CHARACTERIZATION OF EXPOSURE TO AGENT ORANGE IN VIETNAM VETERANS AS A BASIS FOR EPIDEMIOLOGICAL STUDIES

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INTRODUCTION

Between 1961 and 1970, the U.S. military engaged in massive chemical defoliation and crop destruction operations in Southeast Asia.[1] In 1985, nearly two decades after the spraying had ceased, a landmark tort settlement was reached between a class of Vietnam veterans and the chemical manufacturers that had supplied the Agent Orange and other military herbicides to the U.S. Department of Defense.[2] It is notable that, at the time of the settlement, there

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[1] WILLIAM A. BUCKINGHAM, JR., OPERATION RANCH HAND: THE AIR FORCE AND HERBICIDES IN SOUTHEAST ASIA 1961-1971 (Office of U.S. Air Force History 1982).

[2] *In re* "Agent Orange" Prod. Liab. Litig., 611 F. Supp. 1396 (E.D.N.Y. 1985).

was little convincing epidemiological evidence available, either positive or negative, on the health consequences to veterans of the herbicide operations. Today, more than three decades after this massive environmental exposure, there is still a dearth of epidemiological data on the extent to which adverse health consequences resulted from the use, storage, and disposal of the herbicides in Vietnam.

This paucity of epidemiological data stands in stark contrast to the extensive amount of experimental data available on dioxin, an important contaminant in about 60% of the herbicide sprayed.[3] Much laboratory data convincingly demonstrate dioxin's extreme toxicity.[4] The scientific literature also is growing with respect to the carcinogenicity of the organic arsenical that was a primary component of the Agent Blue used to destroy enemy food crops.[5] Many epidemiological studies have been carried out on other, much smaller populations exposed to the same chemicals. Indeed, when the Institute of Medicine (IOM) conducts its biennial review of the scientific literature and provides the Department of Veterans

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3 The chemical composition of three major herbicides used in Vietnam and the quantity dispersed are as follows:

Agent	Composition	Gallons
Agent Orange	2,4-D, 2,4,5-T*	12,066,840
Agent White	Picloram, 2,4-D	5,430,462
Agent Blue	Dimethylarsinic acid (Synonym: Cacodylic acid)	1,252,541

*Contaminated with 2,3,7,8-TCDD (dioxin)

More detailed data are given in Jeanne Mager Stellman et al., *The Extent and Patterns of Usage of Agent Orange and Other Herbicides in Vietnam*, 422 NATURE 681 (2003) [hereinafter Stellman et al., *The Extent and Patterns of Usage of Agent Orange and Other Herbicides in Vietnam*].

4 *See, e.g.,* OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT, U.S. ENVTL. PROTECTION AGENCY, NO. EPA/600/8-84/014F, HEALTH ASSESSMENT DOCUMENT FOR POLYCHLORINATED DIBENZO-P-DIOXINS, FINAL REPORT (1985).

5 Hideki Wanibuchi et al., *Carcinogenicity of an Organic Arsenical, Dimethylarsinic Acid and Related Arsenicals in Rat Urinary Bladder*, 40 PROC. OF THE AM. ASS'N FOR CANCER RES. 349 (1999); Min Wei et al., *Urinary Bladder Carcinogenicity of Dimethylarsinic Acid in Male F344 Rats*, 20 CARCINOGENESIS 1873 (1999).

Affairs (VA) with a summary, including its appraisal of the relationship between herbicide exposures and a list of health outcomes, it relies to a large extent on studies carried out on non-veteran populations to support its conclusions.[6] The degree to which these other studies correctly estimate health effects in Vietnam veterans is not known. Thus there continue to be practical ramifications to the paucity of definitive epidemiological studies on a sufficiently large exposed population of either veterans or Vietnamese citizens.[7]

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[6] In accordance with the Agent Orange Act of 1991, Pub. L. No. 102-4, 105 Stat. 11 (1991) (codified as amended at 38 U.S.C. § 1116), the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides was asked "to determine (to the extent that available data permit meaningful determinations)" the following regarding associations between specific health outcomes and exposure to TCDD and other chemical compounds in herbicides:

> A) whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association; B) the increased risk of the disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and C) whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

38 U.S.C. § 1116. *See* COMMITTEE TO REVIEW THE HEALTH EFFECTS IN VIETNAM VETERANS OF EXPOSURE TO HERBICIDES, INSTITUTE OF MEDICINE, VETERANS AND AGENT ORANGE: HEALTH EFFECTS OF HERBICIDES USED IN VIETNAM (1994) [hereinafter 1994 IOM REPORT], *available at* http://books.nap.edu/books/0309048877/html/index.html. The Institute of Medicine publishes biennial updates based upon the deliberations of its Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. The series is VETERANS AND AGENT ORANGE of which there are 1996, 1998, 2000, 2002 and 2004 publications.

[7] Epidemiological studies can be used to support arguments that a disease or dysfunction is more likely than not to have arisen from a particular causative agent. Epidemiological studies examine the statistical distribution of a disease (or other outcome) in two populations: one that was "exposed" to the agent or condition under study and another "control" population not exposed and as alike as possible in every other way to the exposed group. If the rate of disease observed in the exposed population is greater than in the control population, and if the rate differences satisfy certain statistical requirements, the rate difference will be called "significant."

This article discusses some of the factors that have contributed to the lack of epidemiological evidence on military herbicide operations. Part I of this article will provide a brief overview of the purposes and methodology of environmental epidemiological studies. Part II will discuss the application of this methodology to exposed Vietnam veterans. In particular, this section will examine the use of exposure opportunity measures in epidemiological studies as well as recent successful work on the development and use of military records for estimating exposure opportunity to military herbicides in Vietnam. This article concludes that while there are sufficiently large populations available for study and appropriate methodologies to carry out such studies, these much-needed epidemiological investigations remain unfunded and undone, so that both legal and public policy decisions must continue to be made with inadequate scientific data.

I. ENVIRONMENTAL EPIDEMIOLOGY

A valid environmental epidemiology study relating an exposure to subsequent risk of disease requires a biologically reasonable hypothesis, an exposed population, and either an unexposed population or a set of disease rates in a reference population to which the rate of disease in the study group can be compared. Usually there are experimental laboratory studies or clinical reports of adverse health effects in individuals that can be used to generate a "null" hypothesis of the form: "Exposure to agent XYZ is not related to development of disease ABC." The purpose of the epidemiological study is to test the null hypothesis. If the null hypothesis is rejected (i.e., a statistically significant difference in rates is observed between the exposed and unexposed), then the study is considered positive and a relationship between the exposure and the outcome is supported.[8]

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[8] Note the use of the word "supported." Epidemiological studies do not establish cause and effect. Rather, they indicate that there is a statistical likelihood that a relationship between the exposure and the outcome exists. Generally, epidemiologists require a 95% certainty that the relationship is not compatible with chance in order to consider an outcome significant. Failure to meet this criterion is a type 1 error.

A successful study of this nature requires a suitably large population with sufficiently great exposure to agent XYZ to elicit the measured health effect.[9] Additionally, the population's exposure to the agent and the subsequent study must be adequately spaced over time to have permitted XYZ an opportunity to induce disease ABC. In fulfilling these requirements, epidemiological studies must endeavor to identify all members of the at-risk population, to successfully find and enroll these individuals in the study, and to take into account other exposures (e.g., cigarette smoking or occupational exposures) that also could lead to the disease under study. It is also critically important that the exposed population truly consist of exposed individuals. Many environmental epidemiology studies have been compromised by the inclusion of non-exposed individuals, for example, non-exposed clerical or management staff in a study of chemical plant workers. Such dilution of a truly exposed population with unexposed individuals is known as "differential misclassification" of exposure and can result in an underestimate of the true association between exposure and disease.[10] There are many instances of such misclassification errors in existing studies of Vietnam veterans.[11]

In all cases, a necessity for the successful design and execution of an environmental epidemiology study is the ability to define "exposure." Poorly defined population exposures can lead to two

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[9] The population size, the anticipated effect size (i.e. the environmental agent's potency as measured by the difference between the disease risk in the exposed group and that in an unexposed reference group), and the desired level of statistical certainty all contribute to the statistical "power" to actually observe an effect if it is present. If there are too few exposed people or the effect size is very small, an epidemiologic study may be useless and failure to reject the null hypothesis (a negative result) non-informative. This is known as a type 2 error.

[10] KENNETH J. ROTHMAN & SANDER GREENLAND, MODERN EPIDEMIOLOGY 126-27 (1998).

[11] JEANNE MAGER STELLMAN & STEVEN D. STELLMAN, INSTITUTE OF MEDICINE, SUBCONTRACT VA-5124-98-0019, CHARACTERIZING EXPOSURE OF VETERANS TO AGENT ORANGE AND OTHER HERBICIDES IN VIETNAM: FINAL REPORT 109 tbl.32 (2003) [hereinafter STELLMAN & STELLMAN, CHARACTERIZING EXPOSURE OF VETERANS TO AGENT ORANGE AND OTHER HERBICIDES IN VIETNAM].

sources of misclassification error: unexposed people are considered exposed or exposed people are considered not exposed. Both types of error may occur in a given study and may lead to unpredictable errors in estimates of exposure-disease associations. For example, in the Air Force Health Study of Vietnam veterans who were assigned to the herbicide spray operations, many in the reference comparison group in fact had elevated blood levels of dioxin, while many in the study population had non-detectable levels.

Assigning exposure levels in epidemiology studies of chronic exposures almost always poses great methodological challenges.[12] Unlike "acute" exposures to an agent suspected of causing a health effect (e.g., reactions to an implanted medical device or exposure to environmental agents arising from industrial accidents or non-industrial events, such as carbon monoxide poisoning from faulty heaters), most chronic environmental exposures are characterized by poor, incomplete, or even nonexistent measurements of actual exposure levels. The "exposed" population may also have been exposed to a host of other agents that could potentially cause the same outcome and will have spent discontinuous—and usually undocumented—periods of time being "exposed." Studies are often carried out years after the exposure has ended, making it difficult, if not impossible, to find extant biological evidence of the

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[12] A valid metric for assigning exposures is a necessary element of an epidemiology study—without it one cannot differentiate the exposed from the controls. In addition, epidemiologists place higher confidence in studies that demonstrate that the higher the dose of the exposure, the more likely the outcome. For example, a cigarette smoker with a lifetime history of smoking one pack per day, on average, has a relative risk of lung cancer eight to ten times that of never-smokers, while a two pack per day smoker has a risk twenty times that of a nonsmoker. Steven D. Stellman et al., *Lung Cancer Risk in White and Black Americans*, 13 ANNALS OF EPIDEMIOLOGY 294, 298 (2003). Thus, it is desirable to have a metric that permits the exposure to be more than simply ever/never, but rather quantified so that a dose-response relationship can be tested and the risk at high doses compared with that at low doses. For a discussion of the importance of dose-response relationships in epidemiological studies, see Leslie Stayner et al., *Sources of Uncertainty in Dose-Response Modeling of Epidemiological Data for Cancer Risk Assessment*, 895 ANNALS OF THE NEW YORK ACADEMY OF SCIENCES 212 (1999).

exposure among individuals thought to have been exposed and, for many environmental exposures, no adequate biomarkers exist.[13] Ubiquitous environmental agents complicate the job of finding a truly unexposed control population.

II. EPIDEMIOLOGY AND VIETNAM VETERANS

Whether the military use of herbicides in Vietnam lends itself to the basic requirements for an environmental epidemiology study merits examination. Such a study could test the following generalized null hypothesis, "Exposure to military herbicides used during the Vietnam War did not lead to adverse health outcomes among the exposed populations or their offspring," or a related, more general hypothesis that "military service in areas sprayed by military herbicides did not lead to adverse health outcomes."

It is clear from the IOM's summaries of available experimental evidence that there exist sufficient toxicological and clinical data to justify undertaking major epidemiology studies for a variety of disease outcomes. In particular, the large quantity of herbicide that the United States sprayed in Vietnam as well as the vast amounts

[13] For many environmental agents, even if one had a scientifically valid exposure metric, the extent of exposure might not yield a population that is large enough for a successful epidemiological study to be carried out because the number of exposed persons is small, the intensity of the exposures is low, or, with the passage of time, the amount of chemical in exposed individuals' bodies declines due to metabolic processes. In any of these cases, the ability to detect an association between exposure and disease is very limited, as expressed numerically by the concept of statistical power. Statistical power is defined as the probability that a statistical test will yield a significant result. JACOB COHEN, STATISTICAL POWER ANALYSIS FOR THE BEHAVIORAL SCIENCES 1 (Academic Press 1977). Thus, a weak environmental agent that does indeed cause a disease (small effect size) would require a very large population N for the observed difference in rates to reach significance. If a legal criterion demands an effect size of a twofold difference between the exposed and non-exposed, the size of the populations studied would also have to be expanded in relation to a criterion which demanded a 50% increase (i.e. twofold relative risk). The necessary population size for the study will also depend on the rate at which the disease is observed in the unexposed population. Agents that cause rare diseases may be less likely to be identified than those that cause common diseases because too few cases ever occur to satisfy the requirements of statistical power.

that it manufactured would provide epidemiological studies with a sufficiently large sample of affected individuals and chemical resources. Nearly 20 million gallons of military herbicides were sprayed in Vietnam and Laos between 1961 and 1971. Agent Orange accounted for more than 12 million gallons of these herbicides. The chemical consists of a 50:50 mixture of two phenoxyherbicides, 2,4-D and 2,4,5-T, with much of the 2,4,5-T component contaminated with dioxins and dibenzofurans. The most notorious and deadly of these contaminants is 2,3,7,8-tetrachloro-p-dibenodioxin, usually simply called dioxin, although the precise levels of contamination are not known.[14] These chemicals are unwanted byproducts of the manufacturing process and are inevitably present unless manufacturing conditions are carefully controlled.[15] Even prior to the 1985 Agent Orange tort settlement, there was no question regarding dioxin's deadly effects.[16]

In order to proceed with an epidemiological study of Agent Orange, there must be a suitable population available for study. The authors have calculated that between 3 and 5 million Vietnamese citizens were directly in the spray path of the herbicide.[17] Many areas, so-called "hotspots," are still highly contaminated with TCDD residues and a variety of bioassays have found that Vietnamese individuals have higher-than-normal levels of dioxin in their tissue,[18] although there is little data on the

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[14] Stellman et al., *The Extent and Patterns of Usage of Agent Orange and Other Herbicides in Vietnam*, *supra* note 3, at 682.

[15] ALASTAIR HAY, THE CHEMICAL SCYTHE: LESSONS OF 2,4,5-T AND DIOXIN (Plenum Press 1982).

[16] Indeed, in its decision with respect to the Agent Orange Class action, the court stated:

> As to the poisonous nature of dioxin and its ability to cause harm to mammals, including homo sapiens, there is no doubt. The form of dioxin implicated in Agent Orange is a dangerous, stable, long lasting chemical. . . . Dioxin is one of the most powerful poisons known . . . .

In re "Agent Orange" Prod. Liab. Litig., 597 F. Supp. 740, 777 (E.D.N.Y. 1984).

[17] Stellman et al., *The Extent and Patterns of Usage of Agent Orange and Other Herbicides in Vietnam*, *supra* note 3, at 684.

[18] Arnold Schecter, *Food As a Source of Dioxin Exposure in the Residents*

relationship between body burden and putative exposure. While the precise number is not known, it is estimated that about 3 million American soldiers served in the Vietnam theatre.[19] Soldiers directly charged with carrying out the Air Force Operation Ranch Hand, the name for the military operation that carried out the great majority of aerial defoliation and crop destruction missions, were potentially exposed to herbicides.[20] Similarly, some, but certainly not all, of those belonging to the Army Chemical Corps, another group that has been studied, were also potentially were exposed. It would be erroneous to classify all of these individuals as potentially exposed.[21] Some Army troops were herbicide handlers or backpack sprayers, or were engaged in missions to keep base camp perimeters free from vision-blocking foliage. There is evidence that those whose missions brought them into recently defoliated areas absorbed the herbicides.[22] Finally, military unit

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of Bien Hoa City, *Vietnam*, 45 J. OF OCCUPATIONAL & ENVTL. MED., 781, 781-82 (2003).

[19] Sharon R. Cohany, *The Vietnam-Era Cohort: Employment and Earnings*, 115 MONTHLY LABOR REV. 3, 5 (1992).

[20] The Air Force Health Study often called the Ranch Hand study, a 20-year longitudinal study examining health, mortality, and reproductive outcomes, has found associations between Ranch Hand service and subsequent risk of prostate cancer and Type II diabetes. Matthew P. Longnecker & Joel E. Michalek, *Serum Dioxin Level in Relation to Diabetes Mellitus among Air Force Veterans with Background Levels of Exposure*, 11 EPIDEMIOLOGY 44 (2000). This study, however, because of its unavoidably small size, is not informative on rarer cancers.

[21] Serum dioxin levels in the Air Force Health Study for the comparison group reach a level nearly twice that of the Ranch Hand low category group in the study population. *See* Akhtar et al., *Cancer in US Air Force Veterans of the Vietnam War*, 46 J. OF OCCUPATIONAL & ENVTL. MED. 123, 127 (2004). Some Air Force personnel not directly assigned to the herbicide operational units did, in fact, have work assignments that brought them into contact with herbicides, while some flight personnel, notably pilots, who never handled herbicides, had access to shower and laundry facilities and flew in air pressurized cabins. *See* BUCKINGHAM, *supra* note 1 (providing an extensive history of the military herbicide program in Vietnam). The exposure misclassification of the comparison group as unexposed would, however, tend to strengthen our confidence in the positive cancer findings. *See supra* note 20.

[22] Peter C. Kahn et al., *Dioxins and Dibenzofurans in Blood and Adipose Tissue of Agent Orange-Exposed Vietnam Veterans and Matched Controls*, 259

history records show that a sufficiently large number of units were directly sprayed during Operation Ranch Hand to justify large-scale studies.[23]

The extent to which soldiers entering into previously sprayed areas or living in base camps in which the perimeters were regularly cleared with defoliants received a biologically significant dose of herbicides or their contaminants is not clear. Because so many years have passed since the exposure, measurement of the current body burden of dioxin is subject to serious misclassification errors, and biomarkers are not available for herbicide formulations that were not contaminated with TCDD.[24]

JAMA 1661 (1988) (showing that the leaders of jungle patrols in heavily sprayed areas, so-called "pointmen," had elevated levels of dioxin compared to a matched unexposed control population).

[23] *See* STELLMAN & STELLMAN, CHARACTERIZING EXPOSURE OF VETERANS TO AGENT ORANGE AND OTHER HERBICIDES IN VIETNAM, *supra* note 11, at 48 tbl.11. Table 11 demonstrates numerous documented instances in which combat units were subject to "direct hits" from herbicide spray. The direct spraying of combat units has been a contentious issue for several decades. The history of the controversy is well described in the IOM's 1994 report. Both the White House Agent Orange Working Group and the Centers for Disease Control, *Centers for Disease Control Veterans Health Studies, Serum 2,3,7,8-Tetrachloro-P-Dibenzo-P-Dioxin Levels in U.S. Army Vietnam-Era Veterans*, 260 JAMA 1249 (1988) [hereinafter CDC Veterans Health Studies], have declared that ground troops were not exposed to herbicides and that only those troops with duties that involved the handling and spraying operations were exposed. Examination of military archives by the U.S. General Accounting Office, COMPTROLLER GENERAL OF THE U.S., U.S. GENERAL ACCOUNTING OFFICE, U.S. GROUND TROOPS IN SOUTH VIETNAM WERE IN AREAS SPRAYED WITH HERBICIDE ORANGE (1979), *available at* http://161.203.16.4/f0302/110930.pdf, and by the CDC itself found a significant number of troops to have been located directly under the spray path. Centers for Disease Control, AGENT ORANGE STUDY: EXPOSURE ASSESSMENT: PROCEDURES AND STATISTICAL ISSUES (CDC Agent Orange Project, Agent Orange Projects Interim Report, Draft, Feb. 1985).

[24] The Institute of Medicine has specifically addressed the difficulties in using current body burden measurements of dioxin to reflect past exposures in Vietnam. First, during its oversight of the original CDC Agent Orange Study, the IOM rejected the CDC proposal to "validate" military records of troop location by using serum dioxin samples obtained at least two decades post-exposure. *See* ADVISORY COMMITTEE ON THE CDC STUDY OF THE HEALTH OF VIETNAM VETERANS, INSTITUTE OF MEDICINE, FIFTH LETTER REPORT, REVIEW

For these soldiers, service in an area with a history of herbicide spraying would be the relevant measure of exposure (called an "exposure opportunity index," or EOI) rather than a measure of biological dose. Such studies would seek to test the hypothesis that military service in defoliated areas increased the risk that soldiers would develop the diseases under study and that the risk was proportional to the soldiers' proximity in time and space to the spraying.[25]

A. Agent Orange and Measures of Exposure

Methodological difficulties in assigning relative Agent Orange

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OF COMPARISON OF SERUM LEVELS OF 2,3,7,8-TCDD WITH INDIRECT ESTIMATES OF AGENT ORANGE EXPOSURE IN VIETNAM VETERANS (1987). The CDC continued its "validation study" notwithstanding, CDC VETERANS HEALTH STUDIES, *supra*, and, as a result of a purported lack of correlation between serum dioxin and a records-based exposure index, abandoned the large Agent Orange Study of III Corps Army combat battalions already underway. Agreeing with the aforementioned IOM critique, a second IOM committee reviewed the conceptual underpinnings of the CDC validation study, and, in contradistinction to the CDC and Agent Orange Working Group conclusion, recommended that a study be conducted on the utility of the historical reconstruction of military records for characterizing exposure to military herbicides in Vietnam. *See* 1994 IOM REPORT, *supra* note 6.

[25] It should be noted that broad studies on the health of Vietnam veterans are not informative with respect to the health effects of Agent Orange because of serious misclassification errors that arise from considering the fact of service in Vietnam to be equivalent to having served in a sprayed area. The large-scale study undertaken by the Centers for Disease Control on the health of troops assigned to Vietnam, CENTERS FOR DISEASE CONTROL, U.S. DEPT. OF HEALTH AND HUMAN SERVICES, HEALTH STATUS OF VIETNAM VETERANS: VIETNAM EXPERIENCE STUDY (1989) (Vols. I-V, Supplements A-C), for example, reveals nothing about Agent Orange and other herbicides, nor was it the intent of the study to address this issue. The same is true for the Selected Cancer Study. *See* SELECTED CANCERS COOPERATIVE STUDY GROUP, ASS'N OF SELECTED CANCERS WITH SERVICE IN THE U.S. MILITARY IN VIETNAM, II. SOFT-TISSUE AND OTHER SARCOMAS, 150 ARCHIVES OF INTERNAL MED. 2485 (1990); SELECTED CANCERS COOPERATIVE STUDY GROUP, ASS'N OF SELECTED CANCERS WITH SERVICE IN THE U.S. MILITARY IN VIETNAM, III. HODGKIN'S DISEASE, NASAL CANCER, NASOPHARYNGEAL CANCER, AND PRIMARY LIVER CANCER, 150 ARCHIVES OF INTERNAL MED. 2495 (1990).

exposure levels to Vietnam veterans have been a major roadblock to carrying out large-scale epidemiology studies of the relationship between exposure to military herbicides and adverse health outcomes. Indeed, the Centers for Disease Control and Prevention (CDC) and the Agent Orange Working Group, a subcommittee of the White House Domestic Policy Council, declared that military records could not be used to reconstruct past exposures, and the CDC Agent Orange Study was abruptly halted, with unused funds being returned to the Treasury.[26]

In 1994, however, the IOM again did not concur with the federal scientists' conclusions that any epidemiological study was *ipso facto* impossible because of the inability to classify exposure based on military records. The IOM recommended that a methodological study be undertaken to determine whether methods involving the historical reconstruction of military records could be used for characterizing exposure to herbicides in Vietnam and as the basis for epidemiology studies of Vietnam veteran health. The National Academy of Sciences (NAS) subsequently received a contract from the VA to seek independent researchers to develop an appropriate methodology to conduct the investigation. The exposure opportunity methodology described in this article is the result of a subcontract from the NAS undertaken by the authors for that purpose.[27] In 1998, a project was begun to refine and validate an EOI methodology that had previously been used in the exposure assessment of claimants to the Agent Orange Veterans Payment Program[28] and in studies of Vietnamese citizens[29] and American

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[26] The abandonment of the Agent Orange Study was the subject of unsuccessful litigation by the American Legion and the Vietnam Veterans of America, who sought to have the congressionally mandated study reinstated. *See* American Legion v. Derwinski, 54 F.3d 789 (D.C. Cir. 1995); American Legion v. Derwinski, 827 F. Supp. 805 (D.D.C. 1993).

[27] *See* 1994 IOM REPORT, *supra* note 6; COMMITTEE ON THE ASSESSMENT OF WARTIME EXPOSURE TO HERBICIDES IN VIETNAM, INSTITUTE OF MEDICINE, CHARACTERIZING EXPOSURE OF VETERANS TO AGENT ORANGE AND OTHER HERBICIDES USED IN VIETNAM: SCIENTIFIC CONSIDERATIONS REGARDING A REQUEST FOR PROPOSALS FOR RESEARCH (1997).

[28] The original methodology was the basis for assessing exposure eligibility for the Agent Orange Veterans Payment Program, established in the Agent Orange class action settlement. *In re* "Agent Orange" Prod. Liab. Litig., 611 F.

Vietnam veterans.[30]

EOI models, which are becoming increasingly common in epidemiological studies, typically represent exposure as a function of proximity in time and space to a toxic agent.[31] An EOI is often used, for example, in occupational or environmental studies as a surrogate estimator of historical exposure where current environmental or biomarker measurements are inadequate estimators of past exposures and where measurements were never made in the past or are unavailable.[32] The EOI concept is complementary to traditional exposure methodologies based upon toxicological models and measures. Exposure opportunity is not in itself a toxicological measure, but EOI scores can be incorporated into toxicological models as "presentation" dosages. Such dosages are intended for use in large-scale studies in which a location history is the principal source of information about an individual or group, such as a military unit. These models are especially applicable to studies in which body burden measurements are impractical or unlikely to reflect exposures in the distant past.

To perfect an EOI model for military herbicides in Vietnam, a Geographical Information System (GIS) for the former Republic of Vietnam was created. The GIS is a relational database whose

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Supp. 1396 (E.D.N.Y. 1985).

[29] Marie-Catherine Ha et al., *Agent Orange and the Risk of Gestational Trophoblastic Disease in Vietnam*, 51 ARCHIVES ENVTL. HEALTH 368 (1996).

[30] A cross-sectional study of American Legionnaires utilized an earlier version of the EOI methods described here. See Steven D. Stellman & Jeanne Mager Stellman, *Estimation of Exposure to Agent Orange and Other Defoliants Among American Troops in Vietnam*: *A Methodological Approach*, 9 AM. J. INDUS. MED. 305 (1986), for the methodology and Steven D. Stellman et al., *Combat and Herbicide Exposure in Vietnam Among American Legionnaires*, 47 ENVTL. RESEARCH 112, 120-21 (1988), for the distribution of EOIs in the cohort.

[31] *See, e.g.,* Kirk R. Smith, *Place Makes the Poison: Wesolowski Award Lecture – 1999*, 12 J. EXPOSURE ANALYSIS. & ENVTL. EPIDEMIOLOGY 167 (2002); Mary H. Ward et al., *Identifying Populations Potentially Exposed to Agricultural Pesticides Using Remote Sensing and a Geographic Information System*, 108 ENVTL. HEALTH PERSPECTIVES 5 (2000).

[32] *See, e.g.,* E. S. Schaeffner et al., *Use of an Asbestos Exposure Score and the Presence of Pleural and Parenchymal Abnormalities in a Lung Cancer Case Series*, 7 INT'L J. OF OCCUPATIONAL & ENVTL. HEALTH 14 (2001).

component tables (the "layers") contain data on herbicide application, military troop location, and other geographically encoded data resources that are designed to be utilized in the assessment of exposure to herbicides and exposure-related health risks for specific populations. Table 1 contains an abbreviated list of data layers that are currently included in the GIS.[33] The GIS is built around two interrelated concepts: the partitioning of Vietnam into 0.01° x 0.01° "square" grids and the association of the geographic center of each grid with a continuous EOI and a vector of four proximity "hit" scores.[34] Data in each layer have been geocoded in a manner compatible with our Vietnam grid system. Unique grid identifiers serve to link data between cartographic layers.

[33] Adapted from Jeanne Mager Stellman et al., *A Geographic Information System for Characterizing Exposure to Agent Orange and Other Herbicides in Vietnam*, 111 ENVTL. HEALTH PERSPECTIVES 321, 322 (2003).

[34] The EOI takes into account entry into areas sprayed in the past as well as being present during an actual spray mission. A conservative first-order decay model is used to simulate the decay of herbicide in the environment. The term "hit" is applied when an individual actually was located in or near the spray path during a mission. The mathematical representations of these two models are given in Steven D. Stellman & Jeanne Mager Stellman, *Exposure Opportunity Models for Agent Orange, Dioxin, and Other Military Herbicides Used in Vietnam*, *1961-1971*, 14 J. EXPOSURE, ANALYSIS & ENVTL. EPIDEMIOLOGY 354 (2004).

Table 1. GIS data tables ("layers") of location and herbicide spray data that can be linked to create exposure opportunity scores.[35]

Type of activity or data	Examples
HERBS file	Flight paths and other details of herbicide spray applications
Civilian habitations	Cities, towns, villages, hamlets, plantations
Vietnam land and water features	Soil typology, land topography, rivers, streams
Civil structures	Roadways, utility lines, rail lines, canals, air fields
Military structures	Military bases, base camps, landing zones, air fields
Troop locations	Headquarters, base camps, depots, and other locations assigned to support and combat support units; tracked locations for combat troops
Operation Ranch Hand Targets	Specific areas designated for defoliation and crop destruction by an elaborate approval mechanism
Herbicide storage, transport, and unplanned dispersal	Locations of known "incidents" such as spills, dumps, and crashes

At the heart of exposure assessment is a comprehensive database, known as the HERBS file, that describes all documented herbicide applications that were carried out by the U.S. military during the Vietnam War. This database was compiled from a wide variety of archival sources under a contract from the NAS. The HERBS file contains information consisting of one or more records that collectively describe the spray coordinates of single or multiple aircraft (known as sorties) during 9,141 missions. The majority of spray (about 18 million gallons) was applied by specially equipped C-123 transport aircraft in Operation Ranch Hand. The chief herbicide uses were defoliation and crop

[35] See Stellman et al., *supra* note 33, for more details.

destruction. During the work undertaken for the NAS, the HERBS file was extensively corrected and validated.[36] U.S. Army (not Air Force) personnel sprayed tens of thousands of gallons along base camp perimeters, waterways, and communication lines by helicopter, backpack, truck, and boat. Each of these modalities was calibrated to spray the phenoxyherbicides at a rate of 3 gallons per acre. A large percentage of these missions were entered into a second HERBS file, sometimes called the Services-HERBS. A major data cleaning and reconciliation effort was undertaken to eliminate redundancies in these two files, and the current version of the HERBS file contained in the GIS reflects those quality control changes.

More than 98% of all herbicide spraying was by fixed-wing aircraft. Key to the usefulness of the HERBS file is the fact that it describes the actual flight paths taken by the Ranch Hand aircraft. For example, the HERBS file contains "leg designators" that permit the reconstruction of the contiguous flight paths of 5,215 fixed-wing Ranch Hand missions, most with multiple sorties.

Although the GIS is a useful tool for visualizing locations of individuals or military units in relation to herbicide applications, the sheer quantity of data in both the herbicide and unit location databases and the almost limitless possibilities for temporal and spatial variation make calculation of exposure opportunity scores a formidable challenge. To reduce this task to manageable proportions, a user-friendly software system called Herbicide Exposure Assessment – Vietnam (HEA-V) was created.[37] The software accepts as input a "location history" database in Microsoft Excel or Access format and produces as output a set of "hits" scores and the EOI score for each input record. The input may pertain equally to a specific military unit that traveled from one place to another or to an individual who belonged to that unit. It may also pertain to a fixed location, such as a village, hamlet, or

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[36] Details of the process whereby the HERBS file was corrected are given in STELLMAN & STELLMAN, CHARACTERIZING EXPOSURE OF VETERANS TO AGENT ORANGE AND OTHER HERBICIDES IN VIETNAM, *supra* note 11, at 5-7.

[37] Stellman & Greene Consulting, Herbicide Exposure Assessment-Vietnam (HEA-V), software manual and appendices (Brooklyn, N.Y., Found. for Worker, Veteran and Envtl. Health, Inc. 2003) (on file with author).

other geographical entity. It is thus equally suited for use in both epidemiological and ecological studies.

B. Military Unit Location Database Core Data Layer

In the course of providing exposure analyses for the Agent Orange Veterans Payment Program (AOVPP), a database was compiled (at the battalion level) reflecting those locations at which AOVPP claimants were stationed. Further troop location data for all Army combat support units assigned to Vietnam have now been compiled from a variety of primary and secondary military sources.[38] Through a Freedom of Information Act request, the Special Master to the AOVPP obtained data files that contained the locations of many Army combat military units. The files had been created in the course of the CDC's aforementioned abandoned Agent Orange Study. The data were compiled by the Department of Defense Environmental Support Group, which had identified and tracked more than sixty combat battalions stationed in the III Corps Tactical Zone, a very heavily sprayed region extending from the southern coast of Vietnam to the Cambodian border and including Saigon. The Support Group tracked the daily activities and locations of individual companies in these battalions between 1967 and 1969 utilizing a wide variety of data sources, such as daily journals and ORLLs (Operations Reports and Lessons Learned). These data have now been updated and extensively "cleaned" to remove obvious typographical errors; the GIS now

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[38] In general, approximately five out of six troops serve in such support units, which we call "stable" units because troops are stationed at specific base camps and are not required to move frequently. The ratio in Vietnam appears to have been lower, with proportionately more troops assigned to combat. There were more than 1,650 "stable" Army units, which together had an average authorized troop strength of just under 200,000. Nearly 1,000 additional units, whose authorized total troop strength was about 162,000, were also largely stationary but had "mobile elements" who routinely left base camps to carry out their missions. These units included Aviation, Engineering, Ordnance, Signal, Transportation, and Medical Corps and Military Police. The stable units provided support for more than 400 highly mobile units, such as Infantry, Armor, Cavalry, and Artillery battalions, whose strength averaged more than 120,606.

contains detailed location data for sixty-three combat battalions for the time period between 1967 and 1969.[39] In addition, non-exhaustive databases for the U.S. Air Force, Navy, and Marines also have been compiled.[40]

With knowledge of the unit to which an individual was assigned and the individual's dates of assignment, it is thus possible to link the individual to various locations over time. These locations and dates then become input data for the exposure opportunity calculations. Thus, for any given location, military unit, or individual, researchers can calculate an EOI as a quantitative spatio-temporal representation of that individual's proximity to a toxic agent. The EOI model takes into account three independent factors that determine an individual's exposure: concentration of the toxicologically active substance, distance from the spray application, and the time during which the exposure may have taken place. Details of this exposure methodology have been published.[41]

Extensive calculations have been carried out to validate EOI measurements. Those locations at which military units were found to have high EOI scores coincide closely with the "hot spots" indicated in EOI surface plots of Vietnam. The log-normal distributions of exposure scores, especially those that show

[39] The CDC had asserted that these extracted files contained location gaps that invalidate them as a data source for epidemiological studies. The data cleaning carried out during the course of our research found many gaps to be the result of clerical error rather than missing data and that sufficient data are available to construct study populations of a size suitable for valid epidemiological studies.

[40] Exposure estimation for these branches of the military is usually simpler because, for example, most Naval units (with known exceptions such as Riverine units) were located offshore and thus had no opportunity for exposure. In addition, there were a limited number of Air Force installations and the Marines belonged to a comparatively small number of units, mostly assigned to I Corps (the northern region) in comparatively restricted areas.

[41] *See* Jeanne Mager Stellman et al., *A Geographic Information System for Characterizing Exposure to Agent Orange and Other Herbicides in Vietnam*, *supra* note 33; Steven D. Stellman & Jeanne Mager Stellman, *Exposure Opportunity Models for Agent Orange, Dioxin, and Other Military Herbicides Used in Vietnam*, *supra* note 34.

systematically higher exposure for the combat units whose locations were in the heavily sprayed areas of III Corps described above, indicate both face and content validity.

Two studies have compared the EOIs calculated in the GIS with serum dioxin. These comparisons provide an objective measure of body burden when samples are taken sufficiently close in time to the exposure event and when the kinetics of metabolism are taken into account. In 1989, Dr. Sylvaine Cordier of France's National Institute of Health and Medical Research (INSERM) requested that the authors help evaluate exposures for a series of twenty-seven patients admitted for abdominal surgery to the Cho Ray Hospital in Ho Chi Minh City, for whom adipose tissue was being collected for subsequent dioxin assay. EOIs were estimated through our then-current algorithms using the subjects' residential locations. Five patients' levels were at background. For the remaining twenty-two patients, the Pearson correlation coefficient[42] was 0.50 for association between the log of serum dioxin and the log of the EOI.[43] The second biomarker study was a pilot project that was part of a collaboration between the authors and the International Agency for Research on Cancer (IARC), which had carried out a case-control study of non-Hodgkin's lymphoma and soft tissue sarcomas in Vietnamese civilians in Ho Chi Minh City between 1993 and 1996.[44] This study also produced a significant correlation.

Apart from this quantitative validation, a qualitative concordance has been observed between extremely high dioxin concentrations in samples of soil taken at an abandoned U.S. air

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[42] The Pearson correlation coefficient is a measure of association between two variables. Its value ranges from -1 to +1. A zero coefficient indicates no association, while a ±1 is either a perfectly direct or perfectly inverse relationship. Squaring the correlation coefficient approximates the degree of variation "explained" by the association. A statistically significant correlation of 0.50 is generally considered strong in environmental studies.

[43] Pierre Verger et al., *Correlation between Dioxin Levels in Adipose Tissue and Estimated Exposure to Agent Orange in South Vietnamese Residents*, 65 ENVTL. RES. 226 (1994).

[44] Eva Kramarova et al., *Exposure to Agent Orange and Occurrence of Soft-Tissue Sarcomas or Non-Hodgkin Lymphomas: An Ongoing Study in Vietnam*, 106 ENVTL. HEALTH PERSPECTIVES 671, 671 (1998).

base in the Ashau Valley[45] and the HERBS file locations of sprayings of Agent Purple at the same location. Agent Purple was an early herbicide with a dioxin contamination level estimated at 10 to 100 times that of Agent Orange.[46]

CONCLUSION

In its review of the methodological work on the GIS described in this article, the IOM confirmed that the exposure opportunity methodology and the resulting GIS system made epidemiological studies possible and, moreover, urged that epidemiological studies be undertaken immediately.[47] The editors of *Nature* similarly agreed that the work on the GIS and on the revised inventory of spraying (the HERBS file) enabled the performance of urgently needed studies on the effects of Agent Orange.[48]

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[45] L. Wayne Dwernychuk et al., *Dioxin Reservoirs in Southern Viet Nam: A Legacy of Agent Orange*, 47 CHEMOSPHERE 117, 121 (2002).

[46] Recently the possibility that the elevated dioxin could be attributed to storage of herbicide at Special Forces base was raised. *See* L. Wayne Dwernychuk, *Dioxin Hotspots in Vietnam*, CHEMOSPHERE (forthcoming). This is highly unlikely since operational records specifically state that all defoliation was to be carried out by C-123 spray mission because tree height made hand spraying impractical and the loading of spray planes is documented to have taken place at Tan Son Nhut Air Force base and not at the camp itself. The camp was only in operation for a relatively brief period of time because it proved to be ineffective against the Viet Cong insurgency, thus making it likely that documentation of spraying is complete. U.S. DEPARTMENT OF DEFENSE. RECORDS OF THE U.S. FORCES IN SOUTHEAST ASIA, HEADQUARTERS, MILITARY ASSISTANCE COMMAND VIETNAM (MACV), ASSISTANT CHIEF OF STAFF FOR OPERATIONS (J3), CHEMICAL OPERATIONS DIVISION (MACJ-3–09). *Herbicide Operations Plans (1966–1967) series*, Record Group 472 (National Archives and Records Administration, College Park, MD; 1950–75).

[47] COMMITTEE ON THE ASSESSMENT OF WARTIME EXPOSURE TO HERBICIDES IN VIETNAM, INSTITUTE OF MEDICINE, CHARACTERIZING EXPOSURE OF VETERANS TO AGENT ORANGE AND OTHER HERBICIDES USED IN VIETNAM: REPORT AND RECOMMENDATIONS (National Academy of Sciences Press, Washington, D.C., 2003).

[48] Some of the work reported here appeared as a cover article in *Nature*, which was accompanied by the following legend: "[T]his work has provided a geographic information system that will allow epidemiologists to piece together health effects that may exist in the region as they now have a much clearer idea

It is of interest that the work undertaken on behalf of the NAS built upon the exposure methodologies adopted by the Special Master for the Agent Orange Veterans Payment Program as a means for determining whether a deceased or disabled claimant met the court-established criteria for exposure. The court had reasoned that the NAS previously had considered the HERBS file to be a unique and valid source of specific information on the military spraying[49] and that "geographic and temporal limits must be set to determine whether a veteran who was in a location near a sprayed area at or subsequent to the time of spraying will be considered exposed."[50] This reasoning has now been affirmed by the IOM.

The IOM recommendations were strongly endorsed with bipartisan support by both the House and Senate Veterans Affairs Committees, which requested that the VA initiate such studies immediately.[51] The VA responded that the studies were still premature, but that "in-house" validation studies would be carried out.[52] Such an internal study by the VA is, in fact, explicitly disallowed by the Agent Orange Act of 1991, which sought to avoid potential conflicts of interest by mandating that a major epidemiological study be carried out by non-governmental researchers. Further correspondence from the VA to the American Legion[53] at the time of this writing indicates that the VA has taken no further steps to launch an external investigation and plans to continue with its internal studies until at least 2007.

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about the distribution of the agents (and dioxin) and about the 'hot spots.'"

[49] COMMITTEE ON THE EFFECTS OF HERBICIDES IN VIETNAM, NATIONAL RESEARCH COUNCIL, THE EFFECTS OF HERBICIDES IN SOUTH VIETNAM; PART A. SUMMARY AND CONCLUSIONS (National Academy of Sciences Press, Washington, D.C., 1974).

[50] *In re* "Agent Orange" Prod. Liab. Litig., 611 F. Supp. 1396, 1417 (E.D.N.Y. 1985).

[51] Letter from U.S. Congress House and Senate Veterans' Affairs Committees to Honorable Anthony Principi (Nov. 24, 2003) (on file with author).

[52] Letter from Honorable Anthony Principi to U.S. Congress House and Veterans Affairs Committees (Dec. 18, 2003) (on file with author).

[53] Letter from Jonathan B. Perlin, Acting Undersecretary for Health, Dep't of Veterans Affairs, to John Sommer (Nov. 12, 2004) (on file with author).

A Geographic Information System for Characterizing Exposure to Agent Orange and Other Herbicides in Vietnam

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Between 1961 and 1971, U.S. military forces dispersed more than 19 million gallons of phenoxy and other herbicidal agents in the Republic of Vietnam, including more than 12 million gallons of dioxin-contaminated Agent Orange, yet only comparatively limited epidemiologic and environmental research has been carried out on the distribution and health effects of this contamination. As part of a response to a National Academy of Sciences' request for development of exposure methodologies for carrying out epidemiologic research, a conceptual framework for estimating exposure opportunity to herbicides and a geographic information system (GIS) have been developed. The GIS is based on a relational database system that integrates extensive data resources on dispersal of herbicides (e.g., HERBS records of Ranch Hand aircraft flight paths, gallonage, and chemical agent), locations of military units and bases, dynamic movement of combat troops in Vietnam, and locations of civilian population centers. The GIS can provide a variety of proximity counts for exposure to 9,141 herbicide application missions. In addition, the GIS can be used to generate a quantitative exposure opportunity index that accounts for quantity of herbicide sprayed, distance, and environmental decay of a toxic factor such as dioxin, and is flexible enough to permit substitution of other mathematical exposure models by the user. The GIS thus provides a basis for estimation of herbicide exposure for use in large-scale epidemiologic studies. To facilitate widespread use of the GIS, a user-friendly software package was developed to permit researchers to assign exposure opportunity indexes to troops, locations, or individuals. ***Key words:*** **Agent Orange, cacodylic acid, defoliants, 2,4-dichlorophenoxy acetic acid, exposure opportunity, geographic information system, GIS, herbicides, military, picloram, 2,4,5-trichlorophenoxy acetic acid, Vietnam. *Environ Health Perspect* 111:321–328 (2003). doi:10.1289/ehp.5755 available via *http://dx.doi.org/* [Online 1 November 2002]**

Between 1961 and 1971, the United States Armed Forces in South Vietnam used nearly 19.5 million gallons of chemical herbicides for tactical defoliation and crop destruction. Several types and combinations of chemicals were used. The mixtures were nicknamed by the color of the identification stripe that appeared on their chemical storage drums (National Research Council 1974). The three most common mixtures were Agent Orange [esters of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T)], Agent White (triisopropanolamine salts of 2,4-D and picloram), and an arsenical called Agent Blue (cacodylic acid). It has been estimated that Agent Orange was contaminated with < 0.05–100 ppm of dioxin (Darrow 1971). The U.S. Air Force in its Operation Ranch Hand dispersed between 97% and 98% of all the herbicides used. Figure 1 shows a typical Ranch Hand mission composed of three C-123 aircraft (each known as a "sortie") flying in typical tight formation and usually spraying at an altitude of 150 feet. Spraying was only carried out in clear weather, with wind speeds less than 8–10 knots and no temperature inversion present.

An estimated 3.2 million American men and women served in the Armed Forces in Vietnam, many of whom were assigned to areas defoliated by herbicides such as Agent Orange (Stellman et al. 1988a). Neither the extent of exposure nor long-range health effects are fully known after 30 years. The Agent Orange Act of 1991 (P.L. 102-4) directed the Secretary of Veterans Affairs to request that the National Academy of Sciences (NAS) conduct a comprehensive review and evaluation of available scientific and medical information about the health effects of Agent Orange and other herbicides. The Academy convened a committee of experts at the Institute of Medicine (IOM), which since 1994 has issued biennial reports that have associated a number of veteran illnesses with herbicide exposure, based on data drawn primarily from nonveteran observations (IOM 1994, 1996, 1998, 2001). The IOM noted that studies of Vietnam veterans were urgently needed but first required development of exposure reconstruction models that could become the basis of the new epidemiologic studies (IOM 1994). In 1996, a request for proposals for such exposure modeling was issued by NAS in a contract with the Department of Veteran Affairs. The system described herein has been developed by the project awarded the NAS subcontract.

Conceptual Framework for Use of a Geographic Information System in Vietnam Studies

We describe here a geographic information system (GIS) that we developed for this study to address requirements of both epidemiologic and environmental studies for a methodology whereby chronologic listings of the dates, amounts, and chemical details of herbicide spray missions can be transformed into vectors consisting of various measures of exposure opportunity. A GIS is a powerful tool that can be used to facilitate exposure assessment by combining and integrating a variety of data resources, such as those encountered in environmental and epidemiologic studies. Studies of veterans in particular will require that data on military assignments and duties be extracted, analyzed, and transformed into a format compatible with the assessment of herbicide exposure opportunity, and the conceptual framework must further be able to take into account potential confounders and covariates of exposure, such as combat stress and occupational hazards, which have been shown to be associated with physical and mental health outcomes (Stellman et al. 1988b).

Our GIS approach to assessment of herbicide exposure in Vietnam uses a framework of records-based exposure reconstruction methodology that is becoming increasingly common in environmental and epidemiologic

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studies. Recent approaches have included such diverse types of studies as estimation of herbicide application in small area tracts in the U.S. Midwest (Ward et al. 2000), residential exposure to agricultural and commercial chemicals on Cape Cod, Massachusetts (Brody et al. 2002), and "pesticide use density" in studies of childhood cancer in California (Gunier et al. 2001). Additional applications are constantly appearing, many of which may be found by linking through a federal website (GIS and Public Health 2003).

The specific function of our Vietnam GIS is to represent spatial and temporal relationships between instances of herbicide application and the locations of exposed individuals, military units, or other defined populations. The Vietnam GIS incorporates several extensive data resources, which include *a*) distribution of herbicide spray based on a cleaned and updated spray record (HERBS file); *b*) Air Force Ranch Hand project and target maps; *c*) databases of locations of military troops; *d*) databases of Vietnamese population centers such as villages and hamlets; and *e*) data on Vietnam land characteristics such as soil typology, waterways, and ecologic parameters. The GIS incorporates spatial and temporal proximity algorithms that operationalize mathematical models to permit assignment of quantitative exposure opportunity indexes (EOIs) to military units or individuals. This functionality makes it a useful tool for epidemiologic investigations of health outcomes.

Corbis

Figure 1. Photo of three C-123 aircraft sorties dispersing herbicides during a Ranch Hand mission over South Vietnam.

Description of the GIS

The GIS is a relational database whose component tables contain exposure data, population or troop occupancy data, geographic data, and other information relevant to exposure estimation (Stellman et al. 2002). The GIS is built around two interrelated concepts: *a*) geographic partitioning of Vietnam into 0.01° × 0.01° "square" grids, and *b*) association of each grid with counts of "hits" from the individual herbicide missions that occurred inside the grid or near it, as well as with estimates of exposure opportunity that are based on more elaborate exposure models. The grid system covers all of South Vietnam (176,060 grids), the island of Phu Quoc, and sprayed areas of Laos and Cambodia.

Using the grid point as the linkage key, the GIS incorporates geocodable external reference data resources (i.e., those that can be expressed in longitude/latitude coordinates). Examples are listed in Table 1. They include locations of inhabited places in South Vietnam during the Vietnam War that have been cataloged in a gazetteer, and on which we have carried out extensive quality control. The coordinates of many constructed locations, such as roadways and utilities, are contained in commercial data sources, such as ADC WorldMap (American Digital Cartography, Inc., Appleton, WI, USA). This resource also provides coordinates of a variety of land features, including elevations and land contours, rivers and streams, mountains and highlands, coastal areas and mangrove forests, and bays and estuaries. By linking to their coordinates (expressed as grid points), exposure estimates can be restricted to or stratified by topographic features. This may be useful if different exposure models are posited for different land types or soil typology, which affects the ground retention time of herbicides (Stellman et al. 2001).

We have also developed a number of special-purpose tables of locations of military bases, base camps, landing zones, and airfields. A unique table, described below, contains the perimeter coordinates of more than 400 targets that were used for carrying out Operation Ranch Hand.

Herbicide Spray Database

The GIS makes use of a comprehensive file of Ranch Hand herbicide spray applications that was originally created by the Department of Defense and is known as the HERBS file (Data Management Agency 1970). A supplementary database called the Services HERBS file, which includes data on nonaircraft herbicide applications as well as previously unrecorded Ranch Hand missions, was released by the U.S. Army and Joint Services Environmental Support Group [now known as the U.S. Armed Services Center for Research of Unit Records (CRUR)] (U.S. Army & Joint Services Environmental Support Group 1985). The combined HERBS database describes nearly 19.5 million gallons of

Table 1. Examples of types of location data available in the GIS to be linked with EOIs.

Type of activity or data	Original sources	GIS Adaptation
Civilian habitations: towns, villages, hamlets, plantations	Gazetteer of Vietnam, Hamlet Evaluation System[a]	Cleaned and incorporated as GIS tables
Vietnam land and water features	FAO map (paper, 40 × 27 in) of Vietnam soil typologies[b]	Scanned (National Reprographics, New York, NY); vectorized (Digital GeoTechnologies, Washington, CT); then processed via point-in-polygon application to create soil region–grid linkages
	ADC WorldMap[c], other commercial sources: land topography, rivers, streams as of about 1970	Unchanged
Civil structures	ADC WorldMap: roadways, utility lines, rail lines, canals, airfields	Unchanged
Military structures: base camps, landing zones, air fields	NARA documentation (paper)	Data entered, proofed, and consistency checked, incorporated into GIS tables
Troop locations	Troop strength lists, Army Post Office lists (~100,000 paper records), assorted military records	Data entered, proofed, and consistency checked, incorporated into GIS tables
Operation Ranch Hand targets	NARA paper documents and folders	Digitized[d] or manually data entered and incorporated into GIS tables
Herbicide storage, transport, and unplanned dispersal	Services HERBS file	Corrected[e] and integrated into HERBS file and GIS

Abbreviations: FAO, U.N. Food and Agricultural Organization; NARA, U.S. National Archives and Records Administration.
[a]Initial data were uncleaned, in an obsolete computer format and on obsolete computer media. [b]Moormann (1961). [c]American Digital Cartography, Inc., Appleton, WI. [d]R2V Software, Able Software, Inc., Belmont, MA. [e]In collaboration with CRUR, Department of Defense.

herbicides, as broken down in Table 2. We have carried out extensive quality control on all spray data, which we validated by meticulous scrutiny of primary sources available from CRUR, the U.S. National Archives, and other sources.

The HERBS file and all military herbicide operations are organized by mission. The Stellman-NAS version of the HERBS file (S-NAS-HERBS) contains data for 9,141 spray missions for all modes of delivery, carried out by both the Air Force (Ranch Hand) and the Army. A Ranch Hand mission consisted of one or more fixed-wing or helicopter sorties, dispersing a specified amount and type of herbicide along a specified route on a specified day. The Services HERBS file also represents as missions the ground applications carried out by truck or backpack spraying or other non-aerial means.

Most mission records in the S-NAS-HERBS file contain data on the chemical agent used, the military purpose of the mission, its date, the number of aircraft flown, the area sprayed, and the coordinates of the path taken by the aircraft or other applicator. Some missions may have null data for fields pertaining to aircraft parameters. Helicopter, truck, or backpack missions differed from aerial spraying in that much smaller amounts of herbicides were used in different patterns and with smaller potential dispersion than from the C-123 fixed-wing aircraft.

The HERBS file provides the actual flight paths taken by Ranch Hand aircraft as they carried out their spray missions. Alphanumeric indicators show the locations at which the aircraft switched directions or turned off and on their spray nozzles. The data are thus structured in a way that emphasizes the continuity of flight of the fixed-wing aircraft that carried out most of the Operation Ranch Hand missions. (Connectivity may not apply to ground perimeter spraying, which generally went from guard post to guard post around the base camp.) To convey this information, each mission within the HERBS file is organized as a sequence of "vertices" that were the starting, turning, and stopping points of spray aircraft as they carried out a mission. Figure 2 illustrates defoliation along a roadway. The flight path consists of four connected segments in which the plane begins spraying at point 1A and continues spraying until it reaches point 1E. Points 1B, 1C, and 1D are intermediate "turning" points at which the plane changes direction while continuing to spray. The dashed line represents a 1-km envelope about the spray path. Planes frequently flew multiple paths in a single mission; additional vertices would be designated 2A, 2B, 3A, 3B, and so on. Spray nozzles would be turned off between ending one path and beginning another.

Table 2. Quantities of documented herbicides used in Vietnam.

Agent	Gallons
Orange	12,066,840
White	5,430,462
Blue	1,252,541
Pink	13,291
Purple	500,018
"Unspecified"[a]	227,538
Total	19,490,690

[a]About 8% (776) of all recorded missions did not specify a specific herbicide agent. Of these, 474 were perimeter sprays that involved comparatively small volumes and were most likely Agent Orange. The remainder of the missions with "unknown" herbicide also had a high probability of being Agent Orange. These data do not include the small quantities of dinoxol and trinoxol tested in 1961 in Vietnam (Stellman et al. In press).

The spray path legs of C-123 missions averaged 8.1 km [95% confidence interval (CI), 8.0–8.2], and the total spray route was on average 16.8 (95% CI, 16.6–17.0) km in length, dispersing 900–1,000 gallons per sortie. Complete spray flight paths exist for the great majority of Ranch Hand missions. Some early 1965 HERBS fixed-wing missions contain records with a single coordinate, generally representing the starting point or center-of-mass of a mission. We have developed schemata to impute the likely flight paths for many of the fixed-wing missions based on flights flown over the same target. Imputed coordinates are always identified as such in the database so that they may be included or not, at the user's option.

By contrast, perimeter spraying may indeed have consisted of a sequence of unconnected coordinates; these "point sources" reflect the manner in which perimeter spraying was carried out. They represent approximately 534,000 gallons of herbicide, or 2.8% of the 18.6 million gallons dispersed by fixed-wing aircraft for which we have records.

Ranch Hand targets. One important source of military data is the targets that comprised Ranch Hand herbicide projects. As described elsewhere (Stellman et al. In press), we have identified 428 known targets which we digitized from maps or transcribed from coordinates found in the Air Force Operation Ranch Hand project folders that we retrieved at the U.S. National Archives. Each target is represented in the GIS database as a uniquely identified polygon. A point-in-polygon application was developed that identifies every Vietnam grid point that fell within each target. A target "containment" table keys a total of 25,296 grids to the targets that contain them.

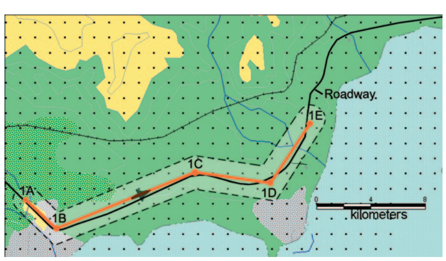

Figure 2. Typical Ranch Hand flight path (orange line) as represented in the HERBS file. Aircraft sprayed Agent Orange defoliant continuously along roadway from 1A to 1B to 1C to 1D to 1E. The dashed line is a 1-km envelope around the spray path. Dots are grid points spaced at 0.01° in longitude and latitude. Each dot represents the origin (southwest corner) of a grid. Hits are referred to the center point of the grid.

The targets represent an independent and previously unrecognized data resource that provides a framework for understanding the spray program. We believe this database contains about 60% of all approved targets, although some targets were approved but never sprayed. All Ranch Hand missions were flown within previously approved targets, and spray paths—represented in the HERBS file as straight lines—generally fall within the target polygons, although spray drift outside the target areas was always possible (missions were generally flown in favorable weather with winds below 8–10 knots). The two databases thus provide mutual corroboration of the geographic coordinates of aerial spray missions.

Herbicide storage, transport, and unplanned dispersal. The Services HERBS file contains a field that describes so-called "incidents," such as an aircraft dumping its load or crashing. A GIS query will yield information as to whether a grid contains or is proximate to such events or to known leaks or other "incidents." Our database also contains information on the locations (airfields or two storage depots) where herbicides were found in bulk.

Soil typology. One specialized feature of the GIS is a soil typology database. The retention times of phenoxy herbicides and dioxin vary with the type of soil, and they disappear over time from different soils at different rates (National Research Council 1974). The GIS herbicide exposure models make use of this fact through their ability to assign different time constants to a first-order exponential decay term in the time factor, depending on the soil type for a particular location. We incorporated a grid-keyed soil table based on our digitization of a soil typology map that was prepared from a 1960 soil survey carried out for the Vietnam Agricultural Ministry by the U.N. Food and Agricultural Organization (Moormann 1961). Researchers wishing to use other than exponential decay will be able to develop their own models within the GIS.

U.S. Troop Location Data

The GIS was developed to facilitate estimation of exposure of U.S. military personnel to herbicides. With the assistance of CRUR, we developed a database of location histories of practically all combat arms support and combat support units assigned to Vietnam.

The majority of the military personnel served in units that moved infrequently or not at all and whose locations are well documented. Daily location data are available for a substantial portion of the remaining combat units, particularly for combat battalions assigned to a heavily sprayed area often referred to as the Iron Triangle in Military Region III, as designated by the U.S. Military Assistance Command–Vietnam. These are units that the CRUR had tracked for the period 1966–1969. We have consolidated these data, cleaned them, and entered them into grid-keyed tables. This Military Unit Database continues to be refined and expanded.

Vietnam Civilian Population Data

A large number of civilian locations, some with specific monthly population figures, are available from various electronic and paper files held in the U.S. National Archives (Carter and Ellis 1976). We have retrieved these data and have carried out extensive quality control. A gazetteer of known populated areas and their specific longitude and latitude is one source. Another is the Hamlet Evaluation System, which is a compendium of data used by program directors in Washington, DC, and Saigon for evaluating the degree of "pacification" of the population in the hamlets and villages of South Vietnam. Monthly surveys were taken to assign a score for perceived level of sympathy with the government of South Vietnam at one end of the scale to complete sympathy with the Vietcong insurgents at the other. The files provide extensive population estimates at the hamlet level of detail.

A similar sequence of data linkage steps can be followed to estimate herbicide EOIs for civilian population centers or particular areas in Vietnam for specific time periods using locations in the gazetteer and Hamlet Evaluation System tables that are contained in the GIS.

Exposure Opportunity Index Table

One function of the GIS is to enable the user to calculate a herbicide exposure opportunity index (EOI) for any entity (e.g., individual, military unit, village) whose location and residence dates are known based on historical reconstruction of spraying activities. An EOI model is a quantitative description of an individual's proximity in time and space to the herbicide application. It is not a toxicologic measure, but may play the part of an external or "presented" dosage within a more elaborate biologic model that might include route of entry, target organs, and metabolic activity. The GIS is model independent but does include an EOI table based on a model we developed (Stellman and Stellman 1986). A relevant property of the EOI we use is that it is quantitative on a ratio scale: An EOI of 1,000 represents twice as much exposure opportunity as an EOI of 500. It is also additive over time: An individual who has an EOI of 1,000 from one source and 500 from another source has a total EOI of 1,500. These properties greatly facilitate database manipulation. A variety of EOI models can be constructed, and sophisticated GIS users could substitute or add different modeling algorithms to this GIS, which is flexible and can accommodate models of arbitrary complexity.

The GIS produces as its output an "exposure opportunity vector" in an easy-to-read format. This is simply an array that contains the calculated EOI as well as the number of "hits" that occurred within 0.5, 1, 2, and 5 km of the center of the GIS grid. EOI data are stored in the "exposure opportunity" table within the GIS. The table contains three essential elements: *a*) the grid-point key, consisting of an integer that uniquely defines the grid; *b*) a mission identifier, consisting of an integer that uniquely defines the mission; and *c*) an exposure vector composed of the EOI and the hit counts, which are described more fully below.

The mission number links to the HERBS file that permits exposure estimates to be confined to a particular herbicide, a range of application dates, and type of application (e.g., fixed-wing aircraft). It thus permits aggregation of EOIs by different types of herbicidal agent, and over different time periods.

The size of the database obviously depends on how many missions contribute to the EOI of each grid. As a practical matter, the database is restricted to exposure arising from missions for which the grid fell within 5 km of any herbicide application; there are approximately 1.45 million such records, with 196,735 at 1 km and 92,635 at 0.5 km.

Both the "hits" and EOIs are always referred to the center point of the 0.01° × 0.01° grid, whether for individuals, military units, hamlets, villages, or any other entity. Grid areas range from 1.18 to 1.22 km^2, depending on latitude, so the center point can be at most about 800 m from the corner of a grid. Where relevant, areas are adjusted to take into account latitude-related variation, and the adjustment factor is a keyed table in the GIS.

Hits Score

A "hit" is defined as an instance of a herbicide spray application falling within a prescribed distance of a receptor point (RP), the location for which exposure opportunity is to be estimated. By definition, a hit has an associated radius, so we speak of hits within 0.5 km, 1 km, 2 km, and so forth, of an RP, which for the GIS is always the center point of a grid. The 0.5-km hits have been expanded to include 3,005 grids for which the point of closest approach of a spray mission fell within the periphery of the grid beyond a 0.5-km radius of the grid's center. These peripheral grids, together with grids whose centers were within 0.5 km of the mission, are counted as "direct hits" to the given grids.

The direct hits model takes into account the continuous flight path of each aerial spray mission. For the flight path shown in Figure 2, for example, any RP falling within the dotted contour (including the semicircles at the two ends) is credited with one hit within 1 km. Contours such as those in Figure 2 are constructed about each flight path for distances of 0.5, 1, 2, and 5 km. This approach is nearly identical to that used by NAS in its first appraisal of the ecologic effects of herbicides used in Vietnam (National Research Council 1974). These four proximity count variables are contained in the keyed exposure opportunity GIS table.

The 5-km limit is an arbitrary figure that merely ensures that computation time is not wasted on distant, irrelevant sprays. The hit scores describe exposure in a fundamental way that is based on trigonometry and not dependent on any model.

The HERBS file includes a small number of "incidents" such as leaks, crashes, and dumps. In computing exposure opportunity, these missions are treated identically to normal missions. The user can cross-reference the GIS "incidents" table and decide how best to interpret scores arising from incidents.

Continuous Exposure Models: Direct and Indirect Exposure

In addition to models that count only discrete hits when they actually occur, we have developed a continuous EOI model that takes both current and past spraying into account and incorporates data about herbicide quantity, distance, and time (Stellman and Stellman 1986; Stellman et al. 1988a). This method was used in our previous studies of health of American Legionnaires (Stellman et al. 1988b) and in a study of dioxin levels in adipose tissue of Vietnamese (Verger et al. 1994). Both discrete and continuous EOI models use all available information on the flight-path structure of the HERBS file.

Time is an essential characteristic of the continuous EOI model. We distinguish between "direct" and "indirect" exposure as illustrated in Figure 3. Any person or entity that is present on the day of spray would be considered to have "direct exposure." Those entering a sprayed location after that time, or those remaining in the location after having been directly exposed, would also be considered to receive "indirect exposure," that is, exposure to any residual herbicide or dioxin that is present.

Exposure opportunity model E4. For every grid point that received at least one direct hit within 5 km, we calculate a function, E4, of both direct and indirect exposure. The EOIs in the GIS use the E4 model. E4 is a refinement of our previously published model, E3 (Stellman and Stellman 1986). The E4 model is the product of three factors: quantity of herbicide sprayed, an individual's distance from spray paths, and residence time at an exposed location:

$$E4 = \text{quantity factor} \times \text{distance factor} \times \text{time factor}$$

The quantity factor is the number of gallons of herbicide sprayed, which is known for the great majority of spray missions. Each "leg" of a spray run (Figure 2 shows a mission with four legs) is treated as an independent source of herbicide exposure and is assigned a gallonage in proportion to its length. E4 for a given mission is the sum of the component E4 values for all its legs. For direct hits, a term is added to reflect the greater likelihood of toxic absorption through all routes of entry and is proportional to the actual amount of toxic substance delivered in a given mission. The distance factor assumes that exposure is inversely proportional to the distance from the spray. It thus gives higher weight to closer sprays. The time factor uses a first-order exponential decay function to take into account the fact that the herbicide (and any toxic constituents) decays continuously from the time of application.

Cohort residence time and herbicide environmental half-life. "Residence time" is the period during which an individual, military unit, and so forth, occupied a given location in Vietnam during the war period. Any query for which exposure is sought requires an "in-date" and an "out-date" that define the residence time. For direct hit models, this pair of dates is used simply to restrict the missions to those sprays that occurred during the interval of residence at that location. The EOI that is stored in the GIS exposure table for every grid point is computed from the date of spray through 31 December 1971. Because the time factor is independent of quantity and distance, the EOI can be reweighted to reflect any specific pair of in/out dates for which an EOI is to be estimated. A different half-life also can be introduced in the adjustment. Thus, a researcher could continue the decay extrapolation if it is desirable to incorporate dates beyond the end of the herbicide program. Ecologic studies might leave the in/out dates intact but vary the half-lives to reflect different ecologic conditions.

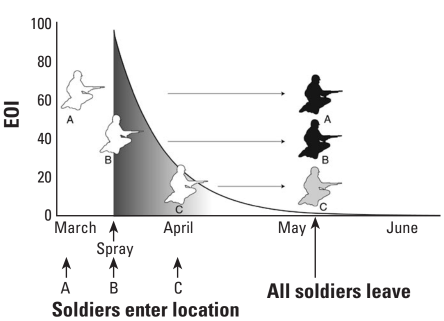

Figure 3. Direct and indirect modes of exposure to herbicide spray. The area under the curve represents the value of the EOI at a given location. Soldiers A and B are present during a direct hit. Soldier C enters the location at a later time and experiences only an indirect exposure opportunity to residual herbicide.

Coordinate Precision and Robustness of GIS

It is important that exposure rankings of individual grids be insensitive to shifts in the location within the grid at which exposure is calculated, because the relative exposure rankings of the grids will ultimately become the basis for assigning exposures to military units, troops, or populations in epidemiologic analyses. Grid rankings depend in turn on the fact that exposure opportunity at any point in Vietnam is computed at the center of the grid that contains it. Every location within the grid is thereby assigned the same exposure score, including its corners, which may be about 800 m from the center.

To test the robustness of the GIS, EOIs were computed at the centers of every grid that fell within 1 km of a spray mission for June 1969, one of the most heavily sprayed months, to provide a wide range of exposures. EOIs were then computed at the same points shifted 0.005° east (half a grid or about 500 m). The data from these two runs were matched on grid point and mission. There were 158,565 grid–mission combinations. The rank-order correlation between the unshifted and shifted exposure scores, computed as Spearman's rho, was 0.972 ($p < 0.001$), indicating that very little change in ranking of exposures is introduced by shifting the locus of exposure calculation from the middle to the edge of a grid.

As an additional test of robustness, the original scores and the scores after shifting were computed for June 1969, for every grid in Vietnam, and summed over missions to yield a total score for each grid. Both sets of scores were sorted into 10 ordered groups, and their category ranks were compared to determine the numbers of grid points whose ranks changed. Of 176,060 grid points spaced at 0.01°, which cover the entire land area of South Vietnam, there were 18,308 grid points with nonzero scores, of which only 2,842 (1.6% of all grid points) experienced a change in exposure rank. In other words, 98.4% of the land area retained its original exposure ranking. Furthermore, the great majority of those 2,842 grids that changed (2,574, or 90.6%) shifted by only a single rank, with 1,424 (50%) shifting to a higher exposure and 1,418 (50%) to a lower exposure. That is, the few category shifts were not to systematically higher or lower levels. Were exposure ranks to be collapsed into fewer categories, most of these grid shifts would result in no change in the assigned category.

Illustrations of the GIS in Action

Hits close to spray paths. To illustrate how the GIS can be used, consider two Ranch Hand missions that were carried out along the coastal waterways south of Saigon on 1 January 1966. A total of 345 of South Vietnam's 176,060 grid points fell within 5 km of these runs, 106 of which were within 2 km, 49 within 1 km, and 23 within 0.5 km. Figure 4 shows the flight paths for these two missions. A simple query in the GIS will determine which grid points were within 0.5, 1, 2, or 5 km of the missions. Conversely, given a grid point, one can identify which mission flight paths were within 0.5, 1, 2, or 5 km. In the illustration, the 5-km "hits" are represented by the small black dots, and the large red, green, and blue dots represent grids within 0.5, 1, and 2 km respectively of the flight path.

Characterization of exposure to Vietnam. The grid structure allows us to characterize exposure variation of broad land areas. Figure 5 shows a choropleth plot of the entire country during June 1969, which we have chosen as our reference month because of its intense herbicide spray history. The map was constructed by computing the E4 score at every grid point in the country. Each E4 value so computed represents the exposure that would have been experienced by an individual who resided continuously at that point from 1 June through 30 June or, equivalently, the June exposure for any portion of a village or hamlet with those coordinates. The E4 score takes into account both direct and indirect exposures. Color is used to code relative levels of herbicide exposure and is keyed to 10 ranks increasing in intensity from dark blue (lowest) to red (highest); the full color scale is shown in Figure 5. The E4 score uses information from all previous sprayings that occurred at each location, based on a first-order decay curve with a half-life of 30 days. Thus, the most intense red "hot spots" generally represent sprays that occurred during the month, and the dark blue regions of low intensity generally reflect exposures to the residue of sprays that occurred in previous months. It is important to note that the relative EOIs rise dramatically with their rank, so that areas shown as red on the map were much greater sources of exposure opportunity during June 1969 than were blue areas.

Calculation of EOIs for noncombat troops. Using the GIS, we estimated the number of "hits" and E4 scores for army units whose missions did not require frequent movement from one location to another. We call these units "stable" and have constructed a database of known locations for these noncombat units over the course of the conflict. We linked the data on the location of the stable units in June 1969 to the spray data for that month and to a separate data source, the troop strength table, which provides the number of troops present for the great majority of military units in all services present. We have used the troop strength entries that span the months May through September 1969 (no data are available for June alone, but the troop strengths remain fairly stable).

We identified 1,957 different "stable" Army units present in Vietnam during June 1969 and 2,095 different grid points that were occupied by these support units (i.e., 138 units shifted from one stable location to another during the month). Of the 2,095 "occupied" points, 937 were not sprayed that month and also had zero residual spray from prior months. We were able to match 815 of the 1,045 units that occupied locations with nonzero scores and could thus estimate the number of people assigned to these units exposed, either directly or indirectly, during June 1969. Figure 6 shows the distribution of the logarithm of E4 in for the 142,583 troops with nonzero E4 scores who were stationed at 815 Army posts during that month. The distribution is approximately log-normal and spans several orders of magnitude, two properties that support the utility of this measure in epidemiologic studies of Army veterans who belonged to stable units.

Automation of the GIS. The GIS used here was developed by us and uses Microsoft Access to store data tables and to implement queries. It contains a master table of hits and E4 scores that have been precalculated for each grid–mission combination. These are the EOIs used by the GIS. Stored E4 scores are based on residence at each location throughout the entire era of spraying (1 January 1961 through 31 December 1971) and use a 30-day half-life. Many queries that would typically be required for an epidemiologic study involve a complex succession of steps that include data subsetting and mathematical transformations of date parameters to different residence intervals and/or half-lives.

To facilitate use of the GIS by researchers, we have designed and are in an advanced development stage of a unique user-friendly software system that implements the GIS and that might serve as a useful model for other epidemiologic software for GIS-based analyses. A function of this system is to permit transformation of date and location inputs into EOI outputs with a minimum of user intervention, and with the facility to impose a variety of selection options such as restriction to specific types of herbicides, ranges of dates, or types of missions. The user inputs dates and locations of residence and receives the EOIs as an output table. The default half-life of 30 days can be changed to any desired value. For spot checking, the GIS can also display the input locations on a thumbnail map of Vietnam, but users will usually wish to import the locations and exposure scores into their own mapping software.

In an epidemiologic study of military troops, the exposure assessment process typically includes the following steps: *a*) input individual veterans' military unit histories as a series of records, each containing the unit identification code, location, and residence time interval for one unit; *b*) specify a set of selection criteria (e.g., specific herbicide types, mission types); *c*) obtain EOIs from the EOI table for each location, using selection criteria as query restrictions; and *d*) adjust EOIs at each location for residence dates and aggregate for each military unit.

The software system is designed to receive military unit histories as its input and carry out the foregoing sequence of operations with a minimum of involvement by the user, producing a set of EOIs and hits at 0.5, 1, 2, and 5 km that can then be used to calculate risks of health outcomes in epidemiologic studies. The system enables estimation of herbicide exposure for both military troops and Vietnamese civilian populations. The software system is represented in Figure 7.

Discussion

We have described a GIS that is suitable for estimation of exposure opportunity of military troops and civilian populations and has been developed in a user-friendly format for use in large-scale epidemiologic studies. It makes use of extensive data on herbicide application, with a level of detail and precision not often available for historical exposure reconstruction.

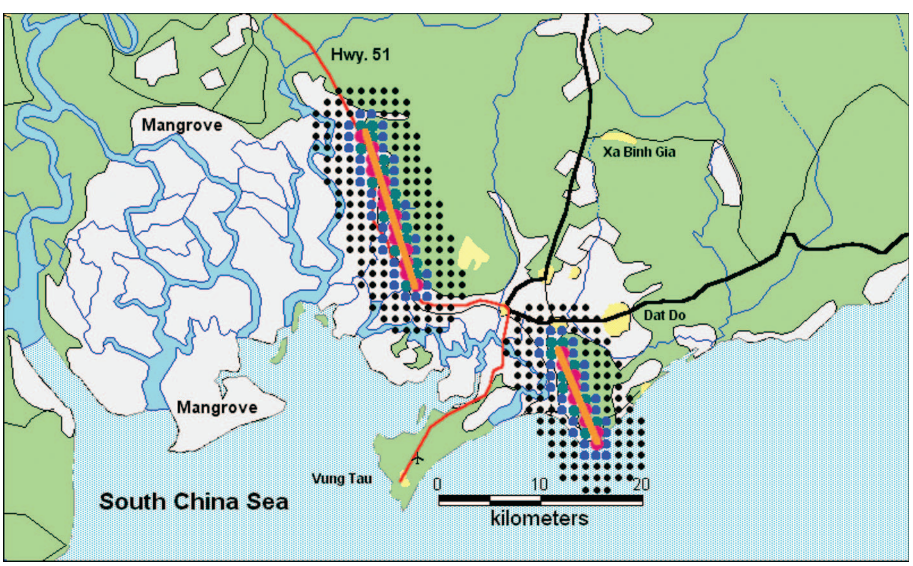

Figure 4. Two Agent Orange herbicide missions (shown as orange lines) flown 1 January 1966 in the Rung Sat Special Zone. The figure shows all grid points whose centers fell within 5 km (small black dots) of the flight paths. Blue, green, and red dots are centers of grids that fell within 2, 1, and 0.5 km, respectively.

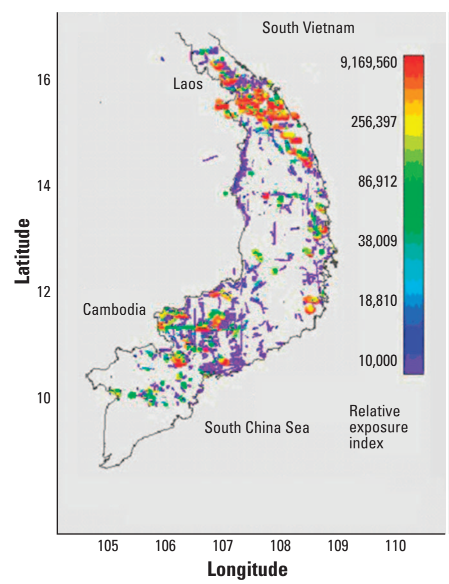

Figure 5. Choropleth plot of Vietnam for June 1969 showing intensity of exposure using the E4 model. A similar map showing the location of "hits" can readily be created.

The utility of the GIS is not limited to epidemiologic studies, however. Researchers who wish to study past or current ecologic conditions in Vietnam (ascertained, say, via satellite imaging) or to compare levels of contamination from biologic or soil sampling could use the GIS to estimate the original exposure levels at the time of spraying.

The utility of the GIS as an exposure reconstruction instrument depends, of course, on how accurately the E4 and hit scores can act as proxies for true toxicologic exposure. Proximity to an environmental insult is a widely used concept and various schema such as job-exposure matrices rely on this conceptual premise (Blair et al. 2001). In the case of exposure to herbicides in Vietnam, which began 40 years ago and ended 30 years ago, no other reliable measure is available for large-scale epidemiologic studies.

It is clear from our analyses of HERBS data and Ranch Hand Project maps that Vietnam was not uniformly sprayed but rather shows substantial geographic and temporal variation in herbicide application. When juxtaposed with locations of residential areas and military troops, the spray patterns are sufficient to justify epidemiologic studies on military and civilian populations as well studies of environmental and ecologic damage.

Both types of applications are facilitated by the keyed grid-point structure of the GIS. Each grid can be linked to the spray missions that overflew it, the type and quantity of herbicide deposited, the distance from the spray run, containment within one or more Ranch Hand targets, and land features such as topography or soil type. Grid-keyed tables of population centers (hamlets and villages), troop locations, and military installations are also included.

One advantage to a grid-based approach that models exposure separately from troop location is that it separates the errors, because each factor is modeled independently. This approach is reasonable because the factors that affect the accuracy and precision of spray mission data may not be the same as the factors that affect the accuracy and precision of troop location data. For example, environmental decay parameters, spray dispersion patterns, and inaccurate gallonage data affect the quality of the spray data but are not relevant to troop location data.

Another advantage is that more elaborate and potentially more accurate models can be built by using empirical knowledge of the variation of EOI over a localized area. For example, if we consider the spray history of all fire support bases within the command of a particular Army division and examine the spray patterns for those units in which record keeping was known to be done well, we can then model the grid locations of other fire support bases using the data set from the "good" record set.

A third advantage is a pragmatic one in that the effect of various military unit movement models can be very readily tested, because the EOI calculations are reduced to straightforward products and sums. To obtain the exposure for a military unit, we place it each day in the grid it occupied and then aggregate the exposure over time. Accurate locations and residence dates, however, may not be available for many combat troops. Rather, locations of headquarters companies or other battalion-based data may be all that are available from unit histories or data files. The GIS is being adapted to accommodate "fuzzy" location and date information. Suppose the location is not precisely known for one day, but it is likely that the unit was not more than one grid away. Then we might assign the average E4 score for all surrounding grids. More generally, if there are different probabilities of being in different elements, we can assign the expected value over those elements. On a given day, adjacent elements are likely to have very similar exposure levels, so many different probability distributions will yield similar values.

The E4 score, which assumes a reciprocal distance and a first-order decay, is included in the GIS as a convenience to investigators. However, the GIS itself is not dependent on any particular model. Many further EOI refinements are being considered, such as introduction of second- or higher-order decay, use of multiple time constants for areas that were sprayed on more than one occasion, and considerations of weather as reported in U.S. Air Force Daily Air Activity Reports, which are available for about 60% of Ranch Hand missions or from historic weather databases. One refinement uses data in the HERBS file on the number of fixed-wing aircraft that flew a given mission. It was routine Ranch Hand procedure for multiple aircraft to disperse their spray over laterally contiguous swaths (a swath is a finite width of spray dispersion), as shown in Figure 1. Our model assumes that the flanking aircraft took flight paths that were parallel to the central aircraft and flew at the same altitude with a horizontal separation of 80 m. Other wind drift models may be available.

The GIS brings together a variety of diverse databases on herbicide spraying, geography, and population and troop location that can enable pursuit of epidemiologic and environmental studies. It is built on the power of a relational database system and provides the ability to do otherwise complex exposure model calculations with rapid, straightforward arithmetic procedures. Lack of coherent data and lack of an exposure reconstruction model no longer need be the major impediments they have been in

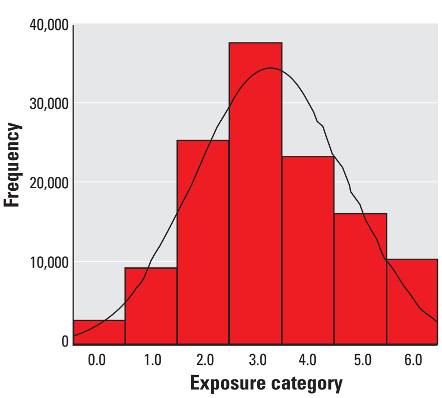

Figure 6. Frequency distribution of the logarithm of the E4 model score for 142,583 troops in 815 units designated as "stable" or "stable with mobile elements," June 1969.

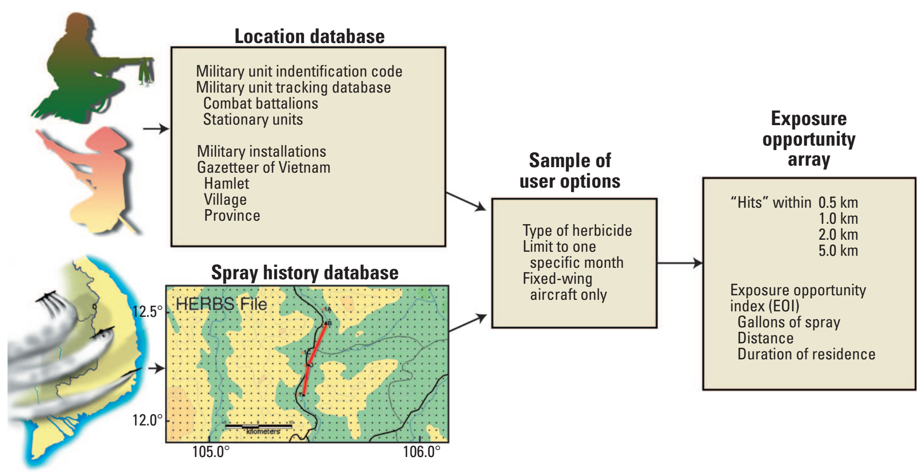

Figure 7. Schematic illustration of the GIS. Databases are linked via the "grid point," which indexes a grid covering the land area of South Vietnam at 0.01° intervals. Individual queries may be restricted to specific types of herbicides, dates, or other variables. Output consists of an array of proximity counts plus the EOIs.

the past to research on health of Vietnam veterans and the residents of Vietnam itself.

Considerable attention has been given to the design of the GIS input and output formats that permit a user to input a table of dates and locations and receive as output a table of exposure variables. With little or no additional processing, outputs that are created in this format can serve as input to most popular statistical software and cartographic packages. With the exception of the E4 model score, data in the supplied tables are not model dependent, making the system highly transferable to other applications. Even broader applications are accessible to researchers who can use SQL or a similar query language to manipulate the geographic exposure information, and the methodology itself may be adapted to other situations in which it is desirable to combine records-based exposure opportunity data with locations of potentially exposed individuals or groups.

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HOW MUCH DIOXIN IN DEFOLIANTS SPRAYED DURING THE VIETNAM WAR?

April 17, 2003

"How much dioxin in defoliants sprayed during the Vietnam War?" is probably a tough question without reasonable answers. Up to date, estimates from studies conducted by the U.S. National Academy of Sciences (NAS) (1974) and the U.S. Air Forces (1978), which have been widely accepted, indicate that the total amount of the defoliants sprayed during the Vietnam War was approximately 19.4 million gallons (73.3 million liters) containing between 170 kg and 180 kilograms of dioxin.

These above estimates, however, are revised upwards by another study conducted by Columbia University in New York for the U.S. Institute of Medicine. Although the study report has not been released, results from the study already appear on the journal *Nature*, Volume 422 dated April 17, 2003 in an article entitled "The extent and patterns of usage of Agent Orange and other herbicides in Vietnam" by Jeanne Mager Stellman, the primary researcher, and other authors. According to this article, the revised estimates have "*...7,131,907 more litres than the 'uncorrected' NAS-1974 inventory and 9,440,028 l more than NAS-1974's 'corrected' inventory...*" As a result, the total amount of defoliants sprayed during the Vietnam War was estimated by the Stellman study to vary from 80.4 to 82.7 million liters. The Stellman study also indicates that "*... the estimate for TCDD* [dioxin] *present in the spray grows to 221 kg from NAS-1974 estimates of 106-163 kg. Applying 32.8 p.p.m. and 65.5 p.p.m. as the average TCDD in Agents Purple and Pink, we obtain an additional 165 kg, or 366 kg in total...*"

The Stellman study was cited by national broadcasting programs such as ABC's World News Tonight on April 16, 2003 and dubbed by Declan Butler as "*... the most detailed and sophisticated computerized maps ever produced of herbicide spraying in Vietnam*" in a story entitled "Vietnam dioxin spray estimate quadruples" dated April 17, 2003 on *Nature Science Update* at www.nature.com\nsu. The story indicates "*A fresh study of long-forgotten flight records of US military aircraft that sprayed Agent Orange over Vietnam has shed unexpected light on one of the darkest episodes of that conflict... For the first time, the authors say, it is possible to calculate an exposure index for individuals and populations that is accurate enough for the epidemiological research that is needed for firm links with health data... The data include flight-path information, the amount and type of agents delivered (including releases caused by leaks, crashes and dumps), troop locations and movements, land features and soil type, and the location of Vietnamese populations... It is possible to tell from the maps, for example, whether individual soldiers or populations were likely to be present in a particular zone on the day of spraying and exposed directly, or whether they arrived later and were exposed indirectly... Using census data for 20,000 Vietnam hamlets for the first time, the study shows that at least 3,000 of them were sprayed directly, affecting between 2 million and 4 million people. The researchers also plan to publish maps of spraying in relation to US troop positions...*"

Those long-forgotten flight records have also shed unexpected light on the “controversial” results of the Stellman study. In fact, if the total sorties, i.e. aircrafts, run between 1961 and 1971 were 19,905 as identified by the Stellman study, the total amount of defoliants sprayed during the Vietnam War can be reasonably estimated at 19,905,000 gallons or 75.2 million liters. That is because the volume of the tank on the plane was 1,000 gallons. This estimate is consistent with 19.4 million gallons or 73.3 million liters estimated by the previous studies. The total amount of defoliants sprayed during the Vietnam War was calculated at 73.7 million liters if the sprayed area of 2,631,297 hectares (estimated by the Stellman study) and the typical rate of 28 liters/hectare were used. The estimate based on parameters from the Stellman study (73.7 million liters) is even closer to the estimate from the previous studies (73.3 million liters).

We know that each sortie covered a land strip of approximately 253 acres or 101 hectares (240 feet wide and 8.7 miles long). As a result, the sprayed area can be reasonably estimated at 5,035,965 acres or 2,010,405 hectares. The previous estimate of 2.3 million hectares appears to be appropriate because it included areas not sprayed by the Ranch Hand.

We also know that the defoliants were not used directly. They were mixed with water, jet fuel, or diesel fuel at a ratio varying from 1:10 to 1:50. Therefore, the quantity of dioxin contained in the defoliants sprayed during the Vietnam War should be re-estimated downwards instead of upwards. Because the TCDD concentration in the defoliants was used for estimation, the estimated quantity of dioxin should be at least 10 times less than 366 kg estimated by the Stellman study, i.e. 36.6 kg.

Because of a lack of data and information, we cannot comment on other issues discussed in the Stellman study at this time. These issues include the dioxin concentration in Agents Purple and Pink (32.8 ppm and 65.5 ppm, respectively), the estimated population (2.1 million to 4.8 million people) that “... were likely to have been sprayed upon directly,” and the land features and soil type used in the study. It appears that the dioxin concentration of Agent Purple is merely the average concentration of 5 (five) samples discussed in the article (17, 22, 33, 47, and 45 ppm). We are making efforts to obtain a copy of the full report of the Stellman study, and we will have additional comments in the near future when such copy is provided.

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NEWS

Mailman School's Dr. Jeanne Stellman Participates in Agent Orange Policy Briefing July 8

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STUDY BY MAILMAN SCHOOL RESEARCHERS INDICATES HERBICIDE SPRAYING IN VIETNAM WAS UNDERESTIMATED

NEW YORK, April 16, 2003 -- The amounts of dioxin-containing herbicide sprays, used during the Vietnam War may have been greatly underestimated, according to the latest research by Columbia University's Mailman School of Public Health. In this week's *Nature* Magazine, Jeanne Mager Stellman, professor of clinical health policy and management, and Steven D. Stellman, professor of clinical epidemiology, co-lead investigators at the Mailman School, and their colleagues confirm that continuing research shows previous approximations underestimated the quantity sprayed by 7 million liters, much of which was heavily dioxin-contaminated. The total amount of dioxin, a known carcinogen contained in some of the herbicides, is at least double prior estimates. Exposures to herbicide sprays such as Agent Orange have been associated with health problems in Vietnam veterans and their children.

“In addition, records show millions of Vietnamese and large numbers of veterans were likely to have been sprayed upon directly,” says Dr. Jeanne Stellman.

The *Nature* article follows a report last month by the Mailman School investigators that they had developed a geographic information system (GIS) under a contract with the National Academy of Sciences to estimate exposures to herbicide sprays by analyzing the relationships between herbicide spraying, geography, population, and troop location. According to Dr. Jeanne Stellman, “Up to now, the lack of such a measure was a major impediment to identifying the consequences of spraying and hampered researchers' ability to identify health risks that veterans may face." With their new methodology, ecological and epidemiological studies of the herbicide spraying can now be undertaken. Says Dr. Steven Stellman, "Our research pinpoints areas likely to be hotspots, so that now additional studies on the health effects of these exposures, which are very much needed, can be done."

Herbicides like Agent Orange were used by United States and Republic of Vietnam forces to defoliate forests and mangroves, to clear the perimeters of military installations and to destroy 'unfriendly' crops - a tactic for decreasing enemy food supplies. Spray missions were directed over carefully defined targets, many of which were sprayed repeatedly.

According to Dr. Jeanne Stellman, "In the case of exposure to herbicides in Vietnam -- which began 40 years ago and ended 30 years ago -- no other reliable measure is available for large scale studies. The people in Vietnam and Vietnam veterans have waited too long for scientific studies to be undertaken. We hope that our user-friendly software will help to spur additional research."

The complete findings of the study are reported in the April 17 *Nature* Magazine article, "The Extent and Patterns of Usage of Agent Orange and Other Herbicides in Vietnam." The GIS software is described in the March issue of *Environmental Health Perspectives*.