From: Sampsel, James, VBAVACO
To: Flynn, Mary A. (SES), VBAVACO
Cc: Flohr, Brad (SES EQV), VBAVACO; Imboden, Jacqueline, VBAVACO
Subject: FW: Ao Exposure Data _Veterans Integrated Service Network
Date: Wednesday, May 15, 2013 3:00:00 PM
Attachments: Ansbaugh_et_al_2013_Cancer_preprint_AO__prostate_cancer_Prepub.pdf
7003._Historical_Records.pdf
7004.Environmental_Fate.pdf

FYI. This study comes from a VHA center in Oregon and one of its authors is supporting Wes Carter and the post-Vietnam C-123 aircrews.

From: Alvin Young [maExemption 6 [redacted]]
Sent: Wednesday, May 15, 2013 2:19 PM
To: Walters, Terry; Peterson, Michael (VHACO) (SES EQV)
Cc: Kang, Han (VHACO); Sampsel, James, VBAVACO; Irons, Terra; Exemption 6 [redacted]; Pharr, Michael, VBAVACO
Subject: Ao Exposure Data _Veterans Integrated Service Network

15 May 2013

Dear Dr. Walters and Dr. Peterson,

I have attached the recent (May 2013) article on "***Agent Orange as a Risk Factor for High-grade Prostate*** Cancer" co-authored by personnel from the Portland Veterans Affairs Medical Center.

I am very concerned about how these scientists determined exposure to Agent Orange. Can you please provide information to me on the "Veterans Integrated Service Network 20 data warehouse" or as also described in the article "Veterans Integrated Service Network 20 Consumer Health Information Performance Sets Data Warehouse". My experiences with the Agent Orange Registry and the Stellman Model are that both approaches have significant problems in determining if actual exposure did occur in Vietnam (much is self reporting). Obviously the Air Force Health Study, the CDC Vietnam Veterans Studies, and Industrial Studies certainly don't support the conclusion that dioxin (TCDD) is responsible for the results reported in this article. What does make sense is that the study is really showing differences in combat vs non-combat settings, and has nothing to do with Agent Orange exposure. Thus, it is of great importance that we determine the basis for concluding that the Veterans Intergrated Service Network can distinguish between exposed and non-exposed veterans to Agent Orange.

This publication certainly complicates the issue of Agent Orange for the Department. It is clear the VA researchers do not understand what really occurred in Vietnam and that the likelihood of exposure to Agent Orange was essentially negligible, especially when you consider what level of exposure would be needed to produce a dose of any significance RE: TCDD. Historical records and environmental fate studies support the conclusion that our troops were never at a significant risk for exposure to Agent Orange (see attached articles).

As you are aware, I am currently preparing monthly reports for the Compensation Services (**Agent Orange Investigative Report Series**) under contract. I have prepared seven reports to date, including one on 2,4,5-T. My current report for May 2013 is on "**Investigation into Sites Where Agent Orange Exposure has been Alleged** (Outside of Vietnam)." Mr. Sampsel determines the monthly topic for a report. Perhaps a report detailing the issue of exposure and dose and what we know from the historical records and other sources would be a report helpful to VA researchers.

Sincerely,

Dr. Young

Alvin L. Young, PhD
Environmental Toxicologist
Colonel, USAF (Retired)
A.L. Young Consulting, Inc.
Cheyenne, WY
[redacted]

Discussion Articles

Assessing Possible Exposures of Ground Troops to Agent Orange During the Vietnam War: The Use of Contemporary Military Records

Alvin L. Young[1]*, Paul F. Cecil, Sr.[2] and John F. Guilmartin, Jr.[3]

[1] Institute of Science and Public Policy, The University of Oklahoma, Norman, Oklahoma, USA
[2] Historian and Archivist, The RANCH HAND Vietnam Association, Fort Walton Beach, Florida, USA
[3] Department of History, The Ohio State University, Columbus, Ohio, USA

* Corresponding author (youngrisk@aol.com)

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Abstract

Background. Potential exposure of ground troops in Vietnam to Agent Orange and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) remains controversial despite the passage of 30 years since the Vietnam War. Because of uncertainty over the serum dioxin levels in ground troops at the end of their service in Vietnam, attempts have been made to develop a methodology for characterizing exposure of ground troops in Vietnam to Agent Orange and other herbicides based upon historical reconstruction from military records. Historical information is often useful in evaluating and modeling exposure, but such information should be reasonably accurate, complete, and reliable.

Methods. This paper reviews the procedures and supporting historical information related to the spraying of herbicides in Vietnam. The historical information is classified into two categories: procedural information and operational information. Procedural information covered the process and procedures followed in spraying herbicides from US Air Force fixed wing aircraft (Operation RANCH HAND) in Vietnam, and included approval procedures for spray missions, the criteria required to conduct a mission, the control exercised by the Forward Air Controller and the Tactical Air Control Center and the characteristics of the equipment used to apply the herbicides. Operational information includes data from the RANCH HAND Daily Air Activities Reports, which included geographic locations of specific spray missions, the amount of herbicide sprayed by a specific mission, reports of battle damage to spray aircraft, reports of fighter aircraft support for aerial spray missions, and any comments, such as reasons for canceling a mission.

Results. Historical information demonstrates that herbicide spray missions were carefully planned and that spraying only occurred when friendly forces were not located in the target area. RANCH HAND spray missions were either not approved or cancelled if approved when there were friendly forces in the area designated for spraying. Stringent criteria had to be met before spray missions could be approved. The operational information shows that spray missions for both defoliation and crop destruction were conducted in an extremely hostile environment. Heavy 'fighter suppression' with antipersonnel ordnance was used to minimize the impact of hostile ground fire on RANCH HAND aircraft. Procedures were in place that prohibited movement of troops into sprayed areas immediately after a mission due to the possible presence of unexploded ordnance delivered by fighter aircraft supporting RANCH HAND missions. The optimal nature of the spray equipment and application procedures minimized the possibility of significant spray drift.

Conclusions. Few friendly troops were sprayed by fixed wing aircraft during Operation RANCH HAND, which delivered 95% of all defoliants used in Vietnam. Similarly, few troops were sprayed during helicopter or surface-based spray operations, which constituted the remaining 5% of defoliants. Detailed policies and procedures for approval and execution of spray missions ensured that friendly forces were not located in the areas targeted for spraying. Fighter aircraft assigned to accompany each spray mission frequently suppressed much of the hostile fire with bombs and other ordnance. Confirmed clearance of the target area was necessary to avoid friendly casualties. Historical records establish that these policies and procedures were strictly followed. Exposure of troops whether from direct spraying or movement through areas recently sprayed was very unlikely.

The wartime military records of troop positions and herbicide operations are valuable for some purposes, but have specific limitations in exposure reconstruction. The completeness and accuracy of the geographic data (maps used by RANCH HAND and military ground units) were dependent upon the inherent precision of the map, the accuracy with which it depicted surface features, and the completeness and accuracy of the information on which it is based. Navigation by the crew using visual orientation and reference to the map was the only means that aircrew on spray missions had for establishing their locations. A Forward Air Controller independent of Operation RANCH HAND was present at the location of each spray target immediately before and during spraying operations to verify the target location and ensure that friendly forces were clear of the target area. Anecdotal reports of direct spraying of troops in Vietnam likely reflect the RANCH HAND missions spraying insecticide for mosquito control at regular intervals from March 1967 through February 1972.

Outlook. The distribution and levels of serum dioxin in RANCH HAND veterans and the US Army Chemical Corps Vietnam veterans (the unit responsible for helicopter and ground-based spray operations) are distinguishable from typical levels in the population decades after the Vietnam conflict. An exposure model similar to that proposed in the 2003 report of the Institute of Medicine's Committee on 'Characterizing Exposure of Veterans to Agent Orange and Other Herbicides Used in Vietnam' was tested in 1988 by the Centers for Disease Control and Prevention and found to be a poor predictor of absorbed dose of TCDD. Military records during the Vietnam War lack the precision to determine that troops were directly sprayed with herbicides during Operation RANCH HAND, especially given the procedures in place to ensure clearance of friendly forces from the target area and the lack of elevated serum levels of TCDD in ground troops judged to have operated in heavily sprayed areas.

Keywords: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD); Agent Orange; historical military records; Operation RANCH HAND; Vietnam

Introduction

Potential exposure of ground troops in Vietnam to dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin [TCDD]) remains controversial despite the passage of 30 years since the Vietnam War. The distribution and levels of serum dioxin in RANCH HAND veterans (the US Air Force unit responsible for spraying herbicides from fixed-wing aircraft) and the US Army Chemical Corps veterans (the US Army unit responsible for helicopter and ground-based spraying) are distinguishable from typical levels in the population decades later [1,2]. However, studies of ground troops did not find elevated levels of TCDD [3]. The lack of elevated levels of serum TCDD in ground troops suggests that any exposure to Agent Orange was not significant. Uncertainty in the dioxin levels in ground troops at the end of their service in Vietnam led to attempts to develop a methodology for characterizing exposure of ground troops in Vietnam to Agent Orange and other herbicides based upon historical reconstruction of relevant military records [4,5].

Seldom in the scientific literature is there a discussion about the types of historical records that provide a basis for estimating exposure in epidemiological studies. Epidemiologists, especially those involved in occupational and environmental studies, often rely heavily upon historical records to construct exposure assessments. However, the factors bearing on the degree of reliability of historical records are not always documented by investigators in published articles or appreciated by scientists seeking to interpret the results of the studies. One of our intentions in this paper is to assist the scientific community in its use and interpretation of historical data on the Vietnam Conflict. And, more generally, we hope to encourage greater attention to and rigorous analysis of the use of historical data in the investigation of health effects of other potential exposures.

One key element suggesting the absence of significant exposure to ground troops is the adherence to procedures governing the RANCH HAND Operation that ensured that no friendly forces were in the areas targeted for spraying. A full discussion of these procedures and supporting historical data has been absent in the debate on whether ground troops were significantly exposed. Indeed, recent publications have proposed an 'exposure opportunity index' for Agent Orange without verification of the proposed index against serum TCDD levels in ground troops or adequate consideration and presentation of the historical data bearing on the likelihood of significant exposure [4,6]. The purpose of this paper is to review the procedures and supporting historical data related to spraying of herbicides in Vietnam most relevant for the design of future epidemiological studies and the interpretation of the existing body of epidemiological studies of Vietnam veterans. Our analysis of these procedures and data indicates that direct spraying of friendly troops in Vietnam was unlikely.

The historical information related to herbicide usage in Vietnam can be classified into two categories: procedural and operational information. 'Procedural information' covers the process and procedures followed in spraying herbicides from fixed wing aircraft in Vietnam, and includes approval procedures for spray missions, the criteria required to conduct a mission, the control exercised by the Forward Air Controller (FAC), and the characteristics of the equipment used to apply the herbicides. 'Operational information' includes the geographic locations of specific spray missions, the amount of herbicide sprayed by a specific mission, reports of battle damage to spray aircraft, reports of fighter support for aerial spray missions, and any comments, such as reasons for canceling a mission.

1 Procedural Information

1.1 The historical records on Operation RANCH HAND

A large body of historical data exists on the use of Agent Orange in Vietnam. The history of Operation RANCH HAND in Vietnam has been thoroughly documented. The National Archives have unit histories of ground troops stationed in Vietnam from 1964 through 1971. In addition, books have documented the histories of the Vietnam conflict [7,8]. Other primary records include Contemporary Historical Evaluation of Combat Operations (CHECO) reports [9,10] and the Special Reviews of Herbicide Operations [11] and the Military Assistance Command, Vietnam [12]. Many of these primary historical records are now available online through the Special Collection Initiative of the National Agricultural Library, US Department of Agriculture, Beltsville, Maryland <http://www.nal.usda.gov/speccoll/findaids/agentorange/index.htm>. The specific web sites for many of these documents are noted with the reference.

1.2 Directive 525-1

Overall policy and procedures for herbicide operations in Vietnam were set forth in detailed directives issued by the Military Assistance Command, Vietnam (MACV). These directives were, in turn, based upon specific guidelines provided by the US Departments of State and Defense. The most important of these directives was MACV Directive 525-1 [13,14], which governed all herbicide use by both US and Free World Military Assistance Forces (FWMAF) troops between 1965 and 1970. It was revised periodically by MACV, in consultation with the Departments of State and Defense. The Directive "prescribed policies, responsibilities, and procedures governing the operational employment of herbicides within [South Vietnam]," including all fixed wing, helicopter, and surface-based methods of herbicide application [13,14].

The use of herbicides for defoliation and crop destruction was primarily a Government of Vietnam (GVN) operation that was supported by the US Government. Initial requests for herbicide projects often originated from the GVN, such as those from Vietnamese province officials, and all such requests, regardless of their derivation, had to be approved by a Vietnamese Province Chief in accordance with Directive 525-1. After receipt, requests were referred to the Chief of the Joint General Staff (Chief, JGS), a Republic of Vietnam Armed Forces General Officer who headed a joint Army of the Republic of Vietnam (ARVN)/Republic of Vietnam Air Force (RVNAF) staff in Saigon. Various tactical benefits and considerations supporting the project were required, and if recommended, the relevant senior US Chemical Corps advisor, who had to endorse the plan's soundness and tactical efficacy, issued the documentation on the project. The JGS request and Chemical Corps recommendation were then forwarded to the US Chemical Operations Division for analysis, staff coordination and evaluation, in light of numerous policy, logistical, technical, and operational considerations and limitations. Disapproved requests were returned to the Chemical Operations Division, which could attempt to obtain clarification or modification from the JGS.

Approved requests were presented, in detail, to the 'MACV 203 Committee.' If approved by the MACV 203 Committee, the plan would then be provided to the US Ambassador and Commander, MACV, for review and consideration. If approved by both, the Chief of Staff, MACV, would forward a letter to the Chief, JGS confirming the decision to proceed with the herbicide project. Thereafter, a coordination meeting was held in the province in which the project was to be conducted, during which the final mission plan was agreed upon. Following the coordination meeting, the Chief of Staff of MACV published an 'operations order' and MACV issued an 'execution' order. The JGS would then requisition the herbicide from appropriate GVN agencies, with ultimate 'releasing authority' residing in the JGS.

Directive 525-1 established detailed 'policies' that formed the foundation of the Directive's procedures governing herbicide use. The policies mandated that (1) defoliation and crop destruction missions were limited to areas of low population; (2) use of US assets for defoliation by fixed-wing aircraft and all crop destruction operations required pre-approval from both Commander, MACV and the US Ambassador (in addition to the approvals required from the GVN); (3) use of US assets to accomplish GVN requests for defoliation by helicopter in support of (i) local base defense, (ii) clearance of small ambush sites and (iii) maintenance of deforested areas, required pre-approval from both the US and GVN; (4) use of US assets to accomplish surface-based spray operations required pre-approval from both the US and GVN; (5) 'care' was to be taken in "planning and executing operations to prevent herbicide damage to rubber trees;" and (6) a "no-spray zone of two kilometers for helicopters and five kilometers for fixed-wing delivery [was to] be maintained around active rubber plantations" [13,14].

All such requests, regardless of type, were required to be detailed and comprehensive. Requests for ground-based defoliation projects, generally transmitted by the Army of the Republic of Vietnam (ARVN) Corps to US Chemical Corps senior advisors, were evaluated based on similar factors to those for fixed-wing projects, and included consideration of whether the default circumstances for clearing were impractical. The default circumstances included hand-cutting, burning or mechanical methods of clearing vegetation [7,8,13].

In light of the elaborate approval matrix dictated by Directive 525-1 and the number of agencies involved, herbicide requests normally took several months to be processed. Critical reviews of the program by outside agencies often cited the "inordinate delays" that impeded timely completion of the projects [8,9]. Even approved targets occasionally could not be sprayed when scheduled, usually because friendly forces were in the area or a military operation was imminent. In contrast, the 'denial' part of the approval process *was* executed in a timely fashion. Later, MACV began refusing mission clearances outright "because of high threat," as when intelligence indicated that strong enemy resistance to RANCH HAND airplanes and accompanying fighter aircraft could be expected [7].

1.3 Post approval procedures in Operation RANCH HAND

RANCH HAND operations and targeting personnel met weekly with the chemical operations section of MACV to discuss approved requests and schedule post approval survey flights. The survey sorties were necessary to identify actual target locations for the individual missions and to plan optimal attack routes. Survey sorties were flown by single, unescorted UC-123s (the unarmed transport aircraft used for the spray program) manned by the RANCH HAND chief or assistant chief of targeting, a copilot, a navigator from the targeting group, and an Army Chemical Corps officer [8].

After the RANCH HAND reconnaissance flight over the designated area, a coordination meeting was held in the field with the Province Chief, local military commanders, and representatives from MACV, ARVN, the Seventh Air Force and RANCH HAND. Details of target requests, intelligence data, and particulars about the target were worked out. An overlay map of the designated target area was prepared. Following the meeting, formal target requests were prepared and forwarded to Saigon for clearance by ARVN and US authorities [7,8]. After consultation with South Vietnamese military and government officials, final approval authority was assigned to the Commander, MACV, for defoliation targets and to the American Ambassador for crop targets [8].

1.4 Coordinating RANCH HAND spray missions

Once final approval was given for a specific target area (referred to as a target box), the RANCH HAND commander and his targeting officer, together with MACV personnel, determined the most effective mission dates and requested orders to implement the mission. The targeting officer planned individual missions, prepared charts of the target area, and drafted the requests for orders for submission to the US Air Force Tactical Air Control Center (TACC). The day before the mission, TACC coordinated the FAC, fighter and rescue support through the Direct Air Support Center (DASC), and issued an approved mission order [7,8,15,16].

Approved herbicide missions that had passed successfully through the gauntlet of requirements established by directives such as 525-1, still had to pass through additional procedural checkpoints. One of the most important of these checkpoints was the TACC. Before a mission could be executed, TACC, in coordination with the DASC, required clearance from all friendly units in the vicinity of the target area.

This clearance was necessary to ensure that the fighter aircraft supporting the herbicide missions were free to deliver the suppressive ordnance essential to the safe and successful execution of the RANCH HAND missions. The target area was declared a 'free fire zone,' indicating that the supporting fighter aircraft could freely expend ordnance on any target in the area after clearance from the FAC without fear of injury to friendly forces [7,8,10]. Unfortunately the elaborate spray approval and coordination procedures made it difficult to maintain operational secrecy, and unarmed RANCH HAND aircraft spraying herbicides at low altitudes frequently became targets of hostile fire [8].

1.5 Developing the concept of fighter suppression

The procedures followed in the program changed over time. Initially, fighter aircraft were used only if rescue operations became necessary or if opposing forces had fired on the spray aircraft and post-strike actions were undertaken. By late 1963, escort fighter cover was routinely scheduled. RANCH HAND aircraft marked the locations where ground fire occurred by dropping smoke grenades, giving the FAC a visual indicator. The escort restriction was changed after 30 April 1964 when fire from .50-caliber antiaircraft and airburst mortar was encountered in the Mekong Delta south of Ca Mau [9]. The copilot of the lead aircraft was wounded and over 40 holes were found in the aircraft. The revised policy permitted the FAC to use fighter aircraft to prestrike suspected ambush sites. This new tactic was intended to force the enemy to seek cover, reducing the threat to the RANCH HAND aircraft [11,12].

Hostile ground fire was such a hazard to the UC-123 planes that in January 1965, approval was given to prestrike targets with fighter aircraft in advance of impending herbicide missions [17]. From that point forward, close-in fighter support was a vital part of the defoliation program and reduced to some extent the deadly hazards posed to RANCH HAND personnel and aircraft by ground fire from opposing forces.

If a spray target were considered 'cool,' the fighters would fly above the RANCH HAND aircraft and conserve their fuel and ammunition for a more lucrative target [8]. On other targets, a low level 'dry run' by the fighters, in which they delivered no ordinance but simply appraised the opposing forces of their presence, would be sufficient to quell enemy fire temporarily [8]. If a herbicide mission was scheduled against a full-blown 'hot target' in a 'free bomb' or 'free fire' zone, mission planners might request a prestrike of the area. The fighter aircraft supporting RANCH HAND missions would drop Cluster Bomb Units (CBUs), napalm, fire 20-mm guns, or all three [15,16].

Use of fighter aircraft advanced as a tactic during July 1968 into 'heavy suppression' to counter increased ground fire from opposing forces [7]. Frequently, between four and twelve fighter aircraft accompanied the spray planes when RANCH HAND aircraft flew over such targets. When possible, pilots of RANCH HAND and fighter aircraft would meet before the mission to decide on tactics; these would be provided to the FAC who had responsibility for coordinating operations in the target area [15,16]. When heavy suppression was involved, fighters would strike strong points in the target area with 500- or 750-pound bombs two or three minutes before the UC-123s began their spray run. At the start of the spray run, fighters would fly slightly ahead of and parallel to the spray planes and drop antipersonnel CBU to force enemy gunners to stay under cover until the spray formation had passed, as shown in **Fig. 1** [7]. CBU-12s containing white phosphorus were highly effective in suppressing ground fire due to their lethal anti-personnel effect, and they provided a dense cloud of white smoke to hide the approaching RANCH HAND aircraft.

Fig. 1: Three RANCH HAND aircraft spraying at 150 feet above the ground are masked from enemy fire by CBU smoke to the right of the run. Meanwhile a fighter aircraft, barely visible above the hills, has just laid CBU to the left of the planned spray path. This photograph was taken in Northern II Corps in 1967. The photo courtesy of the Plant Science Laboratories, Fort Detrick, MD

1.6 The critical role of the Forward Air Controller

The role of the FAC was critical to every RANCH HAND mission that occurred after 1964. The Air Force basic work unit was a Tactical Air Control Party (TACP), an autonomous Air Force unit co-located with the US Army. At a minimum, it consisted of an officer, the Air Liaison Officer or the FAC, who was assigned to an Army unit, and the ROMAD (Radio Operator Maintenance Driver), an enlisted member of the TACP who was a mobile (jeep) radio operator [16]. The FAC had major responsibilities for executing the RANCH HAND mission. The FAC flew a small observation aircraft and was the individual most familiar with the Area of Operations (AO). The mission order alerted the RANCH HAND aircraft, the accompanying fighter escort, and the ROMAD who was directed to keep in constant contact with any ground forces (including Special Operation units) that potentially could be near the target box along with other mission information [16].

Usually one or two hours before the RANCH HAND mission, the FAC arrived at the target coordinates to observe the weather and to check if there were observable hostile forces in the area. The FAC, in coordination with the ROMAD and the Direct Air Support Center, ensured that there were no friendly units in the target area [16]. If there were imminent operations or friendly forces in the area, the FAC would cancel the mission or divert the spray mission to an alternate target. This action prevented accidental attack on friendly personnel by the escorting fighters and kept field forces from entering the area too soon after the use of CBU or other heavy suppression munitions [8,16].

About two percent of CBU ordnance used in advance of RANCH HAND missions were duds. The approval procedures for a mission 'cautioned' field commanders not to send friendly troops immediately into areas sprayed because of this unexploded ordnance [8,15,16]. Moreover, about 2-3 weeks were required before defoliation began to improve combat visibility in heavily vegetated areas. Consequently, movement of ground troops immediately into an area sprayed by RANCH HAND aircraft would mean such operations would not have any of the benefit of the defoliation. Thus, movement through sprayed areas soon after spraying would have been unproductive.

As described above, elaborate procedures were developed and implemented, and exhaustive efforts undertaken, to ensure that areas approved for defoliation missions were clear of friendly forces well in advance of the mission start time. The mission order provided the target coordinates, specific radio contact data for the FAC, RANCH HAND formation, and accompanying fighter escort, and served as a warning order to field units that might be near the target. These troop-clearing procedures were strictly observed by the various MACV, TACC, and TACP personnel associated with fighter support missions, as evidenced by the lack of reports of friendly fire casualties associated with suppression of hostile fire against RANCH HAND missions [18,19].

1.7 Conducting the spray mission

The FAC coordinated both the approaching RANCH HAND aircraft and the accompanying fighter support. If weather conditions in the target were not acceptable (e.g., wind greater than 10 knots, rain, poor visibility), the FAC would cancel the mission or send the aircraft to the alternate target. If the mission was to be executed, the FAC marked the initial point of the target by using a rocket that produced a plume of white smoke [16]. The RANCH HAND aircraft would descend to the appropriate altitude and air speed, and the lead pilot would call 'spray on' at the start of the spray run. All aircraft in the flight would simultaneously turn on their spray systems and would continue spraying until the lead pilot ordered, 'spray off.' If the target area was known to be 'hot' (hostile ground forces present), or if the RANCH HAND aircraft received ground fire, the FAC would direct the fighter aircraft to deliver their ordnance [15] at the appropriate location. If RANCH HAND or escort aircraft were crippled or crashed, the FAC would request air rescue (helicopter) assistance [16].

2 Vietnam War Records: Operational Information

2.1 Collection and maintenance of records: An overview

The availability of military records from the Vietnam War was dependent upon the quality and quantities of records maintained by the military administrative units responsible for record keeping. Christian and White described the history of records management in Southeast Asia [20]. Army record managers did not have an effective records management program established and operative until 1969. After the war ended, more than 10,000 linear meters of Vietnam War Records were returned to various archive centers in the US. The records from Vietnam arrived in an assortment of conditions and in many different types of containers because "the troops were fighting a war and were not worrying about such niceties, a price that was paid later in trying to find the records at the centers" [20].

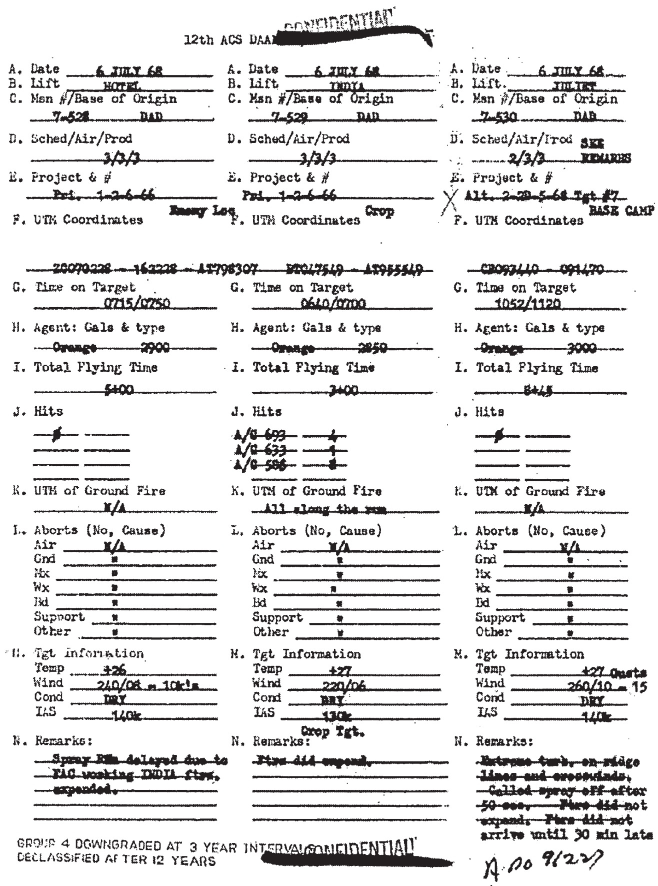
The challenge of using military records to determine troop locations and other data was four-fold [23]. First, many of the records from early in the war may not have been retained because it was only late in the war that all records were prevented from destruction. Second, soldiers on one-year tours barely had time to organize their files before they were transferred and someone else took over. Third, many military records were maintained by Vietnamese civilians and military, for example, the receipt and distribution of herbicides to military units. Last, many of the records created during the period 1961 to 1964 may be of little use because of the nature of the US advisory role and the locations of advisors for those years. Nevertheless, tracking military units through the use of records such as Battalion Daily Journals, Situation Reports, Command Chronologies, Unit Histories, and Morning Reports seemed feasible. In May 1980, the Army's Office of the Adjutant General established a Joint Service Environmental Support Group (later the US Armed Services Center for Research of Unit Records) to reconstruct the movements of combat battalions in Vietnam [20]. They concluded that the military records were created for combat purposes and now "we have to make them work for us in an entirely new and complex manner, [i.e., for epidemiological studies,] never before attempted in the history of records management" [20].

2.2 Battle damage to RANCH HAND aircraft and crews

On days with clear weather and relatively unobstructed visibility, the RANCH HAND Aircraft would generally cruise to the target at about 3,000 feet above the ground and then descend rapidly at about 2,500 feet per minute to the 'spray-on point,' in order to reduce their exposure to hostile ordinance [7]. However, if clouds were low and ground-to-air visibility was poor, the aircraft generally would fly a low-level approach to the spray-on point, after which they would begin to disseminate the herbicide [7]. In either case, the aircraft regularly received heavy, sustained automatic weapons fire from opposing forces, who were often alerted to the impending herbicide mission by the sound of the preceding fighter aircraft. The low altitude and slow rate of speed of the UC-123 aircraft, coupled with the open cockpit windows and troop doors, meant that the RANCH HAND crews could clearly hear – and at times see – the weapons being fired at them. The odor of enemy gunpowder often filled the planes [8]. Sufficiently intense ground fire could cause the UC-123s to abandon a target after only one spray pass [7].

Resistance by opposing forces to RANCH HAND operations was so frequent and intense, that during its nine years of operation, RANCH HAND aircraft received more than 5,000 hits, lost nine spray aircraft to hostile fire and had 28 RANCH HAND personnel die in combat [7,8]. While enemy resistance to missions grew in strength over time, even the early RANCH HAND crews were subjected to heavy hostile fire during herbicide operations. For example, almost half of the aircrew members assigned to Operation RANCH HAND in December 1965 had been wounded at least once, and the aircraft employed during that period sustained a total of nearly 800 hits. One of the older planes, nicknamed 'The Leper Colony,' had been hit 230 times, and its occupants had earned eight 'Purple Heart' medals [8]. RANCH HAND crews had the reputation of being the "most shot-at airmen operating in South Vietnam" [21]. Each year, as the number of RANCH HAND aircraft and sorties increased, so did the number of 'hits' received by the UC-123s from ground fire.

The Viet Cong actually offered a special bonus or bounty to anyone who shot down a RANCH HAND aircraft, and a reward was offered for the capture or death of individual crewmembers [8]. Because of the great hazards posed by enemy fire, modifications were made to the RANCH HAND aircraft, including the installation of specially engineered armor plating in the crew areas and around the fuel tank for the spray pump engine [8]. RANCH HAND crews, in turn, were provided with additional protective equipment, including heavy ceramic flak jackets and specially modified flying helmets equipped with a clear visor that could be lowered to protect the eyes [8]. Used in place of the standard radio headset, the helmet, together with the flak jacket, offered pilots and navigators extra protection from flying shrapnel and glass generated during ground-to-air fire. Twice in December 1965 alone, this additional protection permitted crews to complete runs despite cockpit damage and crew injuries sustained during heavy fire directed at the aircraft. New operational flight tactics also were developed to minimize the RANCH HAND aircraft's 'time on the target' and, therefore, reduce their vulnerability to hostile groundfire [9,10].



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A. Date 6 JULY 68	A. Date 6 JULY 68	A. Date 6 JULY 68
B. Lift HOTEL	B. Lift INDIA	B. Lift. JULIET
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D. Sched/Air/Prod 3/3/3	D. Sched/Air/Prod 3/3/3	D. Sched/Air/Prod 2/3/3 SEE REMARKS
E. Project & # Pri. 1-2-6-66 Enemy Loc	E. Project & # Pri. 1-2-6-66 Crop	E. Project & # Alt. 2-2D-5-68 Tgt #7 BASE CAMP
F. UTM Coordinates ZC070228 - 162228 - AT798307	F. UTM Coordinates BT017549 - AT955549	F. UTM Coordinates CB093440 - 094470
G. Time on Target 0715/0750	G. Time on Target 0640/0700	G. Time on Target 1052/1120
H. Agent: Gals & type Orange 2900	H. Agent: Gals & type Orange 2850	H. Agent: Gals & type Orange 3000
I. Total Flying Time 5+00	I. Total Flying Time 3+00	I. Total Flying Time 8+45
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K. UTM of Ground Fire N/A	K. UTM of Ground Fire All along the run	K. UTM of Ground Fire N/A
L. Aborts (No, Cause) Air N/A; Gnd "; Mx "; Wx "; Bd "; Support "; Other "	L. Aborts (No, Cause) Air N/A; Gnd "; Mx "; Wx "; Bd "; Support "; Other "	L. Aborts (No, Cause) Air N/A; Gnd "; Mx "; Wx "; Bd "; Support "; Other "
M. Tgt Information Temp +26; Wind 240/06 - 10k's; Cond DRY; IAS 140k	M. Tgt Information Temp +27; Wind 220/06; Cond DRY; IAS 130k	M. Tgt Information Temp +27 Gusts; Wind 260/10 - 15; Cond DRY; IAS 140k
N. Remarks: Spray Rln delayed due to FAC working INDIA ftrs. expended.	N. Remarks: Crop Tgt. Ftrs did expend.	N. Remarks: Extreme turb. on ridge lines and crosswinds. Called spray off after 50 sec. Ftrs did not expend. Ftrs did not arrive until 30 min late

GROUP 4 DOWNGRADED AT 3 YEAR INTERVALS CONFIDENTIAL
DECLASSIFIED AFTER 12 YEARS [redacted]

A. DO 9/22/7

Fig. 2: A Daily Air Activity Report (DAAR) describing three spray missions that occurred on 6 July 1968 in Vietnam

2.3 RANCH HAND daily air activity reports

Daily Air Activity Reports (DAARs) contained information about the RANCH HAND spraying missions (**Fig. 2**). Specific daily missions were known as 'lifts' and were designated by alphabetical letters that were also used as part of the formation call sign; that is, the first mission from Bien Hoa Air Base each day was the 'Alpha' lift with the radio call sign 'Cowboy Alpha.' The second mission was the 'Bravo' lift, etc. The earliest morning missions were planned to strike their targets at sunrise, and takeoff times were adjusted according to the distance of the target from the launch base. After returning from the first target, the Alpha crews would re-brief while the aircraft were being serviced and relaunch at 0900 to 0930 hours to another target. This second mission would become 'Charlie' lift. The Bravo crews were also turned around for a second mission and would become the 'Delta' lift. Most missions normally were flown from the RANCH HAND home base at Bien Hoa, with additional sorties from small detachments located at Da Nang and, later, Phu Cat and Nha Trang. During the 'good weather' season in I Corps, the Da Nang detachment might be augmented with additional aircraft to allow four or five missions instead of two. If sufficient aircraft and crews were available, and target approval had been obtained, additional missions were scheduled as 'Echo,' 'Hotel,' 'India,' 'Juliet,' and 'Kilo' lifts. Generally three or four aircraft constituted a 'lift,' although by 1967 the first mission out of Bien Hoa frequently consisted of up to eight UC-123s [8].

Fig. 2 is a photograph of the 12th Air Commando Squadron (RANCH HAND) daily record of three missions that were flown from Da Nang Airbase, Vietnam, on 6 July 1968. This record is typical of the daily reports at this time and location. The six aircraft of 'Hotel' and 'India' (missions 7-526 and 7-529) were 'on target' at 0715 and 0640 hours, respectively. The 'Hotel' lift struck as a primary target an enemy line of communications (LOC), while 'India's' primary target was against crops. Both were in the same target box (#1-2-6-66). 'India' took ground fire all along the run damaging all three aircraft. The lead aircraft received 4 hits, the second received 1, and the last aircraft received 8 hits. The attack by 'Hotel' was delayed due to the FAC working the run for 'India.' Fighters expended munitions during both 'Hotel' and 'India' missions. The 'Juliet' lift used the same spray aircraft as 'Hotel,' after they were reloaded with herbicide, with the scheduler anticipating having only two in-commission aircraft available. This explains the 2/3/3 entry for item 'D' which indicates two aircraft scheduled, three launched, and three productive. However, 'Juliet' lift, which was flown against an alternate target of a base camp for opposing forces, encountered extreme turbulence on the ridgelines and called 'spray off' after 50 seconds. Remarks indicate no hits were taken, fighters arrived 30 minutes late, and no munitions were expended. Since the 'Juliet' lift sprayed for only 50 seconds, the amount of Agent Orange recorded on the form (3,000 gallons) had to be in error, particularly since it was impossible to completely empty the spray tank except by using the emergency dump valve.

The UTM coordinates provided a 'start' and a 'stop' point, but the alphanumeric indicators in the UTM coordinates for the 'Hotel' mission indicated that it did not follow a straight line since there was a third set of coordinates. The 'Hotel' mission was in the mountainous terrain of I Corps, and the flight likely followed the contours of the terrain. The 'India' target was crop destruction, and this possibly required the crews to repeatedly turn on and off the spray system and to make frequent turns, but this is not noted in the UTM coordinates or in the remarks. As a result, the flight paths based literally on the recorded UTM coordinates might at some points have differed by a kilometer or more from the coordinates of the actual flight paths.

Inspection of other DAARs suggests that the DAAR in Fig. 2 is not atypical. The discussion of the DAAR in Fig. 2 indicates both the importance of DAARs as a source of detailed information on RANCH HAND spray operations and also their limitations – limitations that are particularly acute for comparisons of coordinates of spray missions with coordinates from records of military operations. The DAARs provide ample evidence that the detailed procedures and policies for the RANCH HAND missions were strictly observed. The remarks section of many DAARs cite reasons for aborted or cancelled missions, such as due to "friendly forces in the area," "cancelled by ARVN," "sent to alternate by DASC," "cancelled by FAC," etc. All of these elaborate troop-clearing efforts resulted in no documented herbicide-related friendly casualties during the long course of Operation RANCH HAND. However, the DAARs data do permit reliable conclusions that troops on the ground were not directly sprayed during a spray mission.

3 The Herbicide Reporting System (HERBS)

In 1970, the US Army's Data Management Agency [22] was tasked to support the Chemical Operations Division (Army Chemical Corps) in developing an Automatic Data Processing system for processing and storing monthly herbicide mission activity data. The result of this effort was the Herbicide Reporting System (HERBS), which was implemented in May 1970. The objectives of the HERBS system were to process the monthly worksheets, prepared by the Chemical Operations Division from information received from the primary data sources (e.g., the Daily Air Activities Report, DAAR); maintain a HERBS mission activity history file, updated monthly; and to produce the monthly update listings and any reports from user requested file inquiries [22]. The HERBS system was used to respond to requests from organizations involved in ecological research, claims investigations, and general inquiries from the Department of Defense and the scientific community [22].

The content of the HERBS system consisted of data from the RANCH HAND spray missions. These data included: the province(s) in which the mission was flown, the mission project number, the UTM coordinate points covered by the mission with identifying additions to distinguish each UTM point as a start, turn, or stop coordinate, the type of herbicide used, the number of gallons sprayed, the type of mission, the number of hits received during a run, and, the number of aborts attributable to maintenance, weather, battle damage, and other factors [22]. The data were recorded by the field units and forwarded to the Chemical Operations Division.

3.1 The evolution of the HERBS tape

The evolution of the HERBS Tape has been an on-going process for more than 30 years. Many organizations have examined the original record of missions developed by the Data Management Agency in 1970 [22]. At that time paper records were converted to 'punch cards' and the first tape was compiled for the US Army Chemical Corps. As noted, the basis for records on RANCH HAND in the HERBS file was the Daily Air Activity Reports (DAARs). In April 1971, the MITRE Corporation, at the request of the Defense Communications Agency, conducted the first quality analysis of the HERBS data file [23] and concluded that 2% had missing data, 6% had serious transcription errors or serious measurement errors, 23% of the records had track length (distance sprayed by RANCH HAND aircraft) that was in error by 50%. Statistically, the overall quality of the data was good and by using error curves, track length data could be adjusted to improve the data quality of a record, if it was considered necessary by the analysis [26]. The presumption was that the UTM coordinates provided in the data set were accurate, although as noted above, the precision of coordinates was limited.

The 1974 report by a committee of scientists of the National Academy of Sciences (NAS) on 'The Effects of Herbicides in South Vietnam' [24] noted that the version of the HERBS tape used in their report covered the period August 1965 through February 1971 and listed a total of 6,542 missions. From this total, 880 missions were considered to contain one or more errors; of these 575 were corrected, while the errors in 305 could not be corrected and were omitted from the tape [24]. The NAS committee attempted to document the impact of spraying on forests ecosystems from aerial photographs taken by the military, but this was done on only a small sample of missions [24]. As with the MITRE report, the NAS committee assumed that the spray coordinates were correct but did not verify this by either aerial photographs or ground observations.

In 1986, the Joint Services Environmental Support Group (the joint Army, Air Force and Navy military record specialists, now the US Armed Services Center for Research of Unit Records, CRUR) completed an extensive search of the military records of the Vietnam era [25]. A database of 2,394 additional military herbicide missions in Vietnam, including an additional 557 RANCH HAND missions, was identified. The Services HERBS tape contained data on helicopter, backpack, and other types of ground spraying. When the two tapes (HERBS and Service HERBS) were combined 8,930 missions were identified and 72,740,400 liters of herbicide were reported sprayed [25]. In the course of combining the two tapes, data on battle damage (hits from ground fire) and comments on the use of fighter suppression were deleted. In 2003, the S-NAS-HERBS was completed, a version of the HERBS tape that combined both NAS and the CRUR databases, plus data from additional review of the records, and imputing data for some missing coordinates [4]. Lathrop [26] concluded that the "map coordinates of the HERBS tapes are largely accurate, but many are inaccurate and based on the guesstimates of RANCH HAND pilots and navigators who were under extreme combat or terrain-flying stress. Straight-line approximations of multi-leg zig-zag patterns can only be viewed as gross approximations of many of the missions in Vietnam. This error source can only be adequately factored into the probabilistic approach (for epidemiological studies) by the use of crude assumptions."

3.2 Accuracy of geographic data

Of particular importance is the accuracy of the geographic data (the maps used by the aircrews and ground troops). Electronic navigation aids gave aircrews the relative bearing of their aircraft from a transmitter (always in friendly territory) and in some cases approximate distance, but were incapable of fixing the location of the aircraft with precision. To fix location within one nautical mile (1,850 meters) for a plane 32 kilometers from a TACAN transmitter would have been exceptional. The signals were not ordinarily received at the low altitudes flown on spray missions. Navigation by the crew using visual orientation and reference to a map was the only means that aircrews on spray missions had for establishing their locations. In turn, this was dependent on the inherent precision of a map, the accuracy with which it depicted surface features, and the skill of the individual pilot or navigator.

Early RANCH HAND missions were flown using maps inherited from the French. By 1964–65, maps produced by the US Army Corps of Engineers were available (in most cases based on the French maps and updated with photogrammetric data); the 1:250,000 Joint Operations Graphic series of maps were commonly used. A sample of representative charts [27,28] shows that these guaranteed a horizontal accuracy of *no better* than 120–240 meters. Moreover, the heavy jungle cover in the areas where most RANCH HAND missions were flown made precise navigation difficult. As a general rule, a pilot or navigator could fix his position accurately within the limitations of the map only if he could orient himself by reference to a nearby and clearly visible landmark, such as a prominent and distinctively shaped elevation, the coastline, or a visible inland waterway with a distinctive shape. Such features were available only occasionally. The depiction of man-made features in remote areas – buildings, trails, cultivated areas, etc. – was notoriously unreliable, although aircrews were able to orient themselves relative to friendly aircraft and ground forces with sufficient accuracy to ensure safety and effective coordination. FACs with intimate knowledge of their areas of operation were an essential element in orienting a mission, but were not helpful with precise accuracy relative to the UTM grid [16].

Finally, to compound the problem, ground troops used an entirely different series of maps, typically of 1:50,000 scale. The often severely limited view (due to the dense vegetation) available to field forces under even the best of conditions made accurate navigation difficult. The fact that ground troops, despite pre-mission warnings, could accidentally enter target areas was the primary reason for the extensive last minute spray cancellation program described earlier. The large number of mission cancellations or diversions documented in the DAARs is ample proof that the program was adhered to.

John Flanagan, a Forward Air Controller, describes the difficulties in tracking locations in the Vietnamese jungles in his book 'Vietnam Above the Treetops' [16]: "This stuff is thick! There are no holes except where the jungle is growing back in some of the grassland area. Some parts of War Zone C had apparently been cultivated at one point. Now the dense elephant grass and bamboo were reclaiming any open area. But 90 percent of the area was double- and triple-jungle canopy."

4 Historical Basis for Anecdotal Information

4.1 Alternative methods of clearing vegetation

Anecdotal reports by soldiers of exposure to Agent Orange commonly mention cleared, barren landscapes. A widely held misconception is that all clearance of vegetation in Vietnam was accomplished by means of herbicides. That was not the case. Simpler and more direct mechanical methods were frequently used and were often preferred depending on the tactical situation and the terrain. A special unit of US Army Corps of Engineers was created for clearing jungle vegetation by means of a variety of mechanical equipment, ranging from the 'Rome plow,' a large bulldozer equipped with a special tree-cutting blade and an armored cab, to chainsaws, hand axes, machetes, and diesel fuel incineration. Units of the Republic of Korea even used aerial ordnance to clear land [29]. Thus, many cleared areas may have been cleared mechanically rather than with herbicides. Indeed, "Hundreds of thousands of acres of what was formerly 'enemy country' was denuded of jungle through mechanical methods [30]".

Herbicide operations entailed considerable disadvantages, both military and diplomatic. They were politically sensitive, required a cumbersome and time-consuming process of approval to which adherence was strict, and involved considerable cost. Herbicides were often in short supply. Moreover, mechanical clearance was immediately effective, while herbicides required a period of weeks to months to reach maximum military effectiveness, particularly at ground level where multiple layers of dense jungle often shielded the lower canopies from the slow-acting defoliant. Consequently, simpler and more direct alternate methods were developed for removing vegetation, and mechanical land clearance became the favored technique.

According to a contemporaneous history of the land clearing operations in Vietnam, "engineer methods of land clearing gained wide acceptance as among the most effective tactical innovations of the war" and was considered to be of the Army's "most effective weapons" [30]. The units, often referred to as 'Jungle Eaters' or 'Land Barons' were described as the "key elements in successful operations aimed at penetrating enemy strongholds, exposing main infiltration routes, denying areas of sanctuary, and opening major transportation routes to both military and civilian traffic [31,32]."

On average, a land clearing company cleared 60–80 hectares of 'medium jungle' each day, although the rate could vary depending on terrain, weather, maintenance requirements and hostile action. For example, Army engineers in support of Operation PAUL BUNYAN managed to clear jungle at a rate of 240 hectares per day. During the first six months of the Operation, the unit cleared a total of 2,025 hectares of double and triple canopy jungle [33].

As noted by a military historian, "from a strategic standpoint, the cumulative effects of land-clearing operations in Vietnam had a decided impact as the enemy was forced increasingly to adjust to the disappearance of his operational bases or to interdiction of connecting trails ... ." Mechanical clearing was also the preferred method for clearing fire zones around bases, camps, and landing areas. The greatly improved capability of allied forces to operate through vast areas once concealed by dense jungle "... represented dramatic progress, not only in a strict military sense but also in terms of pacification and economic development [30]."

4.2 RANCH HAND insecticide operations

In the CDC study published in 1988 [3], a substantial portion of Vietnam veterans (25%) reported having experienced direct exposure to Agent Orange by RANCH HAND aircraft. As noted, it was highly unlikely that the RANCH HAND aircraft were spraying Agent Orange. Instead, it was ***highly likely*** that the aircraft was spraying insecticide.

In late 1966, Headquarters USAF recommended the modification of one of the RANCH HAND UC-123 aircraft to an insecticide-spray configuration [8]. Operation FLYSWATTER commenced on 6 March 1967 [8,9].

From March 1967 through February 1972, from one to three UC-123 RANCH HAND aircraft and crews were used to spray malathion, an organo-phosphate insecticide, for mosquito and malaria control [34]. The low-flying insecticide-spraying aircraft were commonly called the 'Silver Bug Birds' because they normally were not camouflaged [8]. These RANCH HAND aircraft routinely sprayed insecticide over military and civilian installations, as well as in areas where military operations were in progress, or about to commence [8,9,10,34]. By 1970, malathion treatment was being applied to 14 bases and their adjacent South Vietnamese cities, and the re-spray interval had been reduced from every fourteen days to every nine days [8,32]. Between 1966 and 1972, more than 3.5 million liters of malathion insecticide were sprayed on approximately 6 million hectares of South Vietnam [8,35].

5 Conclusions

Through detailed policies and procedures, the circumstances in which spraying could occur were carefully controlled, and as a result, spraying of troops with Agent Orange in Vietnam was highly unlikely. The historical documentation details these policies and procedures and the evidence that they were followed. Even after RANCH HAND had launched on an approved mission, the FAC or other control agencies would cancel mission if there were friendly forces in the target area. In addition, the often heavy application of 'fighter suppression' to minimize the ground fire from opposing forces [7,8,9] suggested the absence of friendly forces. The stringent criteria for spray missions, such as meteorological conditions, and the empirically studied and highly optimized nature of the equipment and application procedures minimized the possibility of significant spray drift [36].

Spray missions for both defoliation and crop destruction were conducted in a hostile environment. This was an unavoidable reality since the herbicides were used to deprive opposing forces of vegetative cover and food sources in areas in which they were active. RANCH HAND aircraft and their FAC and fighter escorts were routinely subjected to ground fire from Viet Cong and North Vietnamese forces [7,8,9]. Air Force fighters expended massive quantities of bombs and ammunition in close support of RANCH HAND aircraft conducting spray missions [7]. On many missions, fighter aircraft preceded the spray planes on the target deploying antipersonnel ordnance (CBU and other fragmentation bombs) [15,16]. Perhaps the most telling evidence of hostile forces in spray areas was the losses in RANCH HAND. Despite intense fire suppression by Air Force fighters, RANCH HAND lost nine aircraft and 28 crewmembers in combat [7,8].

If friendly forces had been present on or near the spray paths, the military records would have reflected numerous casualties due to 'friendly fire,' but there is no indication that this occurred. The wartime military records of troop positions and herbicide operations are valuable for some purposes, but are not sufficiently accurate to permit a reliable conclusion that a particular herbicide mission passed over a specific military unit, especially since procedures were followed which ensured that friendly forces were cleared from the target area before the mission could proceed. Reliance on wartime military records of the Vietnam Conflict of troop positions and herbicide operations to estimate an opportunity for exposure needs to consider the procedural and operational details for mission approvals that make apparent the clearing of friendly forces when spraying occurred. This conclusion is confirmed by the lack of reports of 'friendly fire' casualties and the lack of elevated serum TCDD levels in ground troops who served in heavily sprayed areas of Vietnam [3].

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Discussion Articles

Environmental Fate and Bioavailability of Agent Orange and Its Associated Dioxin During the Vietnam War

Alvin L. Young[1]*, John P. Giesy[2], Paul D. Jones[2] and Michael Newton[3]

[1] Institute for Science and Public Policy, The University of Oklahoma, Norman, Oklahoma, USA
[2] Department of Zoology, National Food Safety and Toxicology Center, and Center for Integrative Toxicology, Michigan State University, East Lansing, Michigan, USA
[3] Department of Forest Science, Oregon State University, Corvallis, Oregon, USA

* Corresponding author (youngrisk@aol.com)

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Abstract

Background. In 1996, the Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam of the National Academy of Sciences' Institute of Medicine (IOM) issued a report on an exposure model for use in epidemiological studies of Vietnam veterans. This exposure model would consider troop locations based on military records; aerial spray mission data; estimated ground spraying activity; estimated exposure opportunity factors; military indications for herbicide use; and considerations of the composition and environmental fate of herbicides, including changes in the TCDD content of the herbicides over time, the persistence of TCDD and herbicides in the environment, and the degree of likely penetration of the herbicides into the ground. When the final report of the IOM Committee was released in October 2003, several components of the exposure model envisioned by the Committee were not addressed. These components included the environmental fate of the herbicides, including changes in the TCDD content over time, the persistence of TCDD and herbicides in the environment, and the degree of likely penetration of herbicides into the ground. This paper is intended to help investigators understand better the fate and transport of herbicides and TCDD from spray missions, particularly in performing epidemiological studies.

Methods. This paper reviews the published scientific literature related to the environmental fate of Agent Orange and the contaminant, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), and discusses how this affected the potential exposure to TCDD of ground troops in Vietnam. Specifically, the mechanisms of dissipation and degradation as they relate to environmental distribution and bioavailability are addressed.

Results. The evaluation of the spray systems used to disseminate herbicides in Vietnam showed that they were capable of highly precise applications both in terms of concentrations sprayed and area treated. Research on tropical forest canopies with leaf area indices (a measure of foliage density) from 2 to 5 indicated that the amount of herbicide and associated TCDD reaching the forest floor would have been between 1 and 6% of the total aerial spray. Studies of the properties of plant surface waxes of the cuticle layer suggested that Agent Orange, including the TCDD, would have dried (i.e., be absorbed into the wax layer of the plant cuticle) upon spraying within minutes and could not be physically dislodged. Studies of Agent Orange and the associated TCDD on both leaf and soil surface have demonstrated that photolysis by sunlight would have rapidly decreased the concentration of TCDD, and this process continued in shade. Studies of 'dislodgeable foliar residues' (DFR, the fraction of a substance that is available for cutaneous uptake from the plant leaves) showed that only 8% of the DFR was present 1 hr after application. This dropped to 1% of the total 24 hrs after application. Studies with human volunteers confirmed that after 2 hrs of saturated contact with bare skin, only 0.15–0.46% of 2,4,5-T, one of the phenoxy acetic acid compounds that was an active ingredient of Agent Orange, entered the body and was eliminated in the urine.

Conclusions. The prospect of exposure to TCDD from Agent Orange in ground troops in Vietnam seems unlikely in light of the environmental dissipation of TCDD, little bioavailability, and the properties of the herbicides and circumstances of application that occurred. Photochemical degradation of TCDD and limited bioavailability of any residual TCDD present in soil or on vegetation suggest that dioxin concentrations in ground troops who served in Vietnam would have been small and indistinguishable from background levels even if they had been in recently treated areas. Laboratory and field data reported in the literature provide compelling evidence on the fate and dislodgeability of herbicide and TCDD in the environment. This evidence of the environmental fate and poor bioavailability of TCDD from Agent Orange is consistent with the observation of little or no exposure in the veterans who served in Vietnam. Appreciable accumulation of TCDD in veterans would have required repeated long-term direct skin contact of the type experienced by United States (US) Air Force RANCH HAND and US Army Chemical Corps personnel who handled or otherwise had direct contact with liquid herbicide, not from incidental exposure under field conditions where Agent Orange had been sprayed.

Keywords: Agent Orange; dislodgeable foliar residues; forest canopy penetration; herbicide dispersal; Operation RANCH HAND; serum TCDD; TCDD exposure; Vietnam

Introduction

From 1962 to 1971, herbicides were sprayed in Vietnam to defoliate the jungle canopy and destroy crops to deny opposing forces strategic cover and food. Spraying was also done to clear tall grasses and bushes from the perimeters of US and allied base camps and outlying fire-support bases. The most widely used herbicides were the phenoxyacetic acids, 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The herbicide 2,4,5-T was found in Agents Orange, Purple, Pink, and Green; the latter three being used only during the testing and trial phases in 1962–1964. The herbicide picloram (4-amino-3,5,6-trichloropicolinic acid) was combined with 2,4,-D as the active components of Agent White. Cacodylic acid (hydroxydimethyl arsine oxide) was the active component of Agent Blue. Only the herbicides containing 2,4,5-T were contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).

1 Background

In 1996, the Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam of the National Academy of Sciences' Institute of Medicine (IOM) issued a report entitled, "Characterizing Exposure of Veterans to Agent Orange and Other Herbicides Used in Vietnam: Scientific Considerations Regarding a Request for Proposals for Research" [1]. In that report, the IOM Committee described an exposure model for use in epidemiological studies of Vietnam veterans. This exposure model was to consider: troop locations based on available military records; aerial spray mission data; estimated ground spraying activity; estimated exposure opportunity factors; military indications for herbicide use; and considerations of the composition and environmental fate of herbicides, including changes in the TCDD content of the herbicides over time, the persistence of TCDD and herbicides in the environment, and the degree of likely penetration of the herbicides into the ground.

The final report of the IOM Committee was released in October 2003 [2]. However, several components of the exposure model envisioned by the Committee in its 1996 report were not addressed. These components included the environmental fate of the herbicides, including changes in the TCDD content over time, the persistence of TCDD and herbicides in the environment, and the degree of likely penetration of herbicides into the ground. This paper reviews the scientific literature related to the environmental fate of Agent Orange and the contaminant TCDD and discusses how this affected the potential exposure of combat ground troops in Vietnam to TCDD. Specifically, the mechanisms of dissipation and degradation as they relate to environmental distribution and bioavailability are addressed. This information is critical to a better understanding of how troops and others may have been exposed to herbicides and associated TCDD from spray missions.

2 Herbicide Spraying in Vietnam

2.1 Development of spray equipment

The United States Air Force (USAF) was responsible for training aircrews, developing aerial tactics for herbicide missions, and developing, testing and evaluating the aerial spray equipment used in Vietnam. The development, testing and evaluation of the spray equipment were conducted mainly at Eglin Air Force Base, Florida, and to a lesser degree at the Pran Buri Calibration Grid in Thailand. Responsibility for the selection of the defoliant rested with the US Army at Fort Detrick, Maryland with cooperation of the US Department of Agriculture [3,4].

The spray equipment test and evaluation projects that occurred at Eglin AFB, Florida, have been recently described [4]. The extensive research into the design and testing of herbicide application equipment resulted in highly precise application systems. The aircraft selected by USAF for the RANCH HAND mission was the Fairchild-built C-123B 'Provider.' The aircraft was a high-wing, twin-engine assault transport with excellent maneuverability [3,4]. The aircraft was ideal for the aerial dissemination of herbicides because the high-mounted wings allowed convenient positioning of wing spray booms, and the large cargo compartment and load capacity were ideal to receive a large spray system for internal carriage [3,4]. The layout of the internal spray system and how it interfaced with the aircraft and loading requirements are provided in a schematic (**Fig. 1**).

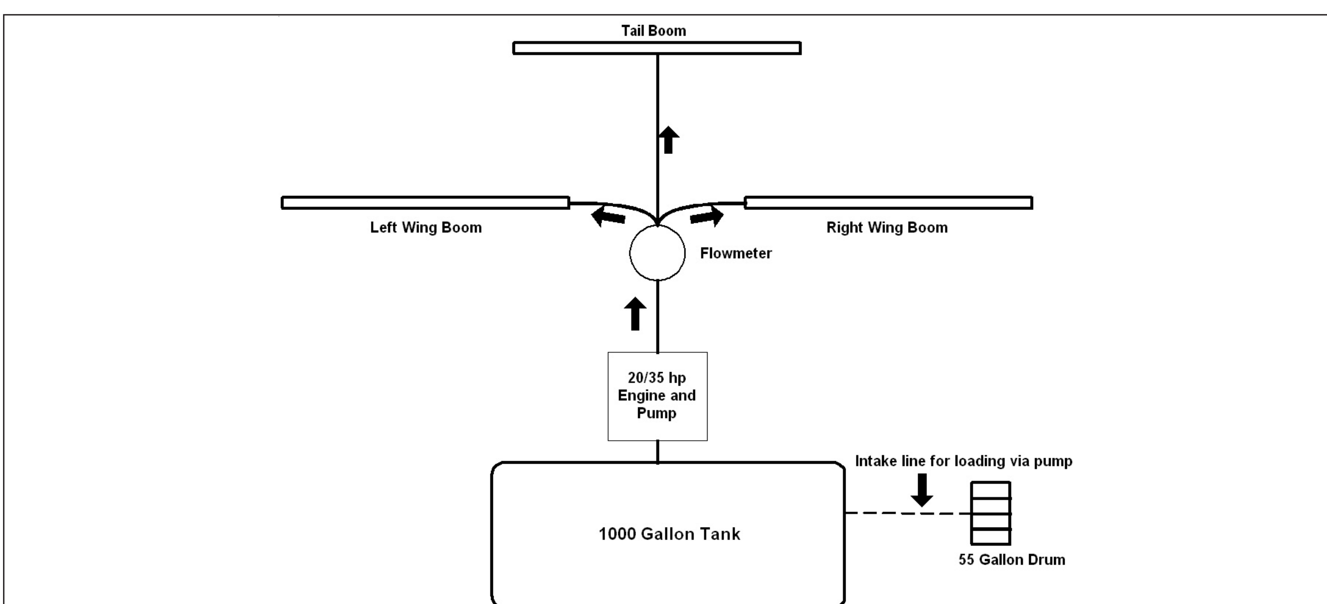

Fig. 1: A schematic of the C-123 'Provider' aircraft with internal spray system

Initially the MC-1 spray tanks, pumps, and spray booms were tested and deployed to Vietnam during the period of 1962–1964 [3,4]. This system was developed in the 1950s for the Korean Conflict but never deployed [3]. Its limitation was that it could only disseminate one-half the desired concentration rate (the minimum biologically effective deposition level), and thus required the aircraft to spray the same area twice to achieve effective defoliation [3]. In 1964, the Air Force developed and tested the AA 45Y-1 Internal Defoliant Dispenser [5]. The added pump and spray booms capacity of the AA 45Y-1 spray system allowed the UC-123 aircraft ('U' designated that the aircraft had been modified to spray herbicides) to make only one spray pass on the mission target in Vietnam [6,7]. Because of intense ground fire in the target area, this modification was critical to the survival of both the aircraft and the aircrews [7,8].

The unwanted dispersal of herbicide droplets by air turbulence was minimized by scheduling RANCH HAND missions only in favorable weather conditions and by controlling droplet size. For actual field application in Vietnam, Agent Orange was most effective in defoliating when applied to target vegetation while the wind was calm (i.e., less than 10 knots), in the absence of precipitation, and at ambient air temperatures near 29°C [7,8]. These operational weather requirements proved critical to mission effectiveness and safety, and were consistently enforced, often resulting in cancellation or retargeting of missions due to unacceptable weather [8].

The responsibility for ensuring that a RANCH HAND mission was either conducted, cancelled, or an alternate target selected rested with the Forward Air Controller (FAC) and the Tactical Air Control Center (TACC) [9]. The procedures implemented by the US Air Force and the US Army, and the role of the FAC to ensure that friendly forces were not in the target area, are described in an accompanying article in this issue [10].

RANCH HAND missions achieved optimum defoliation by flying at 130–140 knots at an altitude of 35–50 meters above ground level (AGL), depending on the vegetation and terrain [7,8]. The UC-123/AA 45Y-1 Spray System was used in more than 90% of the defoliation and crop destruction missions during the Vietnam War. The system consisted of 16 nozzles on each wing boom and eight nozzles on the tail boom. The nozzles were designed to produce a median spray droplet size of 320 to 350 µm. Indeed, 22% of the particles were 500 µm or greater, 76% were between 100 and 500 µm, and only 2% were less than 100 µm [6,11]. Thus, 98% of the droplets produced were greater than 100 µm, resulting in a rapid settling velocity [6,11]. A full tank of herbicide contained 3,600 liters (with 200 liters remaining in the spray system) and was sprayed in approximately 3.5 to 4 min over a spray swath 80 m wide (±6 m) and 14 km in length, for total area coverage of 130 ha [3,7,8]. The total deposition per m^2 was, on average, approximately 2.9 ml.

2.2 Deposition patterns from aerial spray equipment used in Vietnam

As described above, the evaluation of the spray systems used to disseminate herbicides in Vietnam showed that they were capable of highly precise applications both in terms of concentrations sprayed and area treated. The occurrences of grossly excessive deposits could only be attributable to an emergency drop, which rarely occurred [7,8]. A spray swath is depicted schematically (**Fig. 2**, adapted from Flynn) [5]. The line segment between A and F is the effective spray swath, the area that received "the minimum biologically effective ground deposition level" of herbicide. The line segments GA and FG are areas that would receive biologically effective deposition of herbicide if two airplanes, flying in close formation, both treated the areas. The line segment between B and E shows the portion of the spray profile that delivered a biologically effective deposition level. One of the goals of

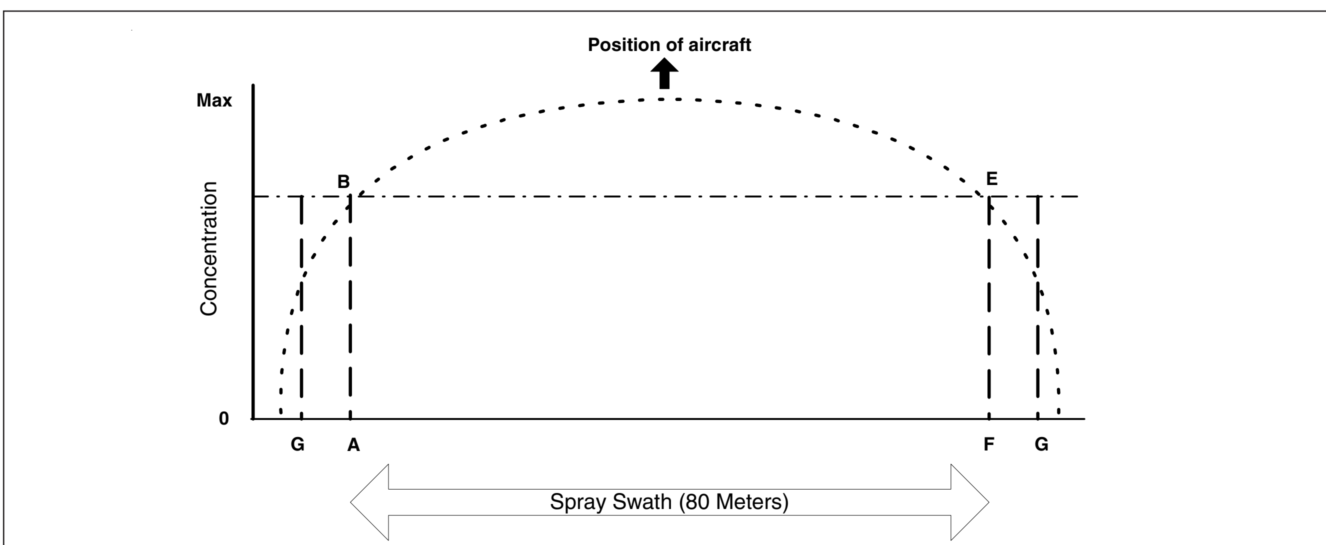

Fig. 2: A schematic cross-section of a deposition concentration profile perpendicular to the direction of flight. The spray system was the A/A45 Y-1 Internal Defoliant Dispenser interfaced with the UC 123 aircraft [adapted from Flynn, 5]. Dashed horizontal line is biologically effective concentration; dotted line is applied concentration

designing the spray systems was to minimize the area of the deposition profile above BE since this represented wasteful excess application of herbicide.

Tests at Eglin AFB, FL showed that 87% of the herbicide would have impacted the vegetation within one minute and within or near to the swath [11]. The remaining 13% of the herbicide took longer to settle due to vortices at the wing tips, drift, or evaporation [11]. Calculations made using Stokes law show that even the <100 µm size droplets, would have a settling velocity of over 30 cm/sec indicating that the droplets would likely have impacted the vegetation less than 3 minutes after spraying. Since spray missions were always undertaken in calm or near-calm wind conditions there was not time for significant lateral movement or 'spray drift.' Any significant lateral movement of spray would require the materials to remain in the air for extended periods of time and they would therefore have been subject to rapid degradation by ultraviolet light (see Section 4.2).

Multiple aircraft were always used to apply herbicide, with the planes flying in close formation to ensure a continuous area of defoliation (**Fig. 3**). The wingmen typically flew so that the pilots could maintain position on the aircraft ahead of them. Forty three percent (43%) of the RANCH HAND spray missions consisted of three aircraft. Just over 70% of the missions consisted of three aircraft or less, although formation of eight and even twelve aircraft occurred beginning in 1967 [8,12]. The total area treated was usually less than one-half km in width and, assuming that the contents of all the tanks were expended, slightly more than 14 km in length.

Review of spray swath information suggested that dissemination of herbicide in Vietnam was very precise and resulted in a pattern of long narrow deposition areas with little herbicide outside the treatment area [13]. This conclusion is supported by biomonitoring data and by drift tests conducted by Taconi and Jones [14]. Application of a variety of products using various technologies that emitted similar drop size spectra provide a comprehensive picture of deposition downward in forested terrain [13,15].

Concentrations of herbicide greater than the biologically effective threshold resulted in defoliation, while concentrations slightly less than the biologically effective threshold resulted in deformed foliage and growing tips by stimulating unequal growth among plant tissues, resulting in slight discoloration [3]. Visual evidence of the precision with which herbicides were applied can be seen in **Fig. 4**.

This aerial photograph displays the very sharp lines of demarcation along the spray swaths in the very sensitive *Avicennia* and *Ceriops* mangroves in Vietnam. Had there been significant drift either way from the swath, traces of

Fig. 4: Aerial photograph taken in 1967 showing the defoliation spray swaths made by three RANCH HAND aircraft in the mangrove region of III Corps. In this instance, the aircraft did not fly in close formation to ensure a continuous area of defoliation. The swaths showed sharp lines of demarcation between treated foliage and untreated foliage. Photo courtesy of the RANCH HAND Collection, Vietnam Archives, Texas Tech University, Lubbock, TX

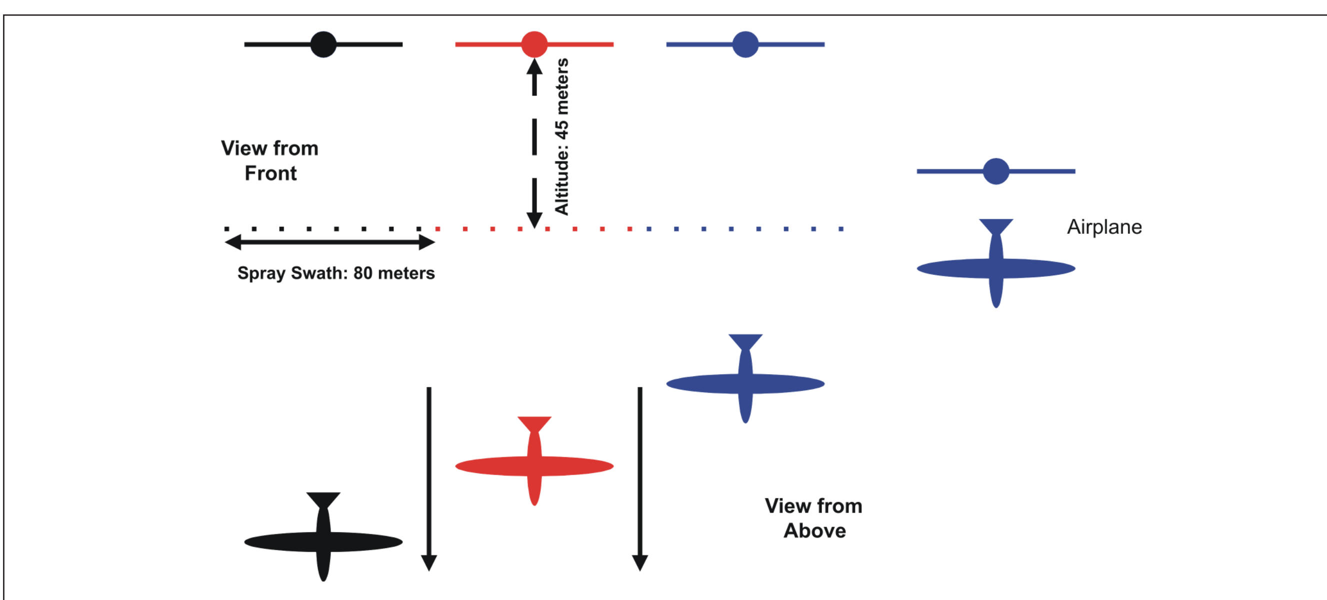

Fig. 3: A schematic of a typical three-airplane spray mission

Fig. 5: Aerial photograph taken in 1968 in III Corps over a mangrove forest sprayed in the Rung Sat Special Zone along the main ship channel to Saigon. Photo courtesy of the RANCH HAND Collection, Vietnam Archives, Texas Tech University, Lubbock, TX

damage would have been visible as streaks of discolored foliage adjacent to the downwind swath margin. Even if wind movement had occurred along the swath, the swaths were long enough that almost any deviation from perfect alignment with the swath would have shown damage away from the swath margin. Other pictures of a spray mission also illustrate the sharp lines of deposited herbicide in a mangrove forest (**Fig. 5**). The second approach in **Fig. 5** is at an angle of 90° to the first.

2.3 Base perimeter spraying

Defoliation by helicopter and ground spraying operations were the responsibility of the US Army Chemical Corps. Helicopter applications were flown at much lower speeds and altitudes and backpack and vehicle-mounted spray systems were effectively used at very low speeds and at ground level [7]. The relatively small proportion of military herbicides applied by these other methods (5% of the total applied [16]) posed less potential for drift than fixed wing applications. These methods did, however, create perhaps the greatest exposure situation for human applicators [17,18,19]. Even such very heavy dermal contact as occurred in these situations still resulted in a large safety factor [17]. Herbicide residues were demonstrated to be difficult to dislodge soon after the spray dried, and workers in sprayed forests were shown to be unlikely to sustain measurable exposure through their clothes [19].

3 The Forest Canopy and the Leaf Area Index

Forests generally have several layers or canopies of foliage structured to receive sunlight and convert it into chemical energy. When gaps occur between leaves, new leaves tend to grow into the spaces where the 'escaped' sunlight can be captured. The amount of sunlight, rain, or herbicide that is intercepted by a forest canopy depends on the density of the vegetation [19]. In a multi-canopy forest, such as in Vietnam, the topmost layer of the canopy receives the largest percentage, and each canopy layer underneath the top layer intercepts a successively smaller portion.

Foliage density can be quantified as a leaf area index (LAI), defined as the total leaf area in proportion to the ground surface below. For example, a value for the LAI of 2.0 means that there are two square meters of leaves per square meter of ground surface. The LAI is used for calculations involving photosynthesis, carbon absorption, and oxygen exchange and to define the amount of canopy penetration by light, rain, or herbicides [19,20,21].

Research has confirmed that the LAI reliably estimates the interception in the forest canopy of aerial herbicide applications such that each unit of LAI intercepts about half of the herbicide that reaches it. Stated mathematically, deposition is equal to deposit reaching the upper canopy times $2^{-(LAI)}$ [19]. A tropical forest with a LAI of 5 is thus likely to intercept about 97% of the total spray. Stems, branches and trunks will generally increase the amount of herbicide intercepted in the forest canopy since they represent lateral deposition surface not accounted for in the leaf area index [19,22]. Total interception by foliage and stems may range up to 99% [22]. In view of the role of ultraviolet light in destruction of TCDD, the interception of light in the same gradient is of considerable importance.

More than half of the Vietnamese jungle subjected to spraying operations was double and triple canopy jungle characterized by dense and diverse tree species [23]. Agent Orange was the herbicide of choice to apply to mature or secondary forests with LAI values ranging from 2 (open secondary) to 5 (mature forest). As the LAI increases, the proportion of applied herbicide intercepted by the foliage increases as well. In relatively undisturbed dense forests, the target canopy with an LAI of 3–5 would nearly always intercept 87–97% of the herbicide sprayed. Vegetation below the canopy receives 3–14% of the spray, with the higher percentage resulting in those areas where the forest was sparse. The underbrush or forest floor received about 1–6% of the total aerial spray [19,22]. These observations, taken together, indicate that little of the Agent Orange and associated TCDD would have penetrated directly to the soil and to any organisms on the ground. Rather, both the Agent Orange and TCDD would have been held on the surfaces of leaves until they fell to the ground. While some Agent Orange might have been washed from the leaves during strong rainfall events, the more lipophilic TCDD would have been less likely to be washed from the waxy surface of the leaves.

The ester formulations of herbicides, such as the n-butyl ester of 2,4-D and 2,4,5-T used in the Agent Orange formulation, exhibited greater herbicidal activity than the parent acids because of improved foliar absorption [24]. The herbicide 2,4,5-T was most effective when applied as the n-butyl ester because of rapid absorption into the leaf surface. Once inside the leaf surface, both the butyl esters of 2,4-D and 2,4,5-T were readily degraded (within hours) through transesterification and β oxidation [24].

3.1 Spray penetration and deposition of particles in forest canopies

Scientists from the US Department of Agriculture studied the penetration and distribution of herbicide sprays through forest canopies in Puerto Rico and Texas [22]. Although the two areas were widely separated geographically, the forests were similar in terms of structure. The test site in Puerto Rico was typical of moist forest formation. The lowest level of vegetation ranged from 2 to 3 m; the intermediate level had a mean height of 9 m; and, the upper canopy had a mean height of >15 m. In Texas, the forest had a dense and relatively unbroken overstory of post and blackjack oak about 12 m in height. The youpon undercanopy also was dense and relatively unbroken (about 5 m in height), but LAI was probably considerably less than that of the Puerto Rico site.

Spray materials were applied from aircraft and from fixed delivery systems. The aircraft were calibrated to deliver 37 L/ha (the UC-123/AA 45Y-1 Spray System used in Vietnam delivered 28 L/ha) at a speed of 65 knots and 5 m above the canopy. The fixed delivery system was mounted on a cableway 5 m above the top canopy, and it was also calibrated to deliver 37 L/ha.

Tests from the fixed cableway and from aircraft provided comparable results. The volume of spray deposited at various levels of the canopy varied with the type of spray material, the type of nozzle, and the nozzle angle. However, variation in volume was not great. The volume of spray reaching lower sampling levels varied proportionately with the amount deposited on the top line above the canopy. On average, about 21% of the spray volume penetrated the upper canopy and about 6% penetrated to the ground level in the experiments conducted in Texas [22].

Similar results were observed in forest brush field ecosystems in the Oregon Coast Range that were aerially treated with glyphosate [20]. Deposits were recorded at various canopy levels to determine interception and residues in foliage, litter, soil, streamwater, sediments and wildlife. The vegetation intercepted nearly all of the applied herbicide with most of the herbicide retained in the tree layers. The authors concluded that most of the herbicide reached its target and then "disappeared rapidly in the moist deciduous forest [20]."

4 Environmental Fate of Agent Orange and TCDD

4.1 Studies of Agent Orange jettisons, storage and disposal sites

From January 1962 to January 1971, RANCH HAND aircraft flew more than 19,000 combat sorties (a sortie is one aircraft mission) in support of defoliation and crop destruction missions [16,25]. In December 1986, the US Army and Joint Services Environmental Support (ESG) [26] released an update of records on helicopter and ground spraying missions, aborts, leaks, and incidents. Included in the category of 'incidents' were instances where RANCH HAND missions ended with emergency jettisons, most of which were considerably less than a full tank. The herbicide was jettisoned in a large diameter stream rather than nozzles in approximately 35 sec (versus 3.5 to 4 min for dissemination during a standard mission) [27]. ESG (now the US Armed Services Center for Research of Unit Records) found records of 48 emergency jettisons/incidents involving Agent Orange/Purple. Eighteen involved the jettison of herbicide at the end of a runway, over jungle or water. Twenty-seven were emergency jettisons that occurred in the target box – three involved aircraft crashes. Therefore although these emergency herbicide dumps may have resulted in increased soil herbicide concentrations, they represented only one quarter of a percent of the total missions flown.

In 1971, a team of scientists from a committee of the National Academy of Sciences (NAS) collected and analyzed five soil samples from an area in Vietnam where 3,700 liters of Agent Orange had been jettisoned in December 1968. No 2,4,5-T herbicide could be detected. However, no analytical methods at the time were sensitive enough to detect small concentrations of TCDD [23, 28]. Additional soil studies conducted in Vietnam and the Philippines by the same NAS team using operational rates of herbicide treatment (i.e., rates similar to those applied by RANCH HAND aircraft, but directly to the soil) found the half-life of 2,4,5-T was short (5 days), and that of 2,4-D was 2 days [28]. Moreover, the team was able to grow several phenoxy-sensitive and locally important vegetables within six weeks of application at rates applied operationally.

These data are consistent with residue studies conducted in 1970 on the spray equipment test site at Eglin AFB, Florida, after receiving repeated aerially applications of Agent Orange (a total of 17,900 liters or approximately 9,500 kg of 2,4,5-T and 9,500 kg of 2,4-D) from January to December 1969 [4,29]. Soil bioassay studies on herbicidal persistence and soil leaching were initiated in April 1970. By considering that all the phytotoxic effects on the bioassay organisms were from 2,4-D and 2,4,5-T, the greatest residue concentration of phenoxy herbicides (in the top 15 cm of soil) was estimated to be 2.8 mg/kg (ppm) (average of 8 soil cores). A follow-up bioassay experiment was conducted eight months later. These bioassays confirmed the rapid disappearance of the herbicides since the phytotoxic effects were less than 0.3 mg of phenoxy herbicides/kg of soil (ppm). Analytical studies of the 14 soil cores collected in December 1970 showed average residues of 8 µg of 2,4-D/kg of soil (ppb) and 4 ppb for 2,4,5-T [4,29].

Recently, the presence was reported of 'high levels' of TCDD in sediment and soil samples in Vietnam [30,31]. Neither reported finding residues of 2,4-D or 2,4,5-T, but did report soil concentrations of TCDD of 0.6 to 1.2 mg TCDD/kg soil (ppm). The source of these samples *was not* from aerial applications of Agent Orange, but rather from highly localized soil on or adjacent to the former Agent Orange storage site at Bien Hoa Air Base north of Ho Chi Minh City. More than 200,000 208-liter drums of Agent Orange were sent to Vietnam and disseminated in spray programs [32]. Sixty-five percent of these drums were sent to Bien Hoa to support RANCH HAND and US Army Chemical Corps Operations from March 1964, when Agent Orange first arrived in Vietnam, to March 1972, when the remaining inventory was re-drummed, removed and sent to Johnston Island in Operation PACER IVY [32]. These data are consistent with studies of Agent Orange storage and disposal operation sites at the Naval Construction Battalion Center, Gulfport, Mississippi, and Johnston Island, Central Pacific Ocean [33,34]. More than 15,000 208-liter drums of Agent Orange were stored at Gulfport, from 1969–1977, and more than 25,000 drums of Agent Orange (the inventory removed from Vietnam) were stored on Johnston Island from 1972–1977. To find such deposits in Vietnam required specific knowledge of location of leaking drums or jettison sites. None of these reflected general distribution of residues available to the general population of soldiers or citizens, and they cannot be used for general exposure indices.

Both inventories of herbicides were destroyed by at-sea incineration in 1977, and a monitoring program was initiated at both locations in January 1978 [33]. Studies of soil residues of 2,4-D and 2,4,5-T confirmed the rapid disappearance (degradation) of the herbicides over a four-year period (1978–1982). In both locations the level of herbicides dramatically decreased from a maximum of 62,000 mg/kg (ppm) (8 samples taken from the top 10 cm of soils from spill sites) to less than 2% of the initial concentration remaining at the end of the 4 years. In the same sampling period and sample sites, the TCDD concentrations decreased from 180 mg/kg (ppm) to less than 100 mg/kg (ppm) (45% loss in 4 yrs). The loss of herbicides and TCDD was attributed to microbial degradation, and volatilization with subsequent photodegradation [33,35]. Both the storage sites were sampled in 1987 (10 yrs after the removal of the drums), and levels of TCDD in composited soil samples ranged from 0.6 to 1.0 mg/kg (ppm) [36].

4.2 The environmental fate of TCDD

Various routes have been proposed for the disappearance of TCDD from the environment. From numerous field and environmental studies conducted on Agent Orange and its associated TCDD in Mississippi, Utah, Kansas, Florida, and Johnston Island, the mechanisms most likely responsible for TCDD disappearance included photodegradation, volatilization, microbial degradation, wind and water movement of contaminated particles, and biomass removal [4,29,33,37]. Of these, the role of sunlight (ultraviolet light), and the subsequent dechlorination of the TCDD molecule, was deemed the most important [4].

Studies of the photodegradation of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans associated with herbicide application have featured experiments that consider the variables influencing fate processes. Most notable are the experiments of Crosby and colleagues, 1973–1983 [38–43], Bentson in 1989 [44], Schuler and colleagues in 1998 [45], and Konstantinov and colleagues in 1999 and 2000 [46,47].

The principal processes that control the fate of nonpolar organic substances such as TCDD deposited on foliage include tissue absorption and adsorption or dissipation by evaporation, and photodegradation. These processes are initiated at the leaf-atmosphere interface. At the leaf surface the cuticular waxes represent a physiologically distinct layer where the fate processes are influenced. The properties of waxes of the leaf cuticle vary among plants, and as a result, influence the relative propensities of the different fate processes [48].

The results of the above studies suggest that Agent Orange, and associated TCDD, would have been absorbed into the wax layer of the leaf cuticle within minutes of spraying and could not then be physically dislodged. TCDD adhering to or absorbed in these organic plant surfaces would be destroyed by light within a few hours or longer depending on the level of sunlight. Because the deposit of herbicide and associated TCDD would decrease with leaf area index, and the radiation intensity decreases at the same rate, the absolute dissipation rate should be similar at all levels of the canopy. Should residues have persisted until humans made contact, the presence of a non-polar organic solvent capable of holding TCDD in solution, e.g., an ester of a phenoxy herbicide, would provide an energy barrier in contact with an aqueous medium such as human skin. This would have greatly restricted transfer of TCDD to that person.

A relatively small proportion of the TCDD might be absorbed more deeply into the plant before degradation, where it would become bound and biologically unavailable [19,24]. Some sunlight and ultraviolet radiation may penetrate within the plant. What is not decomposed, however, would not be mobile in the plant or readily dislodged. While a small amount of TCDD might have evaporated from foliage before degradation this TCDD would experience rapid photodegradation, the same fate as the herbicide dispersed in the atmosphere during application [49]. Due to photolysis by sunlight, the atmospheric half-life of TCDD in the vapor phase has been shown to be in the order of 1.0 hr [50,51]. From experimental studies investigating only the OH radical oxidation of TCDD, the atmospheric lifetime of TCDD was about 3 days [52].

When Agent Orange was spread on leaves and exposed to natural sunlight, the half-life of its TCDD content was less than 6 hr [40]. Photodegradation would continue with additional exposure to sunlight, destroying half of any remaining TCDD every 6 hours of full daylight. When Agent Orange was applied to loam soil and exposed to sunlight, degradation of TCDD "was somewhat slower, presumably because of shading of lower layers by soil particles." The requirements for photodegradation of TCDD were: dissolution in a light-transmitting film or material, the presence of a hydrogen-donor (such as herbicide or the waxy cuticle), and ultraviolet light [40,41].

Concentrations of TCDD in rangeland grasses following application of 2,4,5-T herbicides decreased rapidly in outdoor sunlight [53]. Photodegradation of TCDD on a number of surfaces and at a range of light intensities has also been demonstrated [44]. This work showed that the decomposition of TCDD continued in reduced light at a reduced rate (cloudy days and in shade). Generally, the reduced light levels contain the same wavelengths as direct sunlight at roughly equally reduced intensities, including the ultraviolet wavelengths that degrade TCDD. Relatively rapid disappearance of TCDD from leaves was confirmed even under low light conditions [54]. A half-life of 7 to 10 hrs was observed even when ultraviolet light intensities were low. Photodegradation continued even in the absence of a hydrogen-donor, with more than 90% of TCDD degraded after 7 days of exposure to ultraviolet light, showing that water vapor can also serve as a hydrogen donor.

Because herbicide spray missions were scheduled in the early morning on days when there was no precipitation, applications of Agent Orange were typically followed by several hours of sunlight [7,8]. Since liquid Agent Orange itself transmits ultraviolet light and is an excellent hydrogen-donor, photodegradation of TCDD in Agent Orange would have proceeded rapidly and would have occurred even in the relatively shady forest understory, though not as rapidly as in direct sunlight. The resultant defoliation of upper canopy layers would permit penetration of additional sunlight increasing the degradation of TCDD in understory vegetation.

Studies of the effect of waxy cuticle of plants on the degradation of dioxins and furans have shown that photodegradation processes continue at a significant rate even in the absence of herbicide adjuvants or carrier solvent, which may not be available as a result of plant absorption or evaporation over time [45]. When the dioxins and furans were incorporated into the leaf waxes of laurel cherry (*Prunus laurocerasus*), photodegradation was relatively unhindered. This is important since the tropical overstories in wet or dry tropics tend to have thick leaves and waxy cuticles. From these experiments, at least half of the starting amount of each of the dioxins and furans, which included 2,3,7,8-TCDD and 2,3,7,8-tetrachlorodibenzofuran, were degraded within an 8-hr exposure to actual sunlight. During the time that it would take for leaves to die and fall from trees, it would be expected that most of the TCDD would be degraded. For instance, in 4 days with average duration of light of 12 hr, less than 2% of the original TCDD would remain on the leaf surface.

Almost all of the Agent Orange would have been intercepted by the forest canopy or photodegraded on plant and ground surfaces. Only a very small proportion of the TCDD would have penetrated the canopy and reached the ground or understory where personal contact would be made. TCDD is relatively persistent and immobile once bound to soil [4]. If TCDD in soil becomes exposed to sunlight due to soil tilling or other disturbances it will degrade by photolysis [40], but forest soils are seldom tilled. Since a person is most likely to encounter surface soil, it would tend to have negligible TCDD levels because sunlight reaches the surface soil, and subsurface residues would not be readily available for contact. In addition, the principal manner of movement of TCDD in soil is by volatilization and re-adsorption. As TCDD volatilizes at the soil surface and enters the air it degrades by photolysis, if it has not already degraded on the surface [55].

Studies conducted with TCDD deposited on soil using spray equipment on the testing grids at Eglin AFB, Florida, demonstrated that photodegradation during and immediately after application destroyed nearly all of the TCDD in the herbicides applied on the test site. Once below the soil surface, the low residues of TCDD (in the absence of herbicide) remained confined in the top 15 cm for at least 14 yr following application of 32,500 kg of 2,4,5-T [4].

As a result of the very low solubility of TCDD in water and strong binding to soil, including bottom sediments, surface water was not determined to be a major contributing source of exposure to TCDD. Typically, TCDD was not detectable in streams or ditches adjacent to areas in the United States where 2,4,5-T was used repeatedly [54]. However, TCDD can be briefly present in surface water bound to floating particles of soil [33,37,56]. Such TCDD would be exposed to sunlight near the surface of the water and degrade within a few hours or days [38,40,57,58]. TCDD also volatilizes from rivers and ponds, with half-lives of approximately 6 and 32 days, respectively [58]. Once volatilized, TCDD photodegrades very rapidly in the atmosphere, with a half-life of less than 1 hr [58].

The above references to TCDD dissipation rates and influences thereon by environmental factors do not properly reflect on dislodgeability of TCDD from the medium on which residues are held. Research indicates that TCDD has a very strong tendency to adsorb to surfaces [69]. Affinity for surfaces removes TCDD from solution rapidly, and also logically retains very strongly residues held in foliage and litter. Removal of TCDD from bound residues most likely requires either considerable energy or organic solvents, neither of which normally accompany human contact with a TCDD-retaining substrate. In the absence of specific data on transferability of bound residue to animal tissue, logic dictates that physiological dosages from such contact would be below detection limits unless the deposit were still liquid immediately after deposition.

5 Applicable Animal and Human Studies of TCDD

5.1 Animal skin absorption studies

Studies examining the dermal uptake of TCDD by rat skin have demonstrated variability in dermal uptake, depending on the age of the animal. For the oldest animals, more than 80% of an applied dermal dose could be removed either by swabbing the application site, or it was bound to the skin at the application site [59]. In one of the few studies to use dermal application of soil to assess availability, TCDD in various test formulations (including soil) was applied to naked rat skin. Application of TCDD in soil to skin reduced penetration into skin, presumably because of almost instantaneous adsorption to mineral surfaces. Soil treatment reduced penetration of TCDD to the liver from 14% observed for organic solvent applications to less than 0.1% [60].

5.2 Human skin absorption studies

The fraction of a residue that is available for cutaneous uptake from the surface of plant leaves is called the 'dislodgeable foliar residue' (DFR) [61]. For chemicals that are absorbed into plant tissues, this fraction decreases as the chemicals penetrate into the leaves. The DFR is usually determined by a gentle washing of the leaf surfaces to determine the amount of chemical that reasonably could be expected to be adsorbed by human skin [61]. The DFR decreases as chemicals penetrate into the leaf tissue and are no longer 'accessible.' No information is available on DFR values for TCDD or Agent Orange. However, for 2,4-D applied to turf grass, the DFR was 8% of the total plant residue 1 hr after application [62]. This DFR was reduced to 1% of the total 24 hr after application. Only three of five human subjects who exposed bare skin to the 2,4-D treated turf accumulated any uptake of the herbicide. In addition, these three individuals were all exposed only 1 hr after the herbicide application. No residues were detected in any subjects exposing bare skin to the treated turf 24 hr after application.

Given its greater hydrophobicity, we would anticipate that the DFR for TCDD would decrease at least as rapidly as that of 2,4-D. Therefore, these results demonstrate that even 24 hr after application essentially no TCDD residues would be available from herbicide treated leaf surfaces.

The rate of skin absorption of a 2,4,5-T herbicide containing commercially acceptable dioxin levels ($<10^{-7}$) was investigated by applying the herbicide to 900 cm^2 areas of skin on volunteers [17]. The concentrations applied were representative of commercial applications at the time, ranging from 2.4 to 38.4 g/L of acid equivalent 2,4,5-T as an ester emulsified in water. After 2 hr of saturated contact with a large area of bare skin, only 0.15–0.46% of the 2,4,5-T penetrated the skin, entered the body, and was eliminated in the urine. Applications of the greatest concentrations of 2,4,5-T resulted in the highest absolute penetration, but in the least proportion of 2,4,5-T applied. Although TCDD was not measured penetrating the skin directly, other evidence suggests that TCDD penetrates with about the same proportion as observed with 2,4,5-T [63]. The lack of liquid with which the residue would be transferred to the skin in a forest exposure surely reduces transfer even further.

5.3 Contamination of food and potential ingestion

From the previous discussion, it appears that the potential for ingestion of TCDD was very small in Vietnam. However, ingestion needs to be considered as a potential pathway since it has been shown to be a major route of human exposure to dioxins [64]. Although food denial through destruction of crops in enemy-controlled areas was a goal of Operation RANCH HAND, it was unlikely that food crops sprayed with Agent Orange were consumed by ground troops. Food crops were sprayed well in advance of harvest before they matured [7,8]. Susceptible (broadleaf) species wilt quickly and would have been destroyed before consumption. Moreover, the phenolic smell of the butyl esters of 2,4-D and 2,4,5-T was offensive and its presence on food would make it unappealing and unpalatable [37].

5.3.1 Contamination of crops

The most important crop in Vietnam was rice, and the bulk of the crop destruction effort was directed at the rice harvest. Rice growing was concentrated in low-lying coastal 'rice bowls,' many of which were in the eastern coastal areas [7,8]. Agent Blue, which contained no 2,4,5-T or TCDD, was used for destruction of rice crops since rice is not susceptible to Agent Orange [7,8]. Indeed, because 2,4,5-T is so highly species-selective, it has been widely used on maturing rice fields to control weeds without harming the rice crop [28].

Even consumption of crops sprayed by mistake shortly before harvest would be unlikely to result in intake of a significant amount of TCDD. Herbicide and TCDD residues would generally be found on the exterior husk or skin, not the interior edible portion of a crop [65,66]. Any such exterior residues would be reduced by photodegradation in sunlight or would be removed with the outer vegetation layers before consumption. The uptake of TCDD in grass and rice has been studied, and no TCDD residues were found in rice grain from crops heavily treated with 2,4,5-T [53].

Uptake of TCDD through plant roots has been found to be extraordinarily low in the few circumstances where it could be measured, and little or no TCDD residue has been found on plant leaves above ground level or in plant seeds [37, 53,66,67]. Given the restrictions placed on the herbicide spray program to avoid damage to friendly crops, there was little possibility of significant TCDD contamination of agricultural fields in friendly regions and, as discussed above, even less probability of human exposure through consumption of food crops.

5.3.2 Contamination of food animals

Livestock and other animals were generally not significantly exposed to TCDD by application of Agent Orange for the same reasons as humans: the herbicide was largely intercepted in the forest canopy, and TCDD photodegraded rapidly in the environment, dried quickly and became non-dislodgeable, or bound strongly to soil. Animals that grazed naturally or were fed from fields treated with Agent Orange would have been expected to accumulate only minimal residues of TCDD in their tissue based on studies of forest herbivores in a hardwood forest aerially treated with a butyl ester of 2,4-D and 2,4,5-T [68]. The likely source of trace levels of TCDD in some herbivorous animals is the incidental ingestion of contaminated soil. Indeed, examination of the ecological niches of animal species containing TCDD residues in the Eglin AFB studies concluded that each of the species were in close contact with contaminated soil [4].

Accumulation of TCDD by aquatic animals is almost entirely dependent on concentrations in water or sediment [4,30,31,33,69,70]. Any TCDD would typically be found in sediments, and benthic, bottom-dwelling species that ingest substantial amounts of bottom sediment are more likely to have detectable levels of TCDD [4]. Studies at Eglin AFB, Florida, confirmed that bottom-feeding fish in ponds in the contaminated test areas had concentrations of 85 ppt TCDD in their guts and 4 ppt in muscle tissue [4]. Similar results were obtained in Bien Hung Lake, a lake receiving contaminated soil from the former Agent Orange storage site at Bien Hoa Air Base, Vietnam [30].

5.3.3 Assimilation after ingestion

Upon ingestion, organic contaminants such as TCDD must be assimilated from the food items into the human body before they can reach sites of toxic action. Contaminants that are tightly bound to the food matrix or ingested soil can be less efficiently assimilated by the body. For this reason, a significant proportion of an ingested dose does not enter the body. It passes harmlessly through the digestive system. The efficiency with which dioxins are assimilated in animals varies with the chemical, the food or soil type, and the species of animal. For example assimilation efficiency for TCDD for environmentally contaminated soils ranged from a maximum of 63% to a minimum of only 0.5% with an average of 31% [71]. Therefore, in these animals less than one third of the ingested TCDD actually entered the body, with the majority of the dose being excreted in the feces. In contrast, dietary absorption of TCDD from food in humans seems to be nearly complete [64,72] due to the more complete digestion of the foods consumed. Little or no data are available on the assimilation of TCDD from soil in humans.

5.3.4 TCDD in serum

Testing of serum dioxin levels has been widely regarded as the 'gold standard' for epidemiological studies of Agent Orange and dioxin since its development in the 1980's [73]. Although such testing is expensive, the major industrial studies since the 1980's have employed it to validate various methodologies for estimation of exposure. Many more studies simply relied upon serum TCDD levels to measure exposure to dioxin-containing materials. While the passage of time complicates the use of serum TCDD results, it remains the best possible evidence of an historical absorbed dose of TCDD. Its superior predictive power has been confirmed repeatedly [73].

5.3.5 Studies of Vietnam veterans

Numerous studies relying on serum dioxin testing have demonstrated that some RANCH HAND and Army Chemical Corps veterans involved in the application of Agent Orange in Vietnam absorbed doses of dioxin that can still be distinguished decades afterwards [74,75]. Similar studies of ground troops have not found elevated levels of dioxin, providing strong evidence that these troops were not significantly exposed to dioxin from Agent Orange [76].

The 1988 serum dioxin study by the Centers for Disease Control and Prevention (CDC) compared levels of serum TCDD in 646 US Army veterans who served as ground troops in the most heavily sprayed regions of Vietnam with those of 97 Vietnam-era veterans who had not served in Vietnam [76]. The distributions of TCDD levels were 'nearly identical' in the two groups, both having means and medians of about 4 ppt TCDD. Neither military and spraying records nor self-reported history of exposure could reliably identify high or low exposure groups, and "most US Army ground troops who served in Vietnam were not heavily exposed to TCDD, except perhaps men whose jobs involved handling herbicides" [76].

These results were consistent with other studies. A planned epidemiological study of ground troops and Agent Orange was discontinued as infeasible. Subsequent CDC investigations of health effects in ground troops focused on whether the overall 'Vietnam experience' increased the risk of cancer or other diseases [77–80]. These studies identified a number of health effects associated with military service in Vietnam. Other studies examined whether such effects were related to secondary indicators of possible exposure to Agent Orange [81,82]. No such relationships were found.

6 Conclusions

The prospect of significant exposure to TCDD from Agent Orange to ground troops in Vietnam seems unlikely in light of the environmental fate of TCDD, low bioavailability, and the properties of the herbicides and the application circumstances that occurred. Photochemical degradation of TCDD and the limited bioavailability of any residual TCDD present in soil or on vegetation lead to the expectation that dioxin levels in ground troops who served in Vietnam would be low and indistinguishable from background levels even if they had been in recently treated areas. Agent Orange was applied as small droplets that absorb into plant tissue or dried very quickly. It has been reported that after three hours it was not possible to detect any 2,4,5-T rubbed from foliage onto cloth patches while walking through forests aerially sprayed with 2,4,5-T [18].

A very narrow window of time – typically a few minutes – was available after spraying before drying. An individual making contact with treated vegetation while wearing almost any clothing at the point of contact would not be in personal contact. The amount of TCDD actually absorbed due to a single exposure would be extremely small even if contact had occurred. Once Agent Orange and TCDD dried on plant surfaces and the TCDD became bound, it was unlikely for the residue to have become bioavailable thereafter. If it was adsorbed onto woody plant tissue sufficiently that sunlight was blocked, it was not bioavailable.

The Centers for Disease Control and Prevention reported that serum concentration of TCDD in over six hundred veterans judged likely to have been exposed to Agent Orange in Vietnam were the same serum TCDD levels as those veterans who never served in Vietnam [76]. Levels of TCDD did not increase with greater likelihood of exposure based upon military records or upon self-reported exposure. This failure to distinguish serum TCDD levels in ground troops with the highest potential for exposure at a time reasonably close to cessation of exposure highlights that exposure reconstructions based upon analysis of military records are poor predictors of actual absorbed dose.

To absorb dioxin from Agent Orange, direct skin contact with liquid Agent Orange would have been necessary. Those Vietnam veterans who had elevated serum levels of TCDD had direct contact with the liquid herbicide and were involved in part of the RANCH HAND operation or were in the Chemical Corps who also handled Agent Orange in Vietnam [74,75,82].

The experimental laboratory and field data summarized here provide compelling evidence on the fate and dislodgeability of herbicide and TCDD in the environment. This evidence of the environmental fate and low bioavailability of TCDD from Agent Orange is consistent with the observation of little or no exposure in the vast majority of Vietnam veterans. Appreciable accumulation of TCDD would have required repeated long-term direct skin contact of the type experienced by RANCH HAND and Chemical Corps, not incidental exposure under field conditions where Agent Orange had been sprayed.

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Original Article

Agent Orange as a Risk Factor for High-Grade Prostate Cancer

Nathan Ansbaugh, MPH[1]; Jackilen Shannon, PhD, RD[1,2,3,4]; Motomi Mori, PhD[4];
Paige E. Farris, MSW[2]; and Mark Garzotto, MD[3,4,5]

BACKGROUND: Agent Orange (AO) exposure (AOe) is a potential risk factor for the development of prostate cancer (PCa). However, it is unknown whether AOe specifically increases the risk of lethal PCa. The objective of this study was to determine the association between AOe and the risk of detecting high grade PCa (HGPCa) (Gleason score ≥7) on biopsy in a US Veteran cohort. **METHODS:** Risk factors included clinicodemographic and laboratory data from veterans who were referred for an initial prostate biopsy. Out comes were defined as the presence versus the absence of PCa, HGPCa, or low grade PCa (LGPCa) (Gleason score ≤6) in biopsy specimens. Risk among AOe veterans relative to unexposed veterans was estimated using multivariate logistic regression. Separate models were used to determine whether AOe was associated with an increased risk of PCa, HGPCa, or LGPCa. **RESULTS:** Of 2720 vet erans who underwent biopsy, PCa was diagnosed in 896 veterans (32.9%), and 459 veterans (16.9%) had HGPCa. AOe was associated with a 52% increase in the overall risk of detecting PCa (adjusted odds ratio, 1.52; 95% confidence interval, 1.07 2.13). AOe did not con fer an increase in the risk of LGPCa (adjusted odds ratio, 1.24; 95% confidence interval, 0.81 1.91), although a 75% increase in the risk of HGPCa was observed (adjusted odds ratio, 1.75; 95% confidence interval, 1.12 2.74). AOe was associated with a 2.1 fold increase (95% confidence interval, 1.22 3.62; $P < .01$) in the risk of detecting PCa with a Gleason score ≥8. **CONCLUSIONS:** The current results indicated that an increased risk of PCa associated with AOe is driven by an increased risk of HGPCa in men who undergo an initial prostate biopsy. These findings may aid in improved PCa screening for Vietnam era veterans. ***Cancer* 2013;000:000–000.** © *2012 American Cancer Society.*

KEYWORDS: prostatic neoplasms, urology, Agent Orange, risk factors, veterans.

INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed visceral malignancy among men in the US and the second leading cause of male cancer-related deaths.[1] Although the treatment of clinically apparent cancer results in improved overall survival,[2] the effectiveness of routine PCa screening for the detection of subclinical disease remains an area of intense controversy. Two large population-based studies of routine PCa screening demonstrated a vast propensity for the detection of clinically insignificant cancer.[3,4] It is noteworthy that no difference in overall survival between screened and nonscreened men was observed in 1 study, and only a modest improvement in survival was observed in the other. These findings recently led to a categorical recommendation against prostate-specific antigen (PSA)-based screening by the US Preventive Services Task Force.[5] The panel cited the need for improved biomarkers for the detection of clinically significant prostate cancer. However, because of limitations in the data, they were unable to assess the effectiveness of prostate screening in special populations, such as Vietnam War veterans exposed to Agent Orange (AO).

AO exposure (AOe) has been studied as a potential risk factor for the development of PCa. AO was a commercially manufactured defoliate that was sprayed extensively during the Vietnam War. Because of a side-product of chemical manufacturing, AO was contaminated with the toxin 2,3,7,8-tetrachlorodibenzo-p-dioxin, a putative carcinogen. Sufficient evidence has linked AOe to several other malignancies, including soft tissue sarcoma, Hodgkin disease, and non-Hodgkin lymphoma.[6] Limited but suggestive evidence exists for an association with respiratory cancers, PCa, and multiple myeloma.[6] Dioxins remain an area of important interest, because these environmental toxins continue to be produced through chemical processing and municipal waste incineration. These chemicals can then enter the food chain through soil contamination.[7]

Corresponding author: Mark Garzotto, MD, 3710 SW US. Veterans Hospital Road (P3GU), Portland, OR 97239; Fax: (503) 721 1479; mark.garzotto@va.gov

[1]Public Health and Preventive Medicine, Oregon Health and Science University, Portland, Oregon; [2]Oregon Health and Science University Center for Research on Occupational and Environmental Toxicology, Portland, Oregon; [3]Division of Urology, Portland Veterans Affairs Medical Center, Portland, Oregon; [4]Oregon Health and Science University Knight Cancer Institute, Portland, Oregon; [5]Departments of Urology and Radiation Medicine, Oregon Health and Science University, Portland, Oregon

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Vietnam veterans are now reaching their mid-60s, the age at which new cases of PCa are most commonly diagnosed in the United States.[8] To more accurately assess the latent effects of AOe on PCa risk, a reassessment of contemporary biopsy data is needed. Roughly 8 million men in the United States are veterans of the Vietnam War.[9] On the basis of national PCa rates between 2005 and 2007, it is predicted that nearly 1.4 million of these men will develop PCa during their lifetime.[8] Although no real estimates exist for the percentage of Vietnam veterans who experienced AOe, roughly 3 million veterans served in Southeast Asia alone, where AO was used extensively in the combat theater. The primary objectives of this study were 1) to estimate the risk of PCa and high-grade PCa (HGPCa) in veterans with AOe relative to the risk for those without exposure, 2) to determine whether AOe is associated with a unique increase in HGPCa or whether there is an equal effect on the risk of low-grade PCa (LGPCa), and 3) to examine AOe by service branch to rule out potential confounding.

MATERIALS AND METHODS

Overview

Our study is an historic cohort analysis of 2720 veterans who were referred to the Portland Veterans Affairs Medical Center (PVAMC) and underwent an initial prostate biopsy. Any patient who had a prior diagnosis of prostate cancer was excluded from the database. Historic information regarding PCa risk factors and AOe were collected for each veteran. To assess possible risk factors for a positive prostate biopsy, clinical information for each patient, including AOe, was recorded using a standard data form before each prostate biopsy procedure and then collated with the prostate biopsy pathology results.

Data Management and Collection

Clinical, laboratory, biopsy parameters, and transrectal ultrasound (TRUS) data were recorded for all patients using a uniform template. Pathology reports were accessed to determine the presence of cancer and the biopsy grade (Gleason score). Patient information in this database was linked to historic information from the Veterans Integrated Service Network 20 Consumer Health Information Performance Sets Data Warehouse. Linking our prostate biopsy database to the data warehouse allowed us to capture additional clinical information, validate existing TRUS biopsy data, and obtain information on AOe.

The study principal investigator performed quality-assurance checks by comparing data against veterans' electronic medical records. Operating under a waiver of informed consent, all study procedures were conducted after receiving approval by the PVAMC Institutional Review Board and Research and Development Committee. For statistical analysis, the data, without personal identifiers, was exported into STATA statistical software (version 11.0: Stata Corporation, College Station, Tex).

Risk Factor Information

Data used in this analysis included AOe, family history of PCa, age, race, PSA, digital rectal examination (DRE), PSA density (PSAD) (PSA/prostate volume = PSAD), body mass index (BMI), and service branch history. For purposes of quality assurance, missing data and outlier data were reviewed before anonymizing the data to assure that appropriate variable definitions were applied. Service branch and PSAD information was recorded in an attempt to reduce the potential for residual and unmeasured confounding.

AOe status, as classified within the Veterans Affairs (VA) electronic medical record, was determined during patient enrollment into the VA hospital system. Each individual was defined as either "exposed" or "unexposed" in accordance with the PVAMC standards for documenting AOe. Individuals who did not have available AOe status were classified as unexposed. This assumption was deemed appropriate: It is probable that individuals who have reported exposure would have this information available in their medical records, because AOe is a known risk factor for many different conditions/diseases.[6] Of the 2720 veterans in the study, only 9 (0.3%) did not have explicitly declared information regarding AOe status and, thus, were characterized as not exposed. The exposure status for the remaining 2711 veterans was obtained directly from the Veterans Integrated Service Network 20 data warehouse. Information in the data warehouse classified veterans as exposed either if their location of military service corresponded with a location where AO was known to have been used or if, at the time of enrollment into the VA hospital system (before prostate biopsy), the veteran reported AOe.

Outcome Definitions

The primary outcomes of this study were the needle-biopsy detection of histologic PCa and clinically significant PCa, defined as PCa with a Gleason score $\geq$7. A secondary objective was the detection of Gleason score $\geq$8 disease. The outcome for the first multivariate model (Model 1) was defined as positive versus negative cancer in the biopsy specimen. The outcome for Model 2 was defined as the detection of HGPCa (Gleason score $\geq$7) versus no HGPCa (low-grade cancer [Gleason score $\leq$6]

TABLE 1. Study Population Demographics Overall and by Prostate Biopsy/Cancer Grade

	Mean (95% CI)	Mean (95% CI)			Mean (95% CI)		
Variable	Total Study Population	Positive Prostate Biopsy, n 896	Negative Prostate Biopsy, n 1824	P^a	HGPCa, n 459	LGPCa/No PCa, n 2261	P^a
AO exposure, %	7.46 (6.48 8.45)	8.3 (6.5 10.1)	7.1 (5.9 8.2)	.268	8.7 (6.1 11.3)	7.2 (6.1 8.3)	.263
Age at biopsy, y	64.7 (64.4 65)	65.7 (65.2 66.2)	64.2 (63.9 64.6)	< .0001	66.5 (65.8 67.2)	64.4 (64.1 64.7)	< .0001
BMI, kg/m^2	29.3 (29.1 29.6)	29.2 (29.3 30.2)	29.1 (28.8 29.5)	< .05	29.7 (29.1 30.3)	29.2 (29.2 29.5)	.186
PSA, ng/mL[b]	9.15 (8.06 10.2)	12.1 (9.3 15)	7.7 (6.8 8.5)	< .001	36.4 (15.4 57.4)	7.5 (6.8 8.2)	< .001
PSAD, ng/mL/mL[c]	0.19 (0.18 0.21)	0.32 (0.12 0.14)	0.13 (0.12 0.14)	< .0001	0.43 (0.34 0.51)	0.15 (0.14 0.16)	< .0001
Family history, %	18.6 (17.1 20)	21.4 (18.8 24.1)	17.2 (15.4 18.9)	.007	22 (18.2 25.8)	17.9 (16.3 19.4)	.038

Abbreviations: AO, Agent Orange; BMI, body mass index; CI, confidence interval; HGPCa, high grade prostate cancer (Gleason score ≥7); LGPCa, low grade prostate cancer (Gleason score ≤6); PCa, prostate cancer; PSA, prostate specific antigen; PSAD, prostate specific antigen density.

[a] *P* values for means were calculated using 2 sample *t* tests with equal variances; *P* values for proportions were calculated using Pearson chi square tests.

[b] Excluding extreme values (>1000 ng/mL).

[c] Excluding extreme values (>20 ng/mL/mL).

or no PCa). To determine whether AOe was associated with an increased risk of either LGPCa or HGPCa, 2 additional models (Models 3 and 4) were built. For Model 3, the outcomes were HGPCa versus no PCa. For Model 4, the outcomes were LGPCa versus no PCa. A final model (Model 5) examined the association between AOe and Gleason score ≥8 PCa.

Statistical Analysis

Separate multiple logistic regression models were built using STATA 11.0 to accomplish the primary objectives of this study. The models were assessed for goodness of fit, and the area under the receiver operating characteristic curve was used as a measure of the model's overall accuracy as well as to determine the cutoff point for the predictive probability of a positive biopsy.

RESULTS

Population Demographics

The study population included 93.6% white men, 3.8% black men, 1% Hispanic men, and <1% Asian and Native American men. No significant association was observed between race and the PCa outcome variables or AOe. The average age (±standard deviation) for all veterans who were referred for prostate biopsy was 64.7 ± 7.4 years. The average age of individuals who had PCa identified on biopsy was 65.7 years compared with 64.2 years for those without PCa ($P < .0001$), as indicated in Table 1.

Information on BMI was available for 61.8% (n = 1681) of the study population. Of these, <1% of men were categorized as underweight (BMI <18.5 kg/m^2), 17.4% were normal weight (BMI 18.5-24.9 kg/m^2), 39.4% were overweight (BMI 25.0-29.9 kg/m^2), and 42.3% were obese (BMI >30 kg/m^2). Table 1 indicates that no difference was observed between the BMI of veterans with and without PCa. There was also no difference in BMI category between AOe and non-AOe veterans (see Table 2).

Of the veterans without PCa, 17.2% reported a family history of PCa compared with 21.4% of veterans with PCa ($P = .007$) (Table 1). No association was observed between PCa family history and history of AOe (Table 2). Finally, PCa was detected in 896 of the 2720 veterans (32.9%) who were referred for prostate biopsy. Of those 896 men with PCa, 459 (16.9%) had HGPCa (Gleason score ≥7).

Agent Orange Exposure

Of the 2720 veterans who underwent a prostate biopsy procedure, 203 (7.5%) met the definition for AOe as reflected in their medical records. In multivariate logistic regression analysis (for the all models of analyses, see Table 3), the primary predictor of interest, AOe, was associated significantly with an increased risk of a positive prostate biopsy (Model 1). The risk of PCa in those with AOe was 52% greater (adjusted odds ratio, 1.52; 95% confidence interval, 1.07-2.13; $P = .017$) than the risk of PCa in those without AOe. Additional independent predictors of PCa included a positive family history, increased age, Marine Corps service, increased PSAD, and abnormal DRE results.

In Model 2, which compared the presence versus the absence of HGPCa, veterans who had AOe had a 74% greater risk of HGPCa compared with those who did not have AOe (adjusted odds ratio, 1.74; 95% confidence interval, 1.14-2.63; $P = .01$). AOe was associated predominantly with HGPCa (adjusted odds ratio, 1.75; 95% confidence interval, 1.12-2.74) versus no PCa in Model 3. In Model 4, no significant association was observed in the analysis of LGPCa versus no PCa (adjusted odds ratio,

TABLE 2. Study Population Demographics by Agent Orange Exposure Status

Variable	Entire Study Population: Mean (95% CI) AO Exposure, n 203	Entire Study Population: Mean (95% CI) No Exposure, n 2517	P[a]	Individuals With Positive Prostate Biopsy: Mean (95% CI) AO Exposure, n 74	Individuals With Positive Prostate Biopsy: Mean (95% CI) No Exposure, n 822	P[a]	Individuals With HGPCa: Mean (95% CI) AO Exposure, n 40	Individuals With HGPCa: Mean (95% CI) No Exposure, n 419	P[a]
Age at biopsy, y	60.6 (60.0 61.2)	65.0 (64.8 65.3)	< .0001	61.4 (60.5 62.3)	66.1 (65.6 66.6)	< .0001	62.1 (60.9 63.3)	66.9 (66.1 67.6)	< .001
BMI, kg/m^2	30.0 (29.2 30.8)	29.3 (29.0 29.6)	.117	30.1 (28.8 31.4)	29.7 (29.2 30.2)	.550	29.3 (27.6 31.1)	29.7 (29.1 30.4)	.686
PSA, ng/mL[b]	11.2 (4.3 18.2)	12.4 (8.6 16.2)	.864	8.8 (6.1 11.5)	23.0 (11.3 34.7)	.478	7.9 (7.6 8.1)	7.7 (7.6 7.8)	.357
PSAD, ng/mL/mL[c]	0.20 (0.13 0.28)	0.19 (0.18 0.21)	.710	0.34 (0.14 0.53)	0.32 (0.27 0.37)	.845	0.30 (0.17 0.42)	0.44 (0.35 0.53)	.344
Family history, %	20.2 (14.7 25.7)	18.4 (16.9 19.9)	.534	25.7 (15.7 35.6)	21 (18.3 23.8)	.353	32.5 (18 47)	21 (17.1 24.9)	.094
Positive biopsy, %	36.5 (29.8 43.1)	32.7 (30.8 34.5)	.268	100	100	NA	100	100	NA

Abbreviations: AO, Agent Orange; BMI, body mass index; CI, confidence interval; HGPCa, high grade prostate cancer (Gleason score ≥7); NA, not applicable; PSA, prostate specific antigen; PSAD, prostate specific antigen density.
[a] P values for means were calculated using 2 sample t tests with equal variances; P values for proportions were calculated using Pearson chi square tests.
[b] Excluding extreme values (>5000 ng/mL).
[c] Excluding extreme values (>20 ng/mL/mL).

TABLE 3. Comparison of Effects Observed in Separate Multivariate Regression Analyses

Variable	Model 1: All PCA (LGPCa & HGPCa) vs No PCa OR	95% CI	P[a]	Model 2: HGPCa vs Other (LGPCa and No PCa) OR	95% CI	P[a]	Model 3: HGPCa vs No PCa OR	95% CI	P[a]	Model 4: LGPCa vs No PCa OR	95% CI	P[a]	Model 5: Gleason ≥8 vs Other OR	95% CI	P[a]
AO exposure	1.52	1.07 2.13	.017	1.74	1.14 2.63	.010	1.75	1.12 2.74	.014	1.24	0.81 1.91	.324	2.10	1.22 3.61	< .01
Age, y															
<60	1.00			1.00			1.00			1.00			1.00		
60 69	1.39	1.10 1.75	.005	1.51	1.11 2.05	.009	1.57	1.13 2.18	.007	1.27	0.96 1.68	.092	1.78	1.15 2.77	.01
≥70	1.54	1.19 2.00	.001	1.81	1.29 2.53	.001	1.92	1.34 2.75	< .001	1.25	0.91 1.72	.168	1.57	0.97 2.55	.07
PSAD, ng/mL/mL															
<0.10	1.00			1.00			1.00			1.00			1.00		
0.10 0.14	2.09	1.61 2.72	< .001	2.03	1.34 3.06	.001	2.30	1.51 3.48	< .001	2.04	1.49 2.79	< .001	2.13	1.07 4.27	.03
0.15 0.19	4.07	3.06 5.42	< .001	4.96	3.31 7.45	< .001	6.20	4.08 9.41	< .001	3.16	2.22 4.50	< .001	4.64	2.37 9.05	< .001
≥0.20	8.85	6.88 11.4	< .001	10.0	7.05 12.3	< .001	14.7	10.1 21.1	< .001	6.20	4.57 8.42	< .001	12.8	7.19 22.7	< .001
DRE															
Normal	1.00			1.00			1.00			1.00			1.00		
Suspicious	1.80	1.48 2.18	< .001	1.88	1.46 2.41	< .001	2.14	1.64 2.79	< .001	1.63	1.29 2.07	< .001	1.60	1.60 3.38	< .001
Cancer likely	10.3	6.63 17.0	< .001	12.8	8.72 18.9	< .001	19.1	11.8 30.9	< .001	4.55	2.55 8.14	< .001	11.4	11.4 26.6	< .001

Abbreviations: CI, confidence interval; DRE, digital rectal examination; HGPCa, high grade prostate cancer (Gleason score ≥7); LGPCa, low grade prostate cancer (Gleason score ≤6); OR, odds ratio; PCa, prostate cancer; PSAD, prostate specific antigen density.
[a] P values were calculated using the Wald test.[b]This was the primary predictor.

1.24; 95% confidence interval, 0.81-1.91). Model 5 demonstrated an even stronger association between AOe and the detection of PCa with a Gleason score ≥8 (adjusted odds ratio, 2.1; 95% confidence interval, 1.22-3.62; $P <$ .01). Additional predictors of HGPCa included increased age, service branch, increased PSAD, and abnormal DRE results. However, our multivariate models only included significant confounders (age, DRE results, and PSAD), because adjustment for the remaining variables had a less than 10% effect on the association between AOe and HGPCa.

Veterans with AOe also presented with abnormal prostate screening parameters and underwent a prostate biopsy roughly 5 years earlier than veterans without AOe (Table 2). Among those with PCa, veterans who had AOe were diagnosed, on average, roughly 5 years earlier than veterans who did not have AOe (mean age at PCa diagnosis: AOe group, 61.4 years; nonexposed group, 66.1 years; $P < .0001$ for the difference). Similar age-range results were observed when we compared age at diagnosis according to AOe status among individuals with HGPCa (mean age at HGPCa diagnosis of HGPCa: AOe group, 62.1 years; nonexposed group, 66.9 years; $P < .001$ for the difference). Although this result suggests that age potentially modifies the effect of AOe on the risk of PCa and HGPCa, the interaction was not identified as significant ($P = .119$) in the multivariate models.

Reported percentages of AOe in each branch of the military and referral for prostate biopsy were as follows: Army, 8.9%; Navy, 4.2%; Air Force, 6.3%; Marine Corps, 14.3%; Coast Guard, 0%; Merchant Marines, 0%; and 3.9% in the unknown group. The frequency of positive biopsy in AOe veterans was compared over different service branches. Air Force veterans were used as the reference category, because this service branch did the majority of AO spraying during the Vietnam War and has received the most attention from research about AOe veterans. This allowed us to compare the frequency of positive biopsy and HGPCa between the AOe Airmen who were responsible for spraying AO versus Marine and Army ground troops. Upon crude comparison, no significant associations between service branch and the frequency of PCa in AOe veterans were observed.

DISCUSSION

Clinically accessible biomarkers are needed to refine current PCa screening practices. Optimizing the detection of potentially lethal PCa is likely to result in an improvement in PCa survival and treatment-induced morbidity. The US Preventive Services Task Force guideline panel has recently recommended against population-based PSA screening[5]; however, it is important to note that the effect of AOe was not addressed by the task force. Our results demonstrate that AOe is positively associated with a 52% increase in the risk of PCa detection at initial prostate biopsy. Other recent studies also suggest that AOe increases the risk of PCa.[10,11] Of chief concern is our finding that AOe was associated with a 75% increase in the risk of PCa with a Gleason score $\geq$7 and a 110% increase in the risk of PCa with a Gleason score $\geq$8 among veterans who are referred for an initial prostate biopsy. AOe appears to have a unique effect on the risk of HGPCa and a weak but nonsignificant increase in the risk of LGPCa. This strongly suggests that aggressive PCa primarily is driving the observed increase in overall PCa risk. Thus, AOe may be a readily identifiable clinical biomarker for the prediction of lethal PCa and would likely increase the sensitivity for detecting cancers in the veteran population that are more likely to be aggressive and potentially lethal without adding to the problem of the overdiagnosis of low-risk cancers.

In the current study, we observed that the veterans with AOe who were at risk for having HGPCa detected presented with abnormal prostate screen findings and, on average, had cancers detected 4 to 5 years earlier than nonexposed veterans. This observation is consistent with the study by Chamie et al, who reported an association between AOe and HGPCa among 363 men with prostate cancer in a population-based study of US Veterans. These findings may have significant implications in the development of effective PCa screening strategies for AOe veterans, because they may develop more life-threatening cancers earlier in their lives than non-AOe veterans or men in the general US population.

The effect of AOe on the risk of PCa detection has been an area of some scientific debate. Early studies failed to demonstrate a significant association between AOe and PCa detection[12,13]; however, the majority of studies, including larger, more recent studies, have demonstrated a positive association between AOe and PCa.[10-13] The small sample sizes in the studies that reported positive but statistically nonsignificant associations warrant caution, because a type II error may account for these nonsignificant findings, in that those studies were not powered to identify an association with the strength we observed in our current study.

Limitations in our methodology should be considered. First, selection bias may have occurred if physicians were more likely to refer a patient for prostate biopsy if the physician knew a veteran had AOe. Not only would this create an inflation of the effect measure, but it also may account for AOe veterans' diagnoses at a younger average age than those without exposure. However, if differential selection bias occurred, then AOe veterans with similar PSA levels, DRE results, age, race, and family histories would be referred for prostate biopsy at a higher rate than similar nonexposed veterans. Thus, we would expect to observe a higher proportion of AOe veterans with no PCa or with LGPCa, because men with HGPCa generally display clinical symptoms, significantly elevated PSA, or abnormal DRE results, which would have caused them to be referred regardless of their AOe status. In our current study, the finding that AOe was associated significantly with a 75% increase in the risk of HGPCa is not consistent with this selection bias by physician referral. In addition, study physicians declined to take AOe into account at the time of prostate biopsy referral.

In the study by Chamie et al, the authors suggested the possibility that AOe may have been associated with an increase in PSA, which may have lead to veterans with AOe being referred for a prostate biopsy. In our study, AOe veterans had a mean maximum PSA of 11.2 ng/mL compared with 12.4 ng/mL in unexposed veterans. Of the veterans who had PCa diagnosed on biopsy, the average PSA of veterans in the AOe group was 8.8 ng/mL compared with 23.0 ng/mL in the nonexposed group. Neither difference was statistically significant; however, these findings suggest that AOe is not associated with a higher PSA level and is an independent predictor of both PCa and HGPCa on biopsy.

An additional consideration in our study was whether individuals changed their AOe status with the VA hospital after being diagnosed with PCa. If a large number of individuals switched exposure status after a positive prostate biopsy, then this would create a differential bias away from the null. In the study by Chamie et al, only 7 of 6214 men (0.11%) with AOe switched their exposure status after a diagnosis of cancer. Given the similar populations in our studies, we can assume that a similar proportion of veterans changed their exposure status. Thus, among our 203 AOe veterans, we expect that, at most, 1 veteran switched exposure status after his PCa diagnosis. If the proportion of veterans switching their exposure status in our study was 25 times the proportion in the study by Chamie et al, then only 5 or 6 veterans in our study made this switch. Thus, a change in AOe status cannot account for the observed association with HGPCa.

In conclusion, biomarkers for the prediction of life-threatening disease are needed to improve current PCa screening strategies. In our study, a history of AOe was associated with a 75% increase in the risk of life-threatening PCa, but it was not associated significantly with an increase in LGPCa. Incorporating AOe history into decision-making for PCa screening among veterans may help to better predict clinically significant PCa while not adding to the number of clinically insignificant PCa diagnoses.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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