meaningful relation has been established between dioxin body burden and cancer, or dioxin exposure and immune system alteration. These and other findings will be discussed.

The fourth presentation will be given by Dr. Han K. Kang from the United States Department of Veterans Affairs, Washington, DC. He will present the "**Health Status of U.S. Army Chemical Corps Vietnam-Era Veterans Relative to Current Serum Dioxin Concentrations**". Members of the United States Army Chemical Corps were responsible for the storage, preparation, and spraying of herbicides around the perimeters of base camps and for the aerial spraying from helicopters. This presentation will describe the preliminary study results for selected health outcomes among the 2,927 veterans who completed the telephone interview and 385 serum assessments by the Centers for Disease Control and Prevention (CDC). Of the 385 dioxin assessments, 332 were Vietnam veterans and 53 were among non-Vietnam veterans. The mean 2,3,7,8-TCDD concentration was 3.63 ppt among the Vietnam veterans compared to a mean value of 2.20 ppt among the non-Vietnam veterans. A t-test of the means showed that the difference in the means was statistically significant at the .05 level. Grouping the Vietnam veterans by TCDD concentrations (low and high, i.e., a mean of 1.79 ppt vs. 7.49 ppt) allowed for the assessment of the risk of certain diseases relative to a specific exposure. Results indicated that the odds ratio for

diabetes in the high TCDD group compared to the low group was statistically significant. None of the other 6 conditions examined were significantly different from unity except for cancer, which showed a significant deficit among the high TCDD concentration Vietnam veterans compared to low TCDD concentration Vietnam Veterans. The significance of these and other observations as well as suggestions for future studies will be discussed.

The fifth presentation will be by Dr. Jack Mandel, from Exponent Inc., Menlo Park, California. He will present "**Epidemiology Studies of Vietnam Veterans: A Critical Review**". As noted earlier, a number of epidemiologic studies of Vietnam veterans have been conducted to evaluate whether there is a causal relationship between exposure to Agent Orange and human health effects. In addition to the studies of RANCH HAND and Army Chemical Corps personnel, other veteran groups have been examined including Australian National Servicemen, Korean Vietnam Veterans, and additional studies of United States veterans conducted by the CDC and the Department of Veterans Affairs. These studies have provided considerable data on the health status of veterans. However, all of these studies are observational and therefore warrant careful attention with respect to bias and confounding. In particular, these studies must be carefully evaluated on: (1) selection of participants; (2) quality of exposure data; (3) methods of outcome ascertainment; (4) appropriateness of statistical analyses; and (5) validity of the authors' conclusions. The specific methodological issues will be assessed and discussed in terms of their impact on the results of the specific studies and on the overall interpretation of the major studies of Vietnam veterans. Dr. Mandel concludes that these studies do not establish a cause and effect relationship between exposure of veterans to Agent Orange and human health effects.

The final three presentations will be by Professor Hans-Olov Adami, Department of Medical Epidemiology, Karolinska Institute, Sweden, and the Harvard School of Public Health; Professor Philip Guzelian, University of Colorado Health Sciences Center, Denver, Colorado; and Professor Dimitrios Trichopoulos, Department of Epidemiology, Harvard School of Public Health. Each of these speakers will critically examine specific health issues attributed in the public literature to Dioxin and/or exposure to Agent Orange.

Professor Adami will address the issue "**Can Studies by a Single Investigator Override Collective Evidence? The Case of Dioxin**". Dr. Adami notes that the epidemiologic evidence that dioxin may increase cancer risk in humans comes largely from one investigator. Dr. Adami identifies numerous sources of potential bias and confounding in that investigator's studies, including case-control design, variations in study base, recall bias, other potential environmental and occupational exposures, and life style factors. The potential role of chance is evaluated in light of the small numbers of study participants and the lack of clear dose response relationship. Analysis of these factors suggests the possibility that the imperfect methodology of the studies resulted in systematically exaggerated risk estimates. Dr. Adami concludes that more ambitious studies would be needed to demonstrate whether or not dioxin is associated with cancer in humans and outlines methodological requirements for such studies.

Professor Guzelian will discuss "**Implications for Veterans of Liver Findings in Humans and Animals Exposed to High Levels of TCDD**". It has become apparent that hepatic effects in animals given TCDD are variable among species and depend on the age, sex, strain, and species. In light of this variability, scientists have struggled to understand the relevance to humans of the

various animal studies. To understand the relevance to humans, Dr. Guzelian will focus on studies of individuals with the highest doses of TCDD, and will evaluate the liver findings according to accepted causation criteria, e.g., Hill's criteria of consistency, strength, dose-response, coherence, and specificity. The populations studied will include occupational cohorts in the United States and Germany, the accident cohort in Seveso, Italy, and the RANCH HAND veteran cohort. Animal and human data regarding enlargement of the liver, enzyme induction, AST/ALT levels, porphyria, and liver cancer will be analyzed. Dr. Guzelian concludes that such analysis fails to establish a cause and effect relationship between TCDD and liver toxicity in humans.

Lastly, Professor Trichopolous will address the issue of cancer in his presentation titled "**No Evidence that Dioxin is a Human Carcinogen**". Dr. Trichopolous will challenge the International Agency for Research on Cancer's conclusions linking TCDD with cancer and on TCDD's possible mode of action as a carcinogen. Mechanistic considerations involving the Ah receptor do not support a conclusion that dioxin is a human carcinogen because of the lack of evidence that this receptor plays a crucial role for carcinogenicity. Attempts to generalize from the available animal evidence are severely limited because of large inter-species variation. The Seveso studies indicate that confounding by smoking and other factors has not received sufficient consideration. Even the few positive epidemiological studies of cancer in TCDD exposed populations report a minimal increase in total cancer. The overriding weight of epidemiological evidence does not support human carcinogenicity and such evidence should take precedence over mechanistic considerations and animal data of uncertain import. Dr. Trichopoulos therefore concludes that there is persuasive evidence that TCDD at low levels is not carcinogenic to humans and that it may not be carcinogenic even at high levels.