

TECHNICAL PROPOSAL

CHARACTERIZING EXPOSURE OF VETERANS TO AGENT ORANGE AND OTHER HERBICIDES USED IN VIETNAM

National Academy of Sciences

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Technical Proposal

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Summary of Projects

The proposed work consists of six interrelated projects on various methodological aspects of characterizing herbicide exposures to American troops that served in Vietnam. Each of the projects is related to an aspect of the historical reconstruction of exposure to herbicides among Vietnam veterans who served in Vietnam. The work described here is specifically *not* an epidemiology study but rather proposes a series of studies and database development projects which would provide the basis for defining essential elements of future epidemiologic studies: *person*; *place*; and *time*.

PROJECT 1: Military Unit Database - Vietnam (MUD-V)

- Assessment and completion of data on troop location;
- Sensitivity analysis of a database comprising coordinates for location of military units in Vietnam for historical reconstruction of exposure to herbicides;
- Compilation of additional data on non-Ranch Hand use of herbicides, such as perimeter spraying through structured interviews of Division Chemical Officers.

The Military Unit Database has been assembled and managed by the Principal Investigator and co-workers and comprises a database of more than one-half million specific locations and dates of service of Marine and Army military units that served in Vietnam. This database is a compilation and extraction of data assembled by the U.S. Joint Services Environmental Support Group (ESG) for various governmental studies (e.g., CDC III Corps Study, VA Army and Marine Mortality studies). The original data has been supplemented by hand-searching of individual military unit records (e.g., ORLLs) by military experts under the direction of Richard Christian.

PROJECT 2: Covariates, Confounders and Consistency: Characterizing the Vietnam Veteran for Epidemiological Studies

- Self-reports of military service, exposure experiences to herbicides, as well as to confounders and covariates of methodological interest (e.g. combat experience);
- Evaluation of validity of veteran recall and various approaches to obtaining self-reported data.

In 1983 the Principal Investigator and co-workers undertook, in collaboration with The American Legion, a cross-sectional study of the health and well-being of 12,500 Vietnam-era randomly selected Legionnaires. The data from this survey represent an important source of information on veteran self-assessment of exposures to defoliants and other environmental factors (e.g., combat). The originally randomly selected cohort, supplemented by appropriately identified groups of women and minority veterans (to ensure generalizability) will be resurveyed to determine the reliability of veteran recall (test-retest) and to quantify potential interacting and confounding factors, as well as to identify and characterize appropriate control populations. Standard measures will be refined, tested and validated. The revisited cohort and new groups will serve as the source of veterans for Projects 3 and 4.

PROJECT 3: Evaluation and Standardization of Personnel Military Records for Epidemiological Studies

- Evaluation and standardization of military personnel records in order to determine whether data on likelihood of exposure to herbicides can be uniformly extracted;
- Evaluation of validity of self-reports of military service and experience.

The issue of reliability of recall and self-report and the extent to which the military personnel records contain relevant data on exposure to herbicides will be addressed by interviewing all veterans who reported situations in which herbicide handling was likely or who were calculated to have been heavily exposed to herbicides (estimated to be approximately 500 veterans.), together with an appropriately selected number of controls. The information obtained from interviews (carried out by interviewers with military knowledge) will be compared to the information abstracted (blind) from the military record. Another aim is to develop standardized data abstraction forms and a guide to obtaining, understanding and abstracting military personnel records which are available for epidemiological study.

PROJECT 4: Biomarkers of TCDD Exposure in Vietnam Veterans

- Biomarkers of TCDD exposure through HRGC/HRMS evaluation of blood serum samples selected from veterans likely to have been heavily exposed and an appropriate selection of Vietnam-era veteran controls;
- Evaluation of utility of CALUX analysis as a lower-cost screening method indicative of TCDD exposure.

The question of to what extent biological samples of individuals are a useful tool in quantifying exposure to herbicides some twenty-five or more years post-exposure will be addressed by analysis of samples drawn from Legionnaires identified as representing a range of possible exposures, with an oversampling of heavily exposed veterans and comparison to the likelihood of exposure calculated from the MUD-V exposure opportunity index and from self-reported herbicide handling situations. A rapid and low-cost screening test, based upon a recombinant cell bioassay system (CALUX) will be run on split samples that represent an appropriate range of concentrations and of dioxin-congeners in order to test reliability of the screening method (i.e. sensitivity and specificity). The ability of the EOs to predict CALUX results will also be tested.

PROJECT 5: Analysis of IARC Tissue Samples of Selected Vietnamese

- Correlation between levels of TCDD and dioxin- and dibenzofuran-congeners in adipose tissue from Vietnamese citizens (International Agency for Research Cancer case-control study tissue archive), lifetime residence history data and herbicide spray records.

In 1993-1996 a series of 1200 blood and adipose samples was collected from patients diagnosed with non-Hodgkins lymphoma and soft tissue sarcoma who resided in various regions of South Vietnam and matched to hospital-based controls. Vietnamese collaborators interviewed these patients in order to obtain historical residential and other lifestyle experience and coded residence locations to the UTM coordinates used in the Military Unit Database and the HERBS tapes. These samples are collected in a tissue archive awaiting analysis. All questionnaire data have been entered. Tissue samples will be selected from equal numbers of patients with low, medium and high exposure opportunity index scores for the correlational analysis. A pilot study on 27 Vietnamese

(Verger et al.) has indicated that this approach may be a useful tool for partial validation of the HERBS-tapes data.

PROJECT 6: Planning and development of epidemiological research priorities

•Development of priorities and methodologies for epidemiological research based upon the findings of Projects 1-5, other health outcome databases that may already be available and additional technical and pragmatic considerations.

This project calls upon the expertise of external advisors (including the NAS Committee) to assist the project team in evaluating the results of Projects 1-5, and in considering the extent to which other already existing databases on health outcomes and identified Vietnam veteran cohorts can be combined to address the outstanding research questions.

OVERVIEW AND BACKGROUND

Between the years 1964 and 1971, the United States armed forces employed approximately 19 million gallons of herbicides for a variety of military purposes, primarily in the area then known as South Vietnam. To date there is no accurate appraisal of the extent to which American troops were exposed to these herbicides.

Exposure Opportunity vs. Toxicological Exposure

In developing our approach to exposure assessment, we distinguish between exposure in the toxicological sense, and the concept of exposure opportunity. In the toxicological concept of exposure, a chemical enters the body via one or more routes (like skin or respiration), is metabolized to a greater or lesser extent, then distributed to "compartments" such as the blood, adipose tissue, or various other organs, where it may be further metabolized, and where it can exert genotoxic or other effects harmful to health. In this context, exposure is frequently quantified as a toxicological dose, meaning the actual measured concentration of a substance in a particular organ or other compartment.

The strength of the toxicological approach is that this dosage can then be related to health outcomes, preferably in a dose-response relationship. However, it has several weaknesses:

1. It requires obtaining a sample of blood or other tissue. For large-scale studies, this can introduce issues of cost and selection bias.
2. It can yield false negatives if biomarker levels of some veterans who were exposed in Vietnam since have decayed to background.
3. Individuals may have been exposed to other sources of the same compounds.
4. Ill health and/or severe weight loss or other circumstance may have contributed to "mobilization" of compounds and subsequent expulsion from the body.

Exposure opportunity index (EOI) is an alternative to toxicological exposure measurement. It may be defined as an estimate of the possibility that an individual may come into contact with a toxic chemical, without regard to route of entry or subsequent metabolism. Table 1 enumerates a variety of surrogate measures of herbicide exposure that have been used in various studies. Their advantages and drawbacks are discussed and it can be seen that few are quantitative and all prone to extensive misclassification.

Battlefield Records Management and Its Relationship to Agent Orange Research

Every war is accompanied by a set of records that describe the troops, their deployment, their successes and failures, their health and well-being and the relationship of their efforts to the overall conduct of the military action. Military action is almost never random and there is a complex and intricately defined military structure of command in each of the branches of the military forces. Much of this structure is the same throughout

the world and is based on centuries-old human experience of war-making. The United States military is no exception.

The military is imbued with a deep sense of history. Each battalion, for example, has an extremely well-documented record of its "existence." Units are anthropomorphized: they are "raised" for battles and "serve" in areas. Most units do not go out of existence at the conclusion of a war: some of the battalions which served in Vietnam date from the American Revolution and Civil War. They may be "retired," and can be "re-raised." Units bear insignias, nicknames and badges. Former soldiers can join any of hundreds of organizations that are devoted to preserving the histories and social bonds for specific military units, with annual reunions and periodical newsletters.

In this culture, the maintenance of accurate records is an essential and integral part of the workings of any military. It is a mistake for civilians to underestimate the importance that the military attaches to records keeping, and the great skill in records management which it brings to the task. Records managers achieve high rank in the military. The data described here, for example, were collected under the direction of a Lieutenant-Colonel (ret.) Richard Christian, a member of the proposed research team.

The accumulation and preservation of military records is a highly organized management function which serves many historical, legal, and financial purposes as well as for research and development. A brief history of records management prior to, during, and especially after the Vietnam war has been given by Christian and White (1983), some of which is summarized here.

When the U.S. military presence in Vietnam began to build in 1965-66, the U.S. Army Command, Vietnam, took the first steps to establish a records program to protect the growing volume of information. A records headquarters was established at Okinawa in 1968, and an effective records management program put in place by 1969. One headquarters' task was to coordinate the flow of records generated by various field headquarters to the battalion-level officers who were responsible for the battalion's records.

In the Fall of 1970 the Army Headquarters staff set about the task of consolidating and making more uniform existing and future records. A team was sent to Vietnam to study in detail the entire Vietnam-theater records creation process, to hold classes and train records personnel, to brief commanders and to fully implement the program. The Daily Journal, which documents a unit's activities for each 24-hour period, was identified as a key record type to be permanently retained for later research. This record would eventually become a decisive primary data source in tracking units.

In October, 1972, when it was obvious that the American presence in Vietnam would soon be drastically reduced or eliminated, the concept of the "Stand Down Records Retrieval Team" was introduced, and plans were developed to organize and ship out war records. By March, 1973, the Army had shipped more than 10,000 linear meters of records to its interim processing point in Hawaii for subsequent transfer to permanent archival in Washington. It is believed that only about 800 meters remained in Vietnam after the final American withdrawal and were abandoned.

When Agent Orange became a topic of public and scientific concern in 1978, the Office of the Adjutant General of the Army anticipated the need for troop data in future scientific studies. In 1980 it established the Army Agent Orange Task Force (AOTF) with a staff of three researchers who were experts in records management and an eventual staff

of 27, including clerical personnel. General orders were issued to prevent destruction of Agent Orange-related records, and Army records managers around the globe were canvassed for reports on relevant data holdings.

In May, 1980, when it appeared that the Veterans Administration would conduct extensive epidemiologic research on health effects of Agent Orange, the AOTF began a series of records research projects to determine the feasibility of reconstructing the movements of combat battalions in Vietnam. Two Army and two Marine battalions were randomly selected and their records thoroughly scrutinized, and from this effort it was established that locations of individual units down to the company level was perfectly feasible, given enough material resources to accomplish the task.

Primary Troop Location and Identification Data Available for Scientific Research

The Army Agent Orange Task Force subsequently became the Army and Joint Services Environmental Support Group (ESG) with a records maintenance, research and retrieval mission encompassing all four military services plus Coast Guard (which had a small contingent in Vietnam). The ESG, under the direction of Col. Christian, developed procedures for locating and tracking military units in Vietnam "to order," that is, specifically for epidemiological studies. One of their initial "clients" was the Veterans Administration; VA, and later work was done for the Centers for Disease Control, CDC, which took over the VA studies in 1983 at the behest of Congress. The ESG continues to carry out similar missions of providing data to individuals and researchers. The ESG's present director has promised full cooperation in the effort proposed here (see Appendix, Letters).

The ESG's tracking procedures rely on a variety of data sources which include not only the Daily Journals but at least a dozen other types of records. Many of these are described in Table 2. Two data sources worth special mention are the Operations Reports and Lessons Learned (ORLLs), which describe significant actions and their locations, and Troop Strength Estimates, which are official authorizations for personnel allocation. ORLLs are an especially useful tracking tool because they contain precise coordinates units as they operated against the enemy in the field. The troop strengths can be used to precisely define sizes of populations "at risk" for exposure, and therefore to determine sample sizes of epidemiological studies.

It is important to realize, moreover, that these data represent a large segment of the computerized data available on the Vietnam war. This war is perhaps the best documented military engagement in history. It occurred concurrently with the development of computers, and at a time when the Department of Defense had made development of electronic information systems a priority. During the conflict, the US Army Combat Developments Command began conducting an inventory of the data available. The product of that effort was a lengthy report covering hundreds of potential data sources. (US Department of the Army, 1970). Examination of this report demonstrates the extensive data holdings available.

Secondary Troop Location and Identification Data Available for Scientific Research

Since its establishment, the AOTF/ESG has assembled several sizable databases for use by federal agencies engaged in Agent Orange research. The most important of these are listed in Table 3.

The first entry, the UICLIST, is the descriptor system for military units. It is the key database upon which nearly all others depend, because troop location data are organized on the basis of the military unit. Every member of the Armed Services was assigned to one of about 6,000 units, and most served in more than one unit at different times. The ESG created a 7-digit Unit Identification Code (UIC) which makes it possible to represent an individual's military history by listing chronologically his/her UIC codes along with service dates for each unit.

Table 3 also lists the data files for the three largest studies for which the ESG provided data: (1) VA-Army mortality study (Bullman, Kang and Wantanabe, 1990), (2) VA-Marine mortality study (Breslin et al., 1988), (3) CDC follow-up study (CDC, 1987). These files contain over half a million troop location records. Also included in Table 3 are the two major herbicide spray files, comprising over 22,000 records described more fully below.

The databases summarized in Table 3 are considered secondary sources, because they are derived from the primary military records of Table 2. The research team that will carry out Project 1 (the MUD-V) has extensively edited and re-organized several of those databases to permit rapid evaluation of exposure for claimants to the Agent Orange Veteran Payment Program (AOVPP) (In re Agent Orange, US Eastern Federal District Court).

Approaches in this proposal

Each of the projects proposed here builds upon existing databases and study populations. The breadth and the detail of the proposed work is only possible because of the extensive experience of the investigators in this area and of the data and collaborative relationships such as with The American Legion, that are already available to them. The proposed work brings together a research team and collaborating organizations and advisers with wide-ranging and in-depth knowledge of the issues at hand.

Project 1 proposes to complete and refine the Military Unit Database-Vietnam (MUD-V) and to carry out appropriate sensitivity analyses and mathematical modeling to provide a reliable exposure opportunity index for the great majority of military units that served in Vietnam. Project 2 directs its attention to the refinement of methodology needed for assessing exposure on an individual veteran level - that is, were there special situations in which the veteran found himself (or herself) which make assigning the military unit as the unit of analysis incorrect. This project also investigates the important covariates, intervening variables and confounders which must be taken into account in any epidemiological study. Project 3 is a systematic investigation of the data that are available from the military personnel records. It tests the null hypothesis that the military personnel record is a more reliable source of information about military experiences than is the veteran. Projects 4 and 5 explore issues related to the use of TCDD as a biomarker of exposure in Vietnam veterans and Vietnamese nationals; test a relatively new biomarker screening assay; and determine whether the results of the analyses could be used as further validation of the exposure opportunity index. Finally, Project 6 is devoted to the synthesis of the findings of these five studies and the development of priorities and recommended methodologies to be used in epidemiological studies of the relationship between the health of Vietnam veterans and the military use of herbicides during the Vietnam War.

The work is proposed as a collaborative effort between researchers at the Columbia University School of Public Health, the American Health Foundation, Midwest Research Institute, Xenobiotic Detection Systems, the Foundation for Worker, Veteran and Environmental Health, as well as an active Advisory Board, Scientific Advisory Board and three consultants to be named for the final phases of this project. The active participation of the NAS Advisory Committee is planned throughout.

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Table 1
SURROGATE MEASURES OF HERBICIDE EXPOSURE

SURROGATE	ADVANTAGES	DRAWBACKS
Any Vietnam-Era military service vs. civilian	Easily verified	60% of Era veterans not in Vietnam, no opportunity for exposure
Military service in Vietnam vs. elsewhere	Agent Orange used almost exclusively in Vietnam	Use was not random; probability of exposure < 20%
Branch of service: Army vs. Navy, etc.	Army and Marines most likely exposed, Navy less; AF Ranch Handers heavily exposed	Even in Army, prob. of exposure was low; some brown-water Navy were exposed; AF exposure at some bases was very high, others unexposed; AF ground crew exposed to leaks
MOS (Military Occupational Specialty), e.g. rifleman, engineer	Identifies herbicide & chemical handlers; some occupations (e.g. clerical) presumably unexposed	No. handlers was small; other specialties correlate poorly with exposure
Combat vs. support roles	Combat troops more likely to be exposed	Most combat troops were not exposed, prob. of misclassification high
Military region: I Corps, II Corps, etc.	III Corps was most heavily sprayed, I Corps less	Saigon (not sprayed) and Iron Triangle (heavily sprayed) both III Corps; spraying was not random in other Corps

Databases Available for Scientific Research - Based on Primary Sources

The data described in this table are the raw data collected by the armed forces during the course of its service in Vietnam
Precise Location Data Include:

Database Description	Data Entries	Military Units
Battalion Daily Journals: To record significant actions and precise locations of the maneuver companies. Emphasis placed on fighting units	UTM locations- daily by operations officer	Battalions <ul style="list-style-type: none"> • field companies • headquarters company
Situation reports (SITREPS): contain information about locations of battalions and their companies, and contain notations on daily combat actions	UTM locations daily	Battalions <ul style="list-style-type: none"> • field companies • headquarters company
Operations Reports and Lessons Learned (ORLL): delineates significant actions and their locations; contains a section on herbicide operations	UTM quarterly reports by Division Commander	Each element of the Division and the staff
Command Post Lists: Provide command locations	UTM and valid dates	Data to the division level
Station lists: base locations	UTM quarterly	To the battalion level
Command Chronologies: A collection of all records and information that reflects significant occurrence		All units in command
Combat Operations After Action Reports: Detailed information regarding major battles	May contain location data	All units in command
Unit Histories: Summarize information available from other databases and cover a broad scope of functions about the unit	Written by unit historian	All units in command
Morning Reports, Muster Rolls and Unit Diaries: Personnel related data containing complete rolls of those present, transferred in or out, casualties and other notations affecting personnel status	Unit commanders	Each company, battery or detachment
Troop Strength Estimates: authorized allocation of personnel per unit; frequently revised to reflect actual (vs. authorized) strengths	Monthly with geographic location of headquarters	Generally on battalion level

Table 3
Secondary Data Sources of Herbicide Spray and Troop Location

In order to provide documentary support to researchers, veterans and others in need of precise information on troop movement, herbicide exposures and other relevant military information, the Department of Defense collected and examined hundreds of thousands of documents from databases listed in Table 1. Additional data has been collected by the Exposure Evaluation Unit of the Agent Orange Veterans Payment Program, U.S. Eastern District Court. Some of these databases are described below.

Database Description	Approx. No. Data Records	Type of Records
UICLIST: Master code list, consisting of 7-digit code, with first digit signifying branch of service, created to facilitate development of secondary database	6,000 units	Created by US Army Agent Orange Task Force, later US Army & Joint Services Environmental Support Group, to facilitate development of secondary databases
Troop Location Data:		
III Corps Batallions	300,000	Company and batallion locations for 50 batallions, 1966-69, abstracted by CDC; weekly or more often
Army mortality file	80,000	Company and batallion unit locations for men in VA Army mortality study
Marine mortality file	40,000	Company and batallion unit locations for men in VA Marine mortality study
FWVEH location support file	450,000	Merged file of 3 above databases, with many location gaps filled in and units with stationary assignments added; assembled under auspices of the Foundation for Worker, Veteran and Environmental Health (FWVEH) in support of the Agent Orange Veterans Payment Program
Herbicide Spray Data		
HERBS tape	17,000	Fixed-wing aircraft: Spray coordinates, date, gallons, mission purpose, type of herbicide
Services HERBS tape	5,000	Helicopter, backpack, truck: Spray coordinates, date, gallons, mission purpose, type of herbicide

GENERAL PROJECT MANAGEMENT

The general management of the project will be under the direction of the Principal Investigator, *Dr. Jeanne Mager Stellman*, assisted by a *Program Coordinator (TBN)* who will be well versed in all aspects of the work and will have strong administrative skills. A research assistant will be brought onto the management team at the beginning stages of the project so that s/he will be well acquainted with each technical aspect and will be able to provide assistance as needed. One *administrative assistant* (senior secretary) will be assigned to general project management with a 30% additional administrative and secretarial support at the American Health Foundation (AHF), a subcontractor to the project. Fiscal management will be under the direction of *Ms. Raluca Marian*, a Divisional Administrator in the sponsoring department at the CU School of Public Health.

Subcontractors

The *American Health Foundation* effort is headed by *Dr. Steven D. Stellman*, the co-investigator with the PI on all Vietnam veteran work. He will assume the lead role for project 1, the Military Unit Database - Vietnam, MUD-V and the statistical consultant, *Dr. Robert Lew*, will work on the AHF subcontract on that project. *Dr. J. Stellman* will assume the lead roles on Projects 2 and 3. In general, however, Drs. J. and S. Stellman will co-direct the scientific aspects of the work.

The *Midwest Research Institute (MRI)*, under the direction of *Dr. John Stanley*, will assume prime responsibility for the protocols, maintenance and distribution of samples to *Xenobiotic Detection Systems*, which will run the CALUX screening assay on the blood serum samples (Project 4)). MRI will carry out all high resolution GC / high resolution MS work on the adipose and blood serum samples in Projects 4 and 5 in its laboratories. *Dr. Stanley* will come to Columbia University for consultations biannually in addition to the regular communications that will be maintained. MRI will provide technical assistance in the complicated logistics involved in obtaining the samples from various States and in assuring that their integrity is maintained in the shipping process. The subcontract to *Xenobiotic Detection Systems* will be under the supervision of *Dr. George Clark*.

The *Foundation for Worker, Veteran and Environmental Health* currently maintains all the military record files which will be the basis of the historical reconstruction for exposure that is proposed here. During the first three months of the project all files will be converted from their current VAX-backup format into a format compatible for current computer systems and all documentation will be updated. The files from the American Legion - Columbia University study will also be updated by the Foundation.

Other Personnel

Lt. Col. Richard Christian (ret) will devote full-time effort to the proposed work and brings to the project his lifetime experience as Director of the office which provides the key military records for this project. Thus Col. Christian will play a key role in Projects #1, #2 and #3, each of which require insight and experience in the role of the military in Vietnam and into the records which exist that document that role. He will participate in Project #6.

We will hire a full-time *Staff Associate* who is thoroughly versed in military personnel records and in the military units that served in Vietnam, as well as in the

experiences of Vietnam veterans. The Agent Orange Veterans Payment Project has recently concluded its work and Ms. Francine Benjamin, MS, a former employee of the Foundation for Worker, Veteran and Environmental Health and director of its exposure evaluation project for the AOVPP, is available and has the qualifications we will be seeking when the position is posted.

Three of the proposed projects (#2,#3,#4) will require interviews. The American Health Foundation is heavily engaged in cancer epidemiology studies and *Ms. Anna Mondora* is responsible for interviewer training and quality control. We intend to hire two full-time interviewers between months 8 and 28 to carry out the bulk of the interviews, whose purposes and contents are described in the individual projects later in this proposal. Ms. Mondora will conduct training sessions. *Dr. Sheila Gorman* is an experienced researcher in studies involving interviews and both she and the PI will work with Ms. Mondora in the establishment and documentation of quality control. A small cadre of additional interviewers, drawn from the ranks of *The American Legion*, will be trained and hired on an hourly basis to assist in interviews that require in-depth knowledge of the military experience on the ground in Vietnam.

Dr. Max Parkin, Chief of the Unit of Descriptive Epidemiology at the International Agency for Cancer Research has made IARC's adipose tissue archive of Vietnamese nationals available to this effort. He will devote time, as needed, to the scientific co-ordination of the work of Project 5 and will participate in the workshop scheduled for Project 6.

Project Management and Direction

In order to coordinate this complex project, weekly staff meetings / conference calls are planned. The AHF personnel will participate, as will other subcontractors when needed. All personnel will have access to e-mail and regular "updates" will be broadcast.

An *Advisory Board* and a *Science Advisory Panel of the Board* will be established for this project. The Advisory Board charge is to provide general oversight on the direction and progress of the work. It will also provide invaluable insight into the practical problems and issues involved in the eventual establishment of priorities and protocols for epidemiological studies on herbicides and veterans health. *Admiral Elmo Zumwalt* has agreed to chair the Advisory Board, should this proposal be approved and *John F. Sommer, Jr.*, Executive Director of the Washington Office of The American Legion and collaborator with the Stellmans on the Columbia University-American Legion Vietnam Veterans Study will also serve. Two additional and as yet unnamed Board members will be invited. *Dr. Shelia Zahm* (epidemiologist, NCI), *Dr. Paolo Boffetta* (Head Epidemiology, IARC) and *Lawrence Garfinkel* (epidemiologist, retired VP American Cancer Society) have agreed to serve on the Science Advisory Panel. Each has extensive relevant epidemiological expertise. The Advisory Board will meet biannually and during the last half of the third year will participate in an intensive planning workshop, as described in Project 6. The scientific sub-panel will participate in additional conference calls and e-mail interchanges as needed.

Biannual reports to the NAS will be the responsibility of the Principal Investigator, who will also meet with the NAS Advisory Committee annually. Each of the principal investigators of the subcontracts and the Advisory Board is available and interested in attending these briefings as well if the NAS desires.

A major strength of the proposal is the extensive ongoing relationship we have established with *The American Legion*, which has agreed to participate in and collaborate fully on the proposed work (see Letters). In addition to a commitment to assist as fully as possible in networking, The Legion's MIS and mailing facilities has agreed to undertake the task of coordinating the proposed mailing itself in their extensive and well-run facilities at the headquarters in Indianapolis.

Human Subjects

Projects #2,#3,#4 and #5 propose research that deals with Human Subjects. Project #2, the survey of American Legionnaires has already received clearance by the Columbia University Institutional Review Board and the protocol is unchanged. The earlier approval will be resubmitted for re-approval. Project #5, analysis of tissue from the IARC archive has already undergone IRB approval at the International Agency for Research on Cancer (IARC) and all subjects have signed an informed consent form. Projects #3 and #4 involve obtaining military personnel records and an interview (#3) and obtaining blood samples and an interview (#4). All protocols will be submitted to the Columbia University Institutional Review Board prior to their being undertaken and approval obtained.

Institutional Resources and Equipment

The institutional resources and relevant experience which are brought to this proposal are summarized in a section at the rear of this proposal. Qualifications of personnel are presented in the curriculum vitae. The data analysis will be supported by the Columbia University Comprehensive Cancer Center computing facility which is described in the resources section. We will also rely heavily on the extensive academic and office facilities of the School of Public Health and the University in General. Laboratory work will all take place off-site at either MRI or the Xenobiotic Detection Systems laboratories.

The extensive analysis and record keeping and administrative monitor will be carried out primarily on PC's which serve as terminals to the mainframe and/or which are equipped with appropriate software to carry out these function. Some field work supervision will require that telephone contact be made via modem as well.

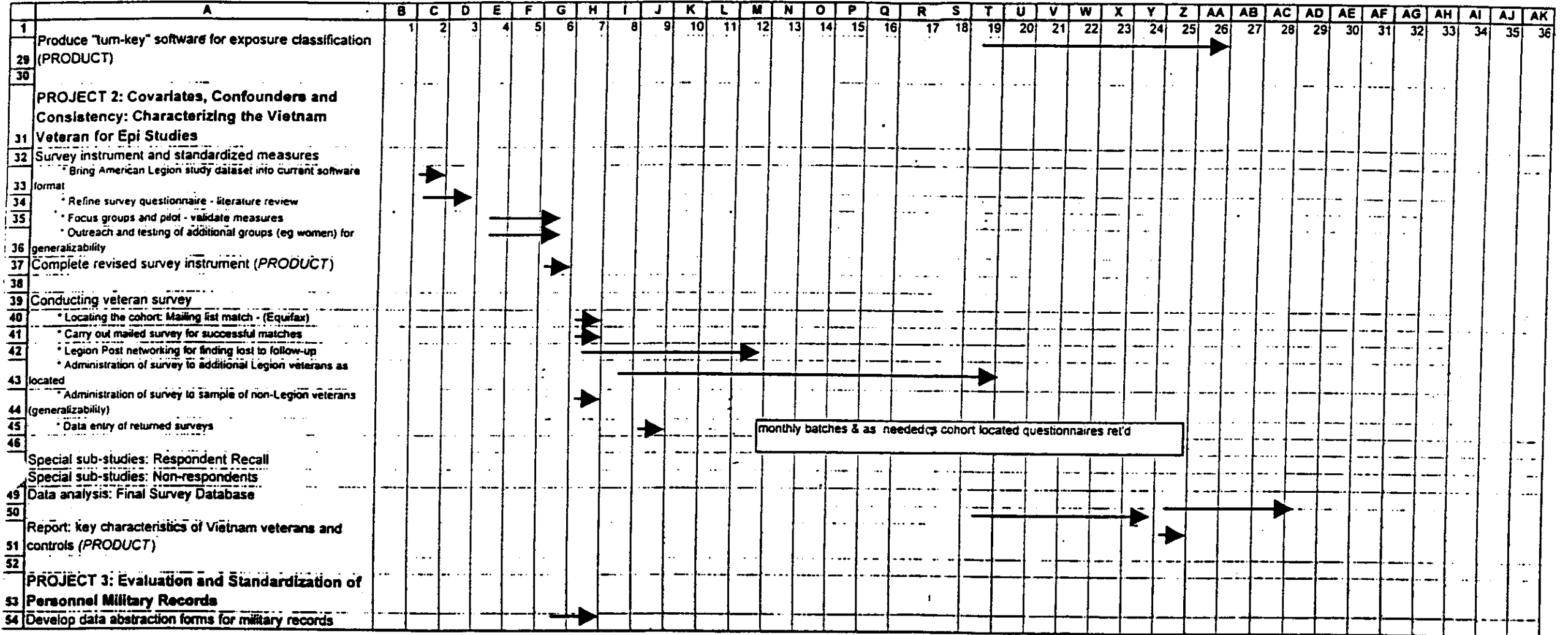
TIMELINE

The timeline and abbreviated tasklists for the overall proposal is presented here in order to provide an overview and to serve as a reference for the more detailed project descriptions that follow.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK			
1																																								
2	General Project Management																																							
3	Set up internal management structure																																							
4	Recruit/Confirm staff																																							
5	Finalize Advisory Board and Science Advisory Panel																																							
6	Consult with NAS Committee on Management																																							
7	Obtain all required institutional approvals																																							
8	Setup telecommunications system and management system with research team & Legion departments																																							
9	Weekly staff meetings																																							
10	Six month / annual reports and presentations (and preparation)																																							
11	Recruitment and training of interviewers																																							
12	Finalize criteria for interviewer qualifications																																							
13	Develop training materials and training protocol																																							
14	Develop quality control procedures for monitoring interviewers																																							
15	Carry out training of interviewers																																							
16																																								
17	PROJECT 1: Military Unit Database - Vietnam (MUD-V)																																							
18	Conversion of existing data to current computer system and formats																																							
19	Revise documentation of dataset sources and creation																																							
20	Completion of "gaps"																																							
21	Standardize naval and air force data into MUD-V format																																							
22	Systematic application of models to database																																							
23	Development of mathematical models for providing scenario options																																							
24	Sensitivity analysis																																							
25	Obtain additional military troop location records if indicated																																							
26	For each model, create finalized troop locations, exposure (with reliabilities) database																																							
27	Division Chemical Officers study																																							
28	Finalize MUD-V and portable database (PRODUCT)																																							

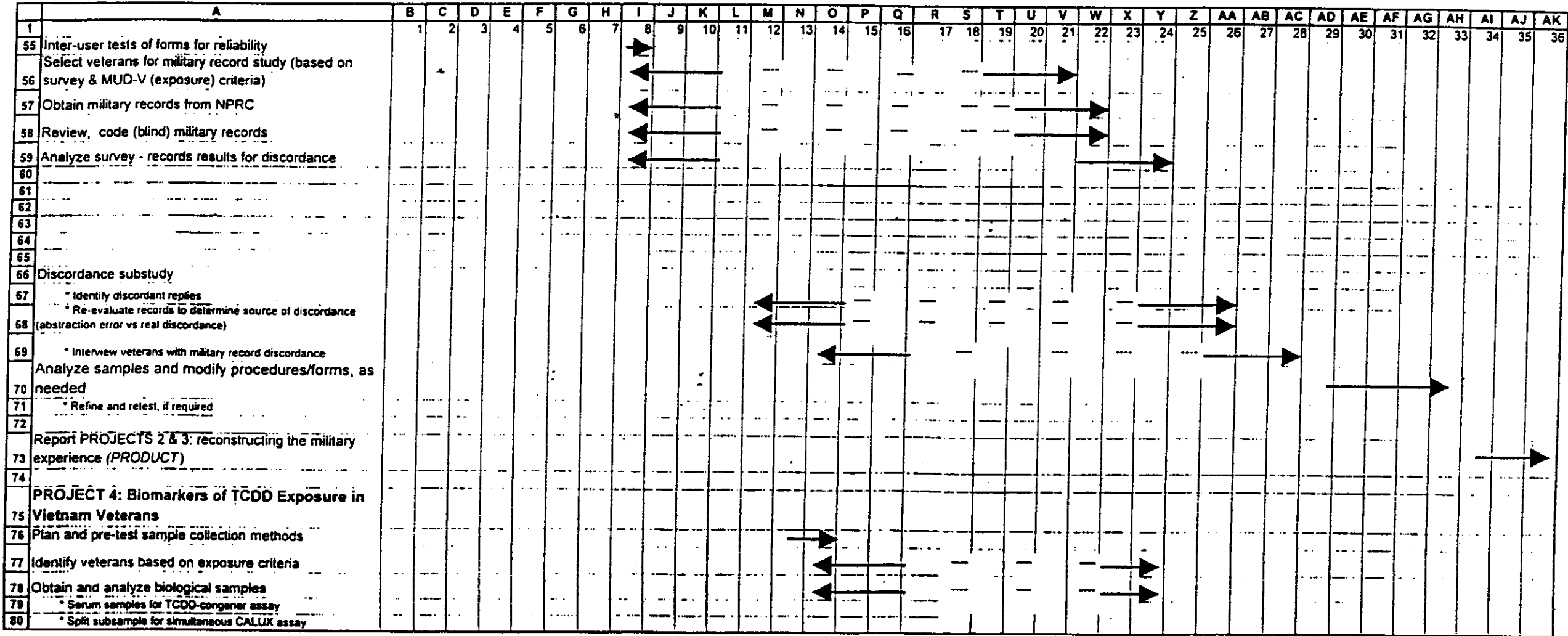
Timeline

Timeline



Timeline

Timeline



Timeline

Timeline

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK
1		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
81	Develop questionnaire for biological monitoring (based on Projects 2/3 and additional background materials)													→																							
82	Obtain additional interview data													←																							
83	Final report - Utility of CALUX screening (PRODUCT)																																				
84	Final report - Utility of biological monitoring in Vietnam Veterans (PRODUCT)																																				
85	PROJECT 5: Analysis of IARC Tissue Samples of Selected Vietnamese																																				
86	Select samples from archive for analysis (based on HERBS tapes)													→																							
87	Analyze samples																																				
88	Calculate correlations between HERBS tape data and results of blind tissue analysis													→																							
89	IARC Tissue Sample Report													→																							
90	PROJECT 6: Planning and development of epidemiological research priorities																																				
91	Meet with Subcontract Advisory committee													→																							
92	Select Consulting Scientists													→																							
93	Preparation studies/documents for workshop													→																							
94	Convene Advisory Board for Study design Workshops													→																							
95	Review materials produced above to assure compatibility																																				
96	Consult with NAS Committee																																				
97	FINAL REPORT																																				

DATES AND LOCATIONS (ARDEN HOUSE, COLUMBIA CAMPUS OR NAS) OF MEETINGS WILL BE DEVELOPED IN CONSULTATION WITH NAS AND WITH PROJECT

PROJECT 1 Military Unit Database - Vietnam (MUD-V)

SUMMARY

The goal of Project 1 is to construct a transportable system for evaluating herbicide exposure of veterans who served Vietnam. This system will be available for use in epidemiological studies. To accomplish this we will pursue the following specific aims:

1. Identify and fill in remaining gaps in the MUD-V by retrieval and evaluation and abstraction of primary source materials
2. Develop additional mathematical models for use as exposure opportunity indices (EOIs)
3. Carry out sensitivity analyses of models in order to characterize robustness of exposure indices to inaccuracies in the locations of the troops
4. Where inaccuracies or inconsistencies are found, attempt to obtain and incorporate additional or alternative troop location data from primary sources
5. Create a database of finalized troop locations that contains alternative exposure estimates from a variety of models, along with their reliabilities
6. Incorporate the finalized database in user-friendly software that will permit future investigators to use our models to assign exposures or to propose their own models
7. Interview Division Chemical Officers that served in Vietnam and served as principal advisors to Division Commanders on the use of all chemicals in order to complete the record of known spray missions as much as possible

Methods

Consolidation, Quality Control, and Standardization of Secondary Source Data Bases

As Exposure Consultants for the AOVPP, we created a military unit database for claim evaluation. This database contained approximately 500,000 records, each of which provided the an exposure opportunity estimate for one military unit during a discrete time period. The exposure for any individual claimant was calculated by summing the tabled exposures for his/her unit(s) during service in Vietnam. This database, while not intended for epidemiological purposes, may be regarded a prototype for that proposed for the present study.

Construction of the AOVPP database initially took place during 1988-89, with continual updating and filling in of "gaps" to evaluate claims not already covered by existing data; these gap-filling activities diminished with time. The work for the AOVPP took place under the auspices of the Foundation for Worker, Veteran and Environmental Health, FWVEH, a not-for-profit organization. The database resides with the FWVEH, which has agreed to make it available to this project and hence the NAS for eventual public availability.

A number of steps were required to process and integrate each of the disparate data sources within the master database:

- All UTM location coordinates were converted to a common Cartesian system to facilitate distance calculations
- All databases in hard copy were data-entered onto electronic media.

- Military units not already in the UICLIST were assigned new UIC's and the UICLIST updated
- Extensive checks for internal consistency were carried out, to detect duplicate records, impossible coordinates or dates
- Distances between infantry companies, artillery batteries, cavalry troops, and other battalion elements were computed, and apparently excessive distances were checked
- Ostensibly erratic movements (e.g., large distances back and forth over short time periods) were checked
- Records resulting from filling gaps were integrated within the master file
- All data sources meeting the above quality checks were placed in a common format
- The original source of each record was also included as a field in the database to facilitate backwards tracing and troubleshooting (e.g., B=CDC Battalion files, M=VA Marine files, etc.)

In the AOVPP database, exposures were calculated using one-month time periods. However, the original data sources contain considerably finer time detail for many military units; in many instances biweekly data exist, and in a few cases daily coordinates were abstracted. We will investigate the sensitivity of the EOIs to different choices of time intervals.

Methodological Issues in the Use of Secondary Military Data

The chief methodological issue in application of these derivative data sources stems from the fact that the primary source material describes locations of groups of people (i.e., military units) and not individuals. Suitability for epidemiologic use hinges on whether an exposure likelihood score computed from the known locations of a military unit may be applied to each of the individuals who served in that unit. If the components of a unit (e.g., companies within battalions) are dispersed in the field during their tours of duty, company locations may give more accurate exposure scores than battalion locations. However, the magnitude of possible exposure score errors which might arise from such dispersions should not be exaggerated.

First, while there are always exceptions, it is generally agreed by military records experts that field companies could be expected to stay together, especially on maneuvers that brought them into contact with opposing forces, where their locations would be carefully documented. Secondly, the locations for many companies on maneuvers can often be ascertained with additional records research, and their scores calculated with the more accurately location data. Most of the troop location data in Table 3 on III Corps battalions contain individual company location data.

A third important issue is the extent to which the database locations for a unit, whether company or higher, represent its true locations. This problem arises because the primary data sources sometimes contain multiple and occasionally conflicting entries for small units. In such cases, ESG has exercised judgment in selecting the most "typical" location for a unit. These decisions were not haphazard, but were based upon intimate knowledge of military operations and the likely deployment of field personnel.

The "Gaps" Problem. The requirement posed by CDC that daily locations be available for all battalion locations unnecessarily created an issue of "gaps" which, in a way, has come to haunt this database. It is necessary to understand the extent of coverage, to evaluate what a gap is, its implications for misclassification of exposure and, given all these considerations, how much usable data still remains for epidemiological investigations.

The ESG defines a gap simply as "no location for one day for one unit." Some gaps are result of lack of movement -- if units either permanently located at a base camp, or combat units did not move -- there was no need to report their locations daily. Such gaps are even now easily filled by consultation with the written records described in Table 2 -- a task that to a large extent has been carried out in the past several years in support of the exposure evaluation of the AOVPP. It is this database, with its "filled-in gaps," which now contains more than half a million records, and which when completed we will call the Military Unit Database-Vietnam (MUD-V), whose completion is the goal of the work proposed here.

A second, more serious type of gap results from the separate movement of units, either companies or platoons, away from their parent units for which data are available. Some of these gaps may be filled from records, but others may not be. Such data need not be considered unusable: it can often be readily documented that no herbicide application took place during the dates in question, or within a defined area of practical importance, say 15 kilometers, of the recorded location of the parent unit. Platoons and companies did not wander through the jungles of Vietnam at will. They rarely moved more than 8 km in a day. Indeed, even those soldiers whose duties included extensive jungle excursions, as with some Special Forces, were typically not expected to travel greater distances. A major aim of this Project is to carry out a sensitivity analysis of the data in the MUD-V to determine the extent to which it can satisfactorily produce a rank-ordered exposure rating for the units contained therein.

Another situation that is found in the MUD-V, where data were missing for periods of time, usually arose because a unit literally remained in one place, often for several weeks and months, and intermediate location reports were not considered necessary. These "gaps" have been readily filled in, are accurate and require no sensitivity analysis (e.g., Bien Hoa Air Force Base or the US Embassy Guard in downtown Saigon did not move).

Based on our experience, we have concluded that many so-called gaps or inconsistencies in the secondary data sources are minor and should not seriously affect the accuracy of epidemiologic studies. Indeed, we have developed methods in the AOVPP for imputing reasonable locations and exposure scores where some data are missing, such as substituting average battalion locations for companies, or utilizing the highest computed exposure among companies whose locations are known for one whose location is not during a particular month. Numerous variations of these imputation schemes are possible which do not lead to serious misclassification of relative ranks of individuals.

Finally, it should be noted that there will always be a small proportion of units for which data will remain incomplete: some gaps are real and give rise to questionable exposure scores. There are several choices in this situation, ranging from exclusion of such units from further epidemiologic studies to acceptance of misclassification, which would

almost certainly be in the conservative direction of underestimating exposure. The sensitivity analyses proposed here will identify those situations.

Quality of ESG data

The data extraction and management activities of the ESG are governed by extensive quality control procedures that include review of 5% of records abstracted in the morning and 5% abstracted in the afternoon each day. Key entry quality is subjected to similar review measures. Discrepancies of gaps are reviewed by a two-person team and often resolved by further data research or exercise of judgment.

The ESG's operations and particularly QC measures were reviewed by an Institute of Medicine Advisory Committee on the CDC Study of the Health of Vietnam Veterans. In a report dated March 7, 1986, the Committee declared itself "satisfied that the ESG is capable of determining locations and filling gaps using a contextual approach, and notes that the ESG exhibits a high degree of competence in recording data gathered from these activities." (IOM, 1986)

In our own work developing the AOVPP database for exposure evaluation we have subjected the ESG data to extensive cross-checks. We verified that most companies were within expected geographic proximity to each other and to related units on specific dates, and that their movements were synchronous and reasonably parallel. The ESG data are also highly consistent with published descriptive sources on the Vietnam military experience, such as published Army historical reports, and unpublished troop strength reports.

Herbicide Spray Data

Role of Herbicide Spray Data in Exposure Assessment

The key to linking a military location with an exposure opportunity lies in computerized records of herbicide application, commonly known as the HERBS files. These records are by far the most important and complete exposure records available for exposure assessment purposes. In the following section we describe the nature of this database; in a subsequent section we describe our approach for estimating exposure opportunity based upon linking the MUD-V troop location data with HERBS file spray data.

Origin of herbicide database

Between 1961 and 1971 the U.S. military sprayed over 19 million gallons of herbicides on South Vietnam, of which nearly 12 million gallons was Agent Orange. Public concern over potential harmful effects on the indigenous population and ecological damage led to a Congressionally funded study by the National Research Council, which found evidence of substantial ecological damage (National Research Council, 1974). Wartime conditions, however, precluded a comprehensive assessment of health effects on the population. Possible effects on American troops were given little consideration. All herbicide spraying ceased in 1971.

An important product of the NRC study was a compilation of herbicide spray records from Operation Ranch Hand, the US Air Force herbicide spray program. The NRC organized the data into a file, known as the HERBS tape, which contained

coordinate points for more than 6,200 missions flown by fixed-wing aircraft, and included date, type of herbicide, gallons applied, and purpose of mission. In the early 1980's the Environmental Support Group at the Pentagon assembled a supplementary tape (the SERVICES-HERBS tape) consisting of helicopter, backpack, truck and other smaller-scale spraying. We have created a composite HERBS data file from these two sources that brings the total information base to over 8,800 individual military spray missions.

Structure and content of herbicide database

Each record in the composite HERBS file contains the following information: date of spraying, UTM (universal transverse mercator) coordinate, type of herbicide, number of gallons, mode of application, type of aircraft (if appropriate), and where available area sprayed. For aircraft-flown missions, the file also contains connectivity indicators which enable one to trace the path of spraying.

We have previously described the patterns of herbicide usage in Vietnam (Stellman and Stellman, 1986). Figure 1 shows the total number of gallons of each of the three herbicides (Orange, White, and Blue), and the number of application missions by type. Defoliation of jungle constituted the most important herbicide use, but millions of gallons were used for destruction of food crops (Fig. 1a) and thousands of gallons were used to clear communication lines, waterways, and base camp perimeters (Fig. 1b). Figure 2 shows the total number of gallons of herbicide applied, by agent, for each quarter from 1965 through the end of the spraying in 1971.

Over 1,000 missions were for clearance of base perimeters. About half of these involved Agent Orange (about 135,000 gallons). This represents only about 1.1% of the 11.8 million gallons of Agent Orange sprayed in Vietnam.

APPROACH TO EXPOSURE ASSESSMENT

Our approach will be to construct quantitative "exposure opportunity" models that utilize records of troop location and herbicide application. This approach is widely accepted as valid in epidemiological studies that rely on historical reconstruction of data needed for exposure evaluation. We recognize that under ideal circumstances one might wish to assign to every individual a number that quantitatively represents the biological dosage of a toxic chemical or mixture. Such conditions are rarely if ever attainable, since requisite environmental or biological measurements were not made in Vietnam.

To be useful in epidemiological studies, an exposure estimate must be quantitative (not merely "exposed" or "not exposed"), and should permit individuals to be ranked in order of increasing exposure. Veterans can then be grouped by percentiles of such a measure, such as tertiles (low, medium, high), quintiles, deciles, etc.

The two data resources required by our quantitative approach are

- locations and dates of the individual's military unit or units
- locations and dates of the herbicide applications

We have created the first of these resources by using military records and other sources to reconstruct the movement history of the military unit in which an individual

served. As the second resource we will use as our primary source the HERBS file and SERVICES-HERBS file. We will also supplement these public use files with herbicide application data that we will reconstruct from other available sources (see above: Division Chemical Officer interviews).

In the present proposal we will produce more generalized models that:

- can accommodate any desired degree of realism for which credible data are available
- have been subjected to sensitivity testing that examines the robustness of rank-ordering to a variety of assumptions of varying plausibility, including dependence on degree of dispersion of individuals within units, and units within parent units
- reflect easily grasped exposure scenarios
- can be subjected, if desired, to possible validation by external measurement of environmental or biological markers (limited, of course, by the extensive time that has elapsed since exposure)

Robustness

We will check our results to see the effect of inaccuracies in D , the measure of distance between the herbicide site and the soldier. Lacking the exact location of the soldier in the small region occupied by his unit, we have computed D for each soldier as the distance from the center of the region to the site. Clearly, the exact distance varies according to the distribution of soldiers within the region; i.e., D is a random variable.

This makes the independent factor, x , a surrogate of the true exposure, X , that uses the exact locations. Hence, following Carroll et al., $x = X + e$ is a random variable with random error e . We obtain an approximate normal distribution for e because x is a sum. If each distance $D = D(\text{true}) + d$, where d is a random error, then by simulating the errors d we simulate the errors e in x .

Such structure allows us to use the SIMEX method described in chapter 4 of Carroll et al. to assess the effect of measurement error in x (or D) on the results of our nonlinear logistic regression model relating exposure to the risk of disease. This analysis will indicate the amount of precision lost by ignorance of the exact locations.

Another concern is the correctness of the formula for $x = \sum x(i)$ where $x(i)$ has the form J/D where J is an integral with exponential terms. We will explore the use of other formulas that for example divide by D^2 instead of D or that an exponent of $\lambda T + aT^2$ instead of λT .

We will furthermore furnish a user-friendly mechanism for incorporating models proposed by future investigators into our computerized database system, so that exposure opportunity assessment can be carried out in future epidemiological studies, at the investigator's option, which:

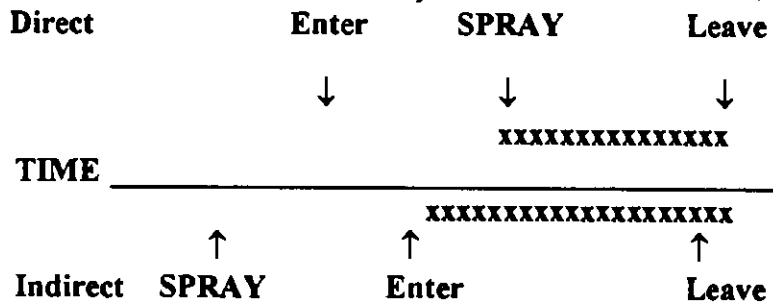
- use our final database and one of our models

- use our final database and a model of the investigator's design
- choose specific herbicidal agents singly or in combination as the exposure medium of interest (e.g., Agent Orange only, all dioxin-contaminated herbicides, 2,4-D containing herbicides, etc.)

Exposure Opportunity Models: Mathematical Description of Current Models and Plan for Future Development

Description of Current Models

Three approaches to quantitative "exposure opportunity" assessment were developed by the authors (Stellman & Stellman, AJIM 1986). Each of these models builds on and is more comprehensive than the previous model. Each of these methods can be applied either to individual military personnel or to military units, using the assigned location (x,y) obtained from our military unit data base for a given date. We assume that our database for that unit contains time of entry and exit from a location of interest:



In the past we developed three mathematical models (see box), that incorporated successively more realistic (and more complex) exposure concepts of distance and time of potential exposure to herbicide application. The simplest of these (E1, the "hit" model) simply counts the instances in which an individual was within a specified distance of a known spray. The second (E2) also counts hits, but makes close hits count more by weighting each hit by the inverse distance from the spray. The third model (E3) begins with distance-weighted hits and also factors in the total time during which the individual is considered exposed. E1 and E2 can be regarded as representing acute exposures, while E3 is analogous to acute followed by a chronic exposure.

In this proposal, we will expand the scope of assessment for these models in three important ways:

- We will give greater consideration to the questions of dispersion of individual troops relative to reported locations of their units, utilizing nonlinear error methods
- We will carry out sensitivity analyses that take into account spray coordinate errors introduced by deviation of aircraft from flight paths, and wind dispersion of herbicides

Mathematical description of exposure opportunity indices E1, E2, E3

Direct hits within a fixed radius (E1)

The simplest approach is based on the Pythagorean distance between the location of a unit and a documented spray location on a specific day. If (x_u, y_u) is the location of the military unit as determined in our data base, and (x_s, y_s) the location of a herbicide spray as given in the HERBS files, then the distance d is:

$$d = \sqrt{(x_u - x_s)^2 + (y_u - y_s)^2}$$

If the distance, d , for any unit location-spray location pair is within the specified radius, it is called a "hit." The index, E1, is the number of such hits that fall within the desired radius, for every possible pairing of unit locations and spray locations for which data exists. For instance, if a 8 km radius is chosen, the number of times a given military unit was within 8 km of any of the spray locations on the HERBS file is called the number of hits within 8 km.

The radius in E1 can be regarded as a parameter of the overall EOI model. A weakness is that setting it very small (e.g., 0.5 km) is equivalent to counting only direct sprays of a unit, and will result in declaring very few units exposed. Setting it very large will designate many units exposed. Another weakness of E1 is that there is no allowance for "strength" of exposure - all units or persons within the chosen radius are assigned identical exposures.

Direct hits, weighted by distance (E2)

This approach recognizes that potential exposure to a point source of exposure must fall off with increasing distance away from the source. To be quantitative, we must adopt a specific mathematical relationship for distance vs. exposure. We have chosen the reciprocal (1/distance). This specific method counts hits as in approach (a), and then weights each hit by the reciprocal of the distance between the subject and the source of exposure. Under this assumption, a unit 2 km from a spray is assigned an EOI twice that of a unit 4 km from the spray. Other choices than reciprocal are also possible. A far more conservative choice (one much less likely to result in calling units exposed) weights each hit by the inverse square of the distance (1 divided by distance-squared). A unit 1 km from a spray is assigned an EOI nine times that of a unit 3 km from the same spray. Adopting an inverse-square relationship is tantamount to calling exposed only the very closest units to documented spraying, and has a result similar to using a very small radius in E1.

Direct hits, weighted by distance and time since spraying (E3)

This approach extends E1 and E2 by incorporating environmental decay. It recognizes that an individual could not only have been exposed directly to a herbicide spray, but could also have been exposed indirectly by entering, working, or living in a previously sprayed area. At the core of our estimate of "indirect" exposure is the assumption that the concentration of an active toxicant, such as TCDD, is governed by a decay factor that depends on the time elapsed since spraying. This occurs naturally due to breakdown by sunlight, bacteria, transport through soil, water, and run-off. It can also include metabolic decay within an individual.

Many mathematical choices are possible to represent such decay. The simplest assumes that the concentration decreases steadily (linearly) with elapsed time. However, this is not a realistic model. One more in keeping with actual measurements of dioxin in soil over time assumes that the rate at which the environmental concentration decreases is proportional to the concentration itself. This situation is well known in chemistry and toxicology as a first-order kinetic model (because the decay rate is proportional to the first power of the concentration). Higher orders of decay, such as second, have also been reported. Generally, the higher the order, the slower the decay -- i.e., the longer the toxic agent lingers in the environment. A first-order decay is conservative, i.e., gives lower EOI estimates than higher orders, thus tending to underestimate rather than exaggerate health effects. In particular, E3 weights each "hit" by an appropriate decay factor, thus ensuring that the more time that elapses between actual spraying and entry into a sprayed location, the lower the EOI score. It thus applies to a directly sprayed unit that remains in one place for an extended period of time, and equally well to a unit that enters a location after spraying occurs.

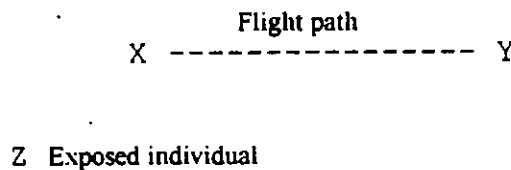
- We will investigate other exposure models as extensions of or alternatives to the above

Plan for Future Development of Models

There are two important areas for improvement of exposure opportunity models.

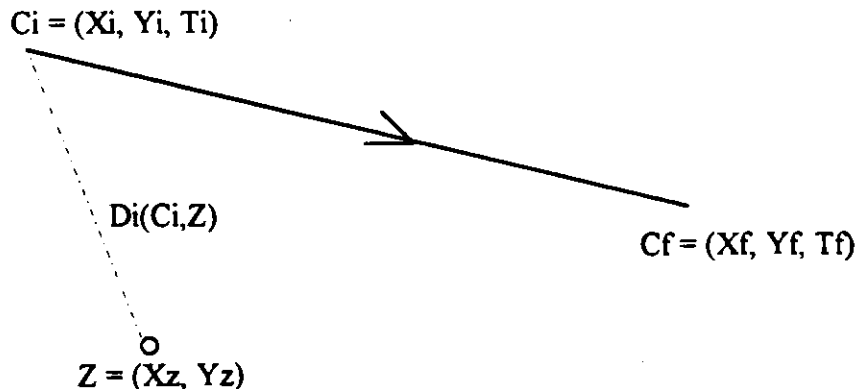
- Incorporation of gallonage of herbicide
- Consideration of connectivity of fixed-wing aircraft flight paths

We propose to extend our published EOI models along the following lines. Consider a C-123 Ranch Hand aircraft fitted with herbicide spray tanks flying over the jungles of Vietnam. The pilot starts spraying at coordinate X and stops at coordinate Y. Suppose one wishes to estimate exposure experienced by a person at point Z (all coordinates are known).



Several measures have been used. Verger et al. (1994) and Le Cao Dai (unpublished) calculated the distance XZ and the distance YZ and counted them as two different "hits." This ignores the spraying in between X and Y, and simply counts the spray mission as if it consisted of two separate point sprays at X and Y. A second method is to treat the data if a single spray occurred at the midpoint of XY, and calculate that distance to Z.

A mathematically more credible alternative is to compute an integrated measure that counts the (infinitesimal) contributions from every one of the (infinite) points on the line XY. This permits us to account explicitly for the nonlinear distance function.



Fix a point Z. The exposure at point Z is calculated using a numerical function $F(D_i(C_i), R)$, where R is the spray rate (in gal/sec) and $D_i(C_i)$ is calculated by

$$D_i(C_i) = \sqrt{(X_i - X_z)^2 + (Y_i - Y_z)^2}$$

Note that $Di(PT)$ can take an ordered pair (X, Y) instead of a single point representation. We may divide the spray into N steps, with R as the spray rate. Define the following variables:

$$\begin{aligned}R &= (\text{gallons sprayed}) \div (Tf - Ti) \\ \Delta X &= (Xf - Xi) \div N \\ \Delta Y &= (Yf - Yi) \div N \\ \Delta T &= (Tf - Ti) \div N\end{aligned}$$

The exposure at point Z can be approximated by the sum:

$$\sum_{i=0}^N F(Di(Xi + \Delta X, Yi + \Delta Y), R)$$

This is not difficult to compute, given a numerical function F .

Since we already have F coded as a numerical function, we may translate this into an integrable sum by taking

$$\lim_{N \rightarrow \infty} \sum_{i=0}^N F(Di(Xi + \Delta X \cdot i, Yi + \Delta Y \cdot i), R)$$

This will have to turn into an integral with respect to dt , meaning $Di(Ci)$ will have to become a function of time. Fixing points Ci and Cf , define:

$$\begin{aligned}X_t &= Xi + t \cdot \frac{Xf - Xi}{T} \\ Y_t &= Yi + t \cdot \frac{Yf - Yi}{T} \\ Di_t(t) &= \sqrt{(X_t - X_z)^2 + (Y_t - Y_z)^2}\end{aligned}$$

The limit then turns into:

$$\int_{Ti}^{Tf} F(Di_t(t), R) dt$$

which can be integrated relatively easily using Romberg's method for numerical integration.

EXPANDING PERIMETER SPRAYING DATABASE - DIVISION CHEMICAL OFFICERS

Background and Objectives

Seven Army Divisions served in Vietnam during the years in which the herbicide spraying activities took place (1965-1970). A Division Chemical Officer, who generally held the rank of Lieutenant Colonel or Major, served in each Division. Each officer served for a one-year tour of duty, although some may have served for shorter periods and some for more than one tour. For purposes of this study we are estimating that there will be between 40 and 50 Division Chemical Officers. The main objective of the exercise

proposed here is to attempt to learn how much perimeter spraying and local spraying took place during the Vietnam War for which no records on the SERVICES-HERBS tape exist.

As was discussed above, the use of herbicides for clearance of foliage on fire support bases was "incidental" in terms of gallonage, but in some instances may have presented a more serious source of exposure for the soldier who came into contact with the sprayed perimeter. It has been suggested that the troops assigned the job of carrying backpacks for spraying or served on the spray-trucks or helicopters may have been heavily exposed. Specific questions about such activities and about coming into contact with sprayed perimeters are included in the survey that is administered in Project 2.

Methods

The Division Chemical Officers will be identified from available military records, such as the Daily Journals and the Morning Reports. Some Daily Journals may currently be housed at the ESG. The official repository for Daily Journals is the Washington National Records Center, located in College Park, Maryland. Morning Reports will be requested from the National Personnel Records Center immediately upon undertaking the work of this project.

A set of user-friendly materials will be prepared for each of the officers showing the data currently held on recorded locations for the Division and its units, as well as known spray missions (other than Ranch Hand) that were recorded and appear on the SERVICES-HERBS tape.

Each Chemical Officer will be located through the Veterans Administration or through the Pentagon if the Officer is still on active duty. If this is unsuccessful, an Equifax search will be undertaken. When the officer is located, Colonel Christian will place a call to him to explain the project and to ask his cooperation. All Officers will be offered an honorarium of \$200 for participating in the project. They will be reimbursed for any photocopying or telephone expenses they may incur in carrying out the task. An appointment will be made for a follow-up phone call. It will be made clear to him that the prime object is to learn the location of the spraying at the main base camps, FSB's, (fire support bases), OP's (outposts) and LP's (listening posts) to the fullest extent possible. They will be informed that the interview will include a third party for note taking.

Upon obtaining their agreement to cooperate they will be sent the package of prepared materials for them to review in order for them to prepare for the follow-up phone call.

The follow-up phone call be directed at answering the following questions:

Did you personally supervise the loading of the helicopters that sprayed around the perimeters? If yes, can you provide the exact location and amount of spray and supplies that were held in that location? Did any accidents or special situations arise that caused unusual spillage? Were there aborted missions leading to dumping of herbicide loads?

The Officers will also be asked to recall, if possible, the names of the 4 or 5 people who reported to them and carried out spray missions and/or supervised the local storage of the herbicides. Where this information has been obtained by us from the military records, the Officer's response will be compared to the information we already hold (during the interview) and any discordance will be noted and then probed in the conversation.

The Officer will be specifically asked if he has any personal diary or other notes to which he can refer, and, if so, whether he would share their contents with us.

At the outset of the interview the Staff Associate assigned to the project will have been introduced to the Officer and his permission obtained for him/her to listen to the interview. The Staff Associate will take notes on the interview and after its completion the Staff Associate and Col. Christian will confer and reach consensus on the information that was obtained.

Where the Daily Journals have indicated that a particular incident or spray activity had taken place during the Officer's tour of duty and it is an incident which it is reasonable for him to have known about, the Officer will be queried in order to determine whether the information can be independently elicited from him. An example of such an incident would be a helicopter inadvertently spraying over a water shed or a stream where water is obtained for troop use (two events which have been known to have happened as a matter of record.) If such independent elicitation does not occur, that will be noted and the Officer will be specifically queried about the event/incident. If he does recall it after prompting, the Officer's recall will be noted as 'incomplete.'

Finally, upon conclusion of the interview the Officer will be asked if he wishes to participate in the survey that is being distributed as part of Project #2. If so, he will be assigned a code number, just as are all the other participants, and will be sent a questionnaire so that he could fill out the form anonymously. If the evaluation of the form places the Officer into the "heavily exposed" category he will, as a matter of study protocol, be invited to participate in the blood serum study, as described in Projects 2 and 3 below.

Limitations

The limitations to the type of anecdotal information that is being proposed here, particular after so many years have elapsed since the events in question, are, of course, obvious. However, the Officers who will participate in this project all held a high rank and many are known to have kept careful records of their service in Vietnam. Further, it may be that a number of them may be able to unequivocally state that certain areas were or were not sprayed. The costs, both in time and money, are comparatively minimal and it appears to be a small project that is worth the effort. It is difficult, however, to predict in advance the degree to which it will be successful. The results obtained will have to be carefully scrutinized and compared very closely to the existing records and a judgment passed on the accuracy of the new information.

The new information received will then be applied to the rank-ordered exposure index described below and it will be determined whether any rank-orderings are altered by the inclusion of the newly obtained information. Changes to the rank-ordering will require further assessment from the research team.

Final Product

Project 1 will result in two important products

- a military unit-location-exposure database
- a software package by which it can be accessed.

Military Unit- Database- Vietnam of location-and exposure: Upon completion of Project 1, we will have created a final database of military unit locations and associated herbicide exposure opportunity indices that can serve as the basis for future epidemiological studies. The database will include, to the extent possible, all known military units that served in Vietnam. Each unit will have a matrix that describes its location history over time, and attached to each time-location coordinate will be a vector of EOIs computed using the models described above. We will also provide an index of robustness of the EOI to imprecision in known coordinates, that will permit an investigator to distinguish units with well-known locations (e.g., Army Post Offices that did not move) from units with poorly documented locations (e.g., some Special Forces units). Each military unit will be identified by a unique UIC code that will permit linkage with data obtained from personnel record sources. This will be available in ASCII format readable by most computer systems.

User-friendly software package: In order to facilitate future epidemiological studies, a software module will be provided that enables a researcher to "look up" location data for any military unit or veteran for whom the UIC is known. A translation module will be included that permits determination of UIC from the name of the military unit. The researcher can then harvest EOIs directly and write them to a file, which can then be linked to health or other veteran data from external sources. A program option will be provided that will permit an investigator to substitute an exposure model of his/her own devising. A working prototype of this software/database system has already been created by the authors and is available for examination. Table 1. Surrogate Measures Of Herbicide Exposure (1)

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Stellman SD, Stellman JM (1986). Estimation of exposure to Agent Orange and other defoliants among American troops in Vietnam: A methodological approach. Am J Indust Med 9:305-321.

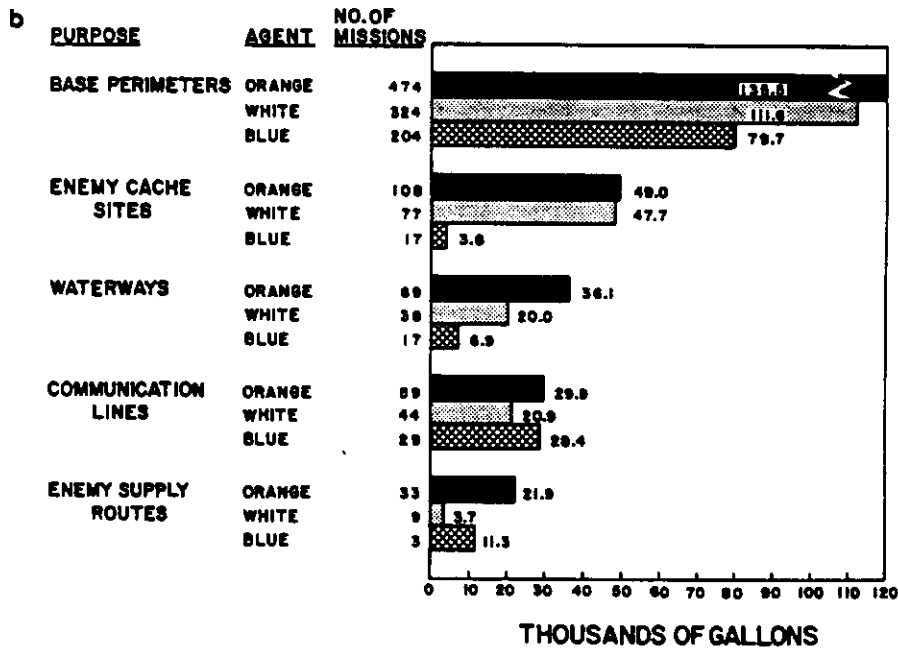
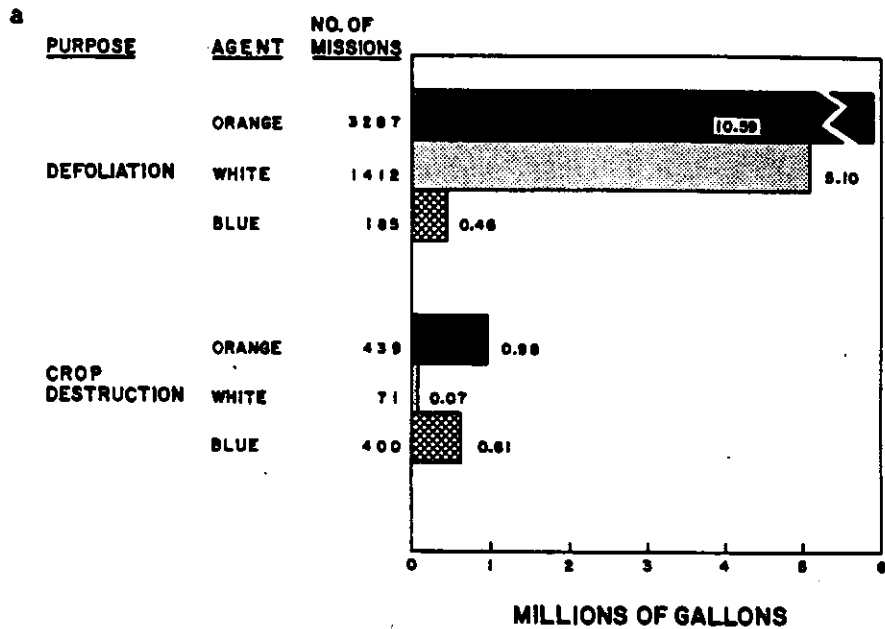


FIG. 1. Quantities of Agents Orange, White, and Blue used in South Vietnam, 1965-1971, by type of missions. (a) Defoliation and crop destruction missions. (b) Five minor types of missions.

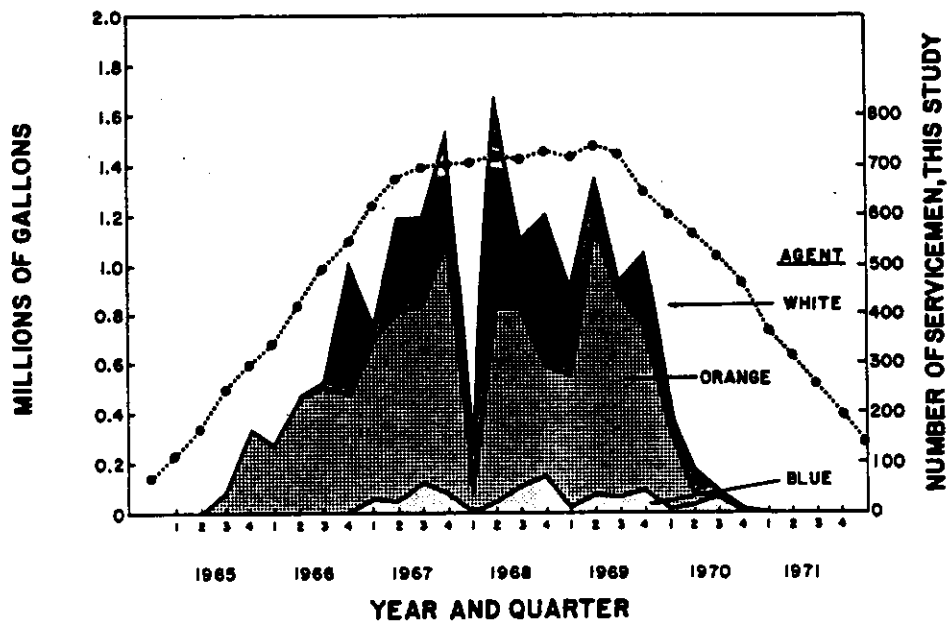


FIG. 2. Quantities of Agents Orange, White, and Blue used in South Vietnam, 1965-1971 (shaded areas), and number of study subjects stationed in South Vietnam (dotted line), by calendar quarter.