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Characterization of Exposure to Agent Orange in Vietnam Veterans as a Basis for Epidemiological Studies

Jeanne Mager Stellman

Steven D. Stellman

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

Jeanne Mager Stellman, Ph.D. & Steven D. Stellman, Ph.D., M.P.H.[*]

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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[*] Jeanne Mager Stellman, Ph.D., and Steven D. Stellman, Ph.D., MPH, are professors of clinical health policy and management and clinical epidemiology, respectively, at the Mailman School of Public Health at Columbia University. The research described was supported by the National Academy of Sciences Subcontract NAS-VA-5124-98-001 and USPHS Grants CA-68384, CA-17613 from the National Cancer Institute. The authors thank Col. Richard Christian (ret.) for his collaboration on all aspects of the research and Donald Hakenson, Director, U.S. Armed Services Center for Research of Unit Records, and his staff for extensive technical support and access to military records. Carrie Tomasallo, Tracy Weber, and Francine Benjamin contributed significantly to the development of the geographic information system.

[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]

[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

[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.

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[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

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[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).