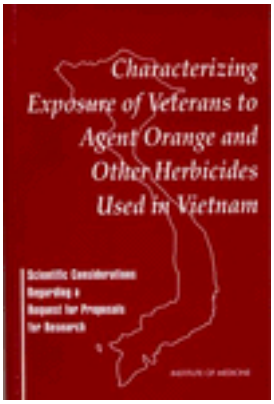

Characterizing Exposure of Veterans to Agent Orange and Other Herbicides Used in Vietnam: Scientific Considerations Regarding a Request for Proposals for Research

Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam, Institute of Medicine

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Division of Health Promotion and Disease Prevention
INSTITUTE OF MEDICINE

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.
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COMMITTEE ON THE ASSESSMENT OF WARTIME EXPOSURE TO HERBICIDES IN VIETNAM

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S. KATHARINE HAMMOND, Associate Professor of Environmental Health Sciences and Director, Industrial Hygiene Program, School of Public Health, University of California at Berkeley

LOREN D. KOLLER, Professor, College of Veterinary Medicine, Oregon State University

DANA P. LOOMIS, Associate Professor, Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill

STEPHEN M. RAPPAPORT, Professor of Occupational Health, Department of Environmental Sciences and Engineering, School of Public Health, University of North Carolina at Chapel Hill

THOMAS J. SMITH, Professor of Industrial Hygiene and Director, Industrial Hygiene Program, Department of Environmental Health, Harvard School of Public Health

DAVID J. TOLLERUD, Professor, Public Health and Medicine, and Chair, Center for Environmental and Occupational Health, School of Public Health, Allegheny University of the Health Sciences

LAUREN ZEISE, Chief, Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health and Hazard Assessment, California Environmental Protection Agency, Berkeley

Staff

DAVID A. BUTLER, Study Director

SANJAY S. BALIGA, Research Associate (as of November 1996)

DEBORAH KATZ, Research Associate (through August 1996)

JAMES A. BOWERS, Project Assistant (as of November 1996)

AMY NOEL O'HARA, Project Assistant (through August 1996)

DONNA D. THOMPSON, Division Assistant

SHARON L. GALLOWAY, Financial Associate

KATHLEEN R. STRATTON, Director, Division of Health Promotion and Disease Prevention (as of January 1997)

MICHAEL STOTO, Director, Division of Health Promotion and Disease Prevention (through December 1996)

* Member, Institute of Medicine.

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Charaterizing Exposure of Veterans to Agent Orange and Other Herbicides Used in Veitnam: Scientific Considerations Regarding a Request for Proposals for Research

INTRODUCTION

The purpose of this report is to delineate the scientific considerations regarding a request for proposals (RFP) for research characterizing exposure of veterans to Agent Orange and other herbicides used in Vietnam. The National Academy of Sciences' (NAS) Institute of Medicine (IOM), under the scientific supervision of the Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam (hereafter, "the committee"), has been requested by the U.S. Department of Veterans Affairs (DVA) to develop an RFP seeking individuals and organizations capable of conducting research to develop one or more historic exposure reconstruction approaches suitable for epidemiologic studies of herbicide exposure among U.S. veterans during the Vietnam War. These approaches would incorporate information from existing databases and other information (e.g., biomarkers of exposure) as detailed below, as well as supplemental information gathered from surveys of military personal, governmental and nongovernmental organizations, and other sources.

The Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam was formed in 1996 under a contract with the DVA. In addition to producing this report, the committee will also lead the evaluation of submissions made in response to a formal, complete RFP—a document that will comprise the scientific input; funding amounts and research time frames; and contractual requirements including proposal format, page limitations, and other submission requirements. These other issues will be resolved when the details of the research funding have been finalized. It is expected that the subcontract or subcontracts envisioned by the RFP will be supported by funds provided by the DVA and administered by the IOM under the scientific supervision of the committee.

IOM is a part of the NAS, a nonprofit, no-fee institution created by congressional charter in 1863 to be an advisor to the federal government on scientific and technological matters. The NAS performs this role primarily

through the use of a committee structure, calling upon a wide cross-section of the nation's leading scientists, physicians, engineers, and other professionals who serve as unpaid volunteers on these committees.

BACKGROUND

In its 1994 report, *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, the IOM Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides encountered a severe lack of information about the exposures of individual Vietnam veterans to herbicides and found that this lack of information had hampered previous attempts to study the effects of exposure to herbicides on the health of Vietnam veterans. The committee responsible for the 1994 report felt, however, that it might be possible to develop better methods of determining exposures among individual veterans by drawing on historic reconstructions. These methods may take into account such factors as troop movements, ground and perimeter spraying, herbicide shipments to various military bases, the type of terrain and foliage typical of the locations sprayed, the military missions of the troops located there, and biochemical techniques that can detect low levels of dioxin (a contaminant in some of the herbicides used in Vietnam) in the blood. If better models of exposure could be developed and validated, a number of important epidemiologic studies of exposure to herbicides and health outcomes might become possible.

The committee that wrote the 1994 report recognized that their recommendation for development of historic exposure reconstruction models might appear at variance with those of other research groups which expressed skepticism that such models could be produced (IOM, 1994:19–20). That committee offered four reasons for making the recommendation. First, it noted that the groups expressing concerns based their opinions in large part on the use of serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) measurements for validating exposure to herbicides used in Vietnam. The 1994 report committee felt that serum TCDD levels were insufficient for validating exposure, although they thought that such data might provide information useful to a larger validation effort (p. 289). Second, it observed that arguments against historic exposure reconstruction implied that exposure measurements might be imprecise, not that they were invalid. Third, the 1994 report committee noted that the use of more, but less formal, data on exposure than was considered by the previous groups—for example, data on perimeter spraying—might yield informative models. Finally, the committee noted that while it did not know whether the approach it proposed would prove valid or yield information useful for future epidemiologic studies, the likelihood that this approach would be successful was sufficient for it to be recommended.

RFP STATEMENT OF WORK

The intent of the RFP is twofold, to:

1. Develop and document a detailed methodology for retrospectively characterizing the exposure of Vietnam veterans to the major herbicides used by the military in Vietnam: 2,4-D; 2,4,5-T; cacodylic acid; picloram; and the trace contaminants TCDD and its congeners. The proposal should address how exposure to this array of chemicals will be evaluated. However, the ability to separately identify or quantify exposures to each of these substances is not necessarily a requirement for a successful proposal. The exposure methodology proposed must be applicable to specific types of epidemiologic investigations that could be conducted at a future date under a separate contract or subcontract.
2. Demonstrate the feasibility and appropriateness of the proposed methodology in sufficient detail to permit the assessment of its potential for use in the conduct of epidemiologic studies.

The final product of the research funded under the RFP should include a written, detailed description of the exposure assessment method proposed, the level of exposure discrimination that can be produced, and the results of the validation studies for that method.

The RFP is not intended as a solicitation for an epidemiologic study of health effects or other outcomes potentially associated with herbicide exposure. Such studies may be solicited in the future, but the current request for proposals is restricted to development and testing of an exposure assessment approach for Vietnam veterans that is appropriate for use in such future epidemiologic studies.

A more detailed description of the activities to be conducted by the successful respondent(s) is provided below.

SUPPLEMENTAL INFORMATION

The focus of the RFP is on exposure assessment approaches for use in studies of Vietnam veterans. Previous IOM reports have cataloged and summarized the available information on the health outcomes associated with exposure to herbicides or the contaminant dioxin. The conclusions in these reports are based largely on studies of nonveteran populations (i.e., occupational cohorts or communities exposed after industrial accidents). A full understanding of the specific risks for Vietnam veterans requires studies of the veterans themselves, which in turn require a better understanding of the herbicide exposures encountered by various military groups during the Vietnam War. The RFP does not preclude the use of exposure assessment models or data developed or validated on non-Vietnam veteran populations, provided they are

used to develop a model of exposure assessment for Vietnam veterans under the subcontract.

The RFP is intended to address assessment of all exposure to herbicides used during the Vietnam War. These herbicides are listed in Table 1. Several different herbicides and herbicide mixtures were used in varying combinations by the United States during the conduct of the war. Furthermore, some of these herbicides were contaminated with dioxins (TCDD and its congeners) at varying levels. Each of these chemicals has characteristics (e.g., half life and solubility) that will affect a person's dose at a given level of exposure. Because these chemicals also have distinctive toxicities, the proposal should acknowledge these complexities, not focus solely on TCDD. The proposal should address how exposure to this array of chemicals will be evaluated.

TABLE 1 Major Herbicides Used in Operation Ranch Hand: 1962–1971

Herbicide Code Name	Formulation	Purpose	No. of Gallons Sprayed	Period of Use
Purple	2,4-D; 2,4,5-T	General defoliation	145,000	1962–1964
Blue (Phytar 560-G)	Cacodylic acid	Rapid defoliation, grassy plant control, and rice destruction	1,124,307	1962–1971
Pink	2,4,5-T	Defoliation	122,792	1962–1964
Green	2,4,5-T	Crop destruction	8,208	1962–1964
Orange, Orange II	2,4-D; 2,4,5-T	General defoliation	11,261,429	1965–1970
White (Tordon 101)	2,4-D; picloram	Forest defoliation, long-term control	5,246,502	1965–1971

SOURCES: MRI, 1967; NAS, 1974; and Young et al., 1988.

A paper included as the Appendix to this report is provided as background for potential respondents. This paper, entitled "The Assessment of Exposure to Herbicides among Vietnam Veterans: A Review and Recommendations for Future Studies," provides an overview of the U.S. military's use of herbicides during the Vietnam War, a review of prior exposure assessment research efforts, and a discussion of potential approaches to herbicide exposure assessment research. This paper was not written by the Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam or any of its members, and it should not be viewed as instruction from the committee regarding the form or content of proposals. Instead, it should be treated as a summary of the information regarding exposure assessment contained in the IOM reports *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam and Veterans and Agent Orange: Update 1996*.

BACKGROUND ON METHODS

Epidemiologic Study Designs

In light of the high priority of research on cancer and reproductive disorders, historic cohort studies and case-control studies are the research designs most likely to be used for epidemiologic studies of Vietnam veterans potentially exposed to herbicides. Either type of study would require retrospective assessment of herbicide exposure. However, the method of exposure reconstruction and the level of detail may differ depending on the design of the epidemiologic study in which it would be applied.

Cohort studies typically begin with estimation of the exposure status of every member of the population of interest and then proceed to ascertainment of health outcomes for each individual. This approach provides exposure estimates for the entire population. However, the need to obtain data for large groups (including many people who did not experience a health event) usually constrains the effort that can be devoted to estimating exposure for any individual. As a result, it is sometimes feasible to characterize exposures only crudely in large cohort studies.

Case-control studies may be conducted as an alternative to improve efficiency and validity by collecting more detailed exposure information for a smaller number of subjects. Because case-control studies include all of the cases of the health outcome of interest but only a sample of the "base" population that produced the cases, it is often feasible to utilize more costly, more time-consuming, or more labor-intensive techniques of estimating exposure than would be feasible in a cohort study including the entire base population. In an occupational study, for example, the exposures of an entire cohort of workers might be estimated from job titles and historic records, whereas a case-control study of selected workers from the same cohort might also utilize worker interviews and field measurements. A similar approach can be used in case-cohort, case-based, and other alternative study designs that involve cases and a sample from the base population.

Various exposure assessment approaches might seek to identify groups or individuals with qualitatively or quantitatively distinct exposures. Groups with qualitatively distinct exposures who served in Vietnam might include those who served in different branches of the military, or in different geographical areas, who had different job titles, or those who were in zones sprayed with herbicides versus those who were not. Alternatively, measuring herbicide or metabolite concentrations in the blood, fat, and tissues or organs of exposed individuals may provide the information needed to quantitate exposure(s). Some combination of environmental exposure patterns and biologic measures may be able to predict exposures with a better degree of confidence than either could alone.

Past Exposure Assessment

A variety of approaches have been developed for estimation of past exposures. The Appendix provides details on these approaches. In brief, previous studies of Vietnam veterans have used the simplest separation of job titles or service areas. These broad categorizations of exposed and unexposed individuals were based on judgment and in some cases spraying records, which may have produced a large degree of misclassification on exposure status. The goal of the RFP is to invite investigators to propose study designs that will improve the assessment of veterans' exposure to herbicides during their service in Vietnam. Regardless of the strategy, the common goal of such retrospective exposure assessments is to develop the most accurate and unbiased estimates of exposure possible within the limitations of the resources.

Quantitative dose-response epidemiologic studies try to approximate the dose to the target tissue as closely as possible because it is the presumptive cause of the adverse effect observed in the epidemiologic outcome. Although it is seldom possible to retrospectively generate precise estimates, these approximations may yield important information about the magnitude of exposures relative to other study subjects and unexposed individuals. A dose index is a single number calculated from (1) a subject's personal data and (2) an exposure model that is intended to summarize a subject's exposure history in a way that is relevant to the risk of an adverse outcome, such as total dose of the suspected agent received by the subject. The epidemiologic dose index that is closest to total administered dose is the cumulative exposure. Cumulative exposure is calculated as the mean exposure in a given category (in an occupational setting, this would typically be a job title) times the duration in the category, summed over all categories. This has been a useful measure in many studies of the relationship between disease incidence and exposure to asbestos, lead, cadmium, and other agents. Other dose indices may also be important for the risk of a particular disease, and the example given above should not be interpreted as precluding the use of other representations of exposure, such as categorical representations.

Responses to the RFP are expected to make clear the underlying relationship(s) hypothesized between exposure to herbicides and the dose indices chosen, including considerations of mechanism where appropriate. For example, if acute exposure is thought to be important, this should be stated and the means by which the proposed dose metric distinguishes and characterizes acute exposures should be detailed.

It is important to recognize that the steps used in extrapolation of past exposures have variable magnitudes of uncertainty. Quantitative estimates of exposure intensity for the distant past generally have the highest uncertainty. However, large uncertainty in the absolute magnitude of exposure may be acceptable if subgroups of subjects with different modes of exposure also have large relative differences in exposure. Respondents are encouraged to consider a

synthesis of a variety of information sources, because information on locations, operations, and activities may be combined to define relative differences in exposure.

AVAILABLE DATA

There are sources of publicly available data on the use of herbicides in Vietnam, veterans' service in the Vietnam theater, and characteristics of other populations exposed to dioxin that may be of use to researchers. Some of these sources are mentioned below or are cited in the Appendix. However, their mention here is for information only and is not intended as a recommendation for their use. Neither should this listing be considered comprehensive. Data regarding individuals may be subject to privacy restrictions.

The HERBS and Service HERBS computer tapes contain information regarding aerial and some ground-spraying activities, including date, type of herbicide, number of gallons sprayed, and location of spraying. These tapes and their limitations are discussed in greater detail in the Appendix and in *Veterans and Agent Orange* (IOM, 1994:96–106). Data from the 1987 Air Force Health Study physical examination of Ranch Hands veterans and a comparison group is available through the National Technical Information Service (NTIS Accession Number A-283-319). These data include date of birth, exposure group, and dioxin levels for approximately 2,500 subjects. The Minnesota Department of Veterans Affairs has compiled service information on approximately 156,000 Vietnam-era veterans—including approximately 68,000 who served in Vietnam—in support of that state's bonus program. The DVA is developing a comprehensive Vietnam veterans roster that will include service branch, rank, occupational codes, and the dates of Vietnam service. This roster is expected to be completed during 1997. The National Institute of Occupational Safety and Health has collected information on 5,172 male workers at 12 plants that produced TCDD-contaminated herbicides. Among these data are vital statistics and duration of exposure; lipid-adjusted, serum TCDD levels are also available for a subset of 253 workers.

POTENTIAL APPROACHES

Exposure reconstruction should consider methods that will identify homogeneously exposed groups, rank-order cohorts by exposure levels, or use some combination of approaches to generate information for epidemiologic studies. This could include, but is not limited to, using biomarkers of exposure; identifying exposure patterns (e.g., from air vs. ground spraying), locations, concentrations, and frequencies; considering types of foliage, weather conditions, troop location and movement in time; date(s) of field service for

individual soldiers; and distinguishing the types of herbicides used. The section entitled "Development of the Exposure Reconstruction Model" in the Appendix (p. 46) discusses this in greater detail.

Biomarkers of exposure require the ability to measure a chemical in a biologic specimen—that is, urine, blood, tissue, organs, hair, and the like. If biomarkers of exposure are chosen as a dose index, such as serum TCDD, then the quantitative relations between the marker and herbicide exposure and its limitations must be discussed. For example, individual clearance rates of TCDD are variable, so low serum TCDD may not equate to low past exposure. There are also other sources of TCDD intake, such as diet, so current high TCDD levels may not necessarily indicate high past exposure. Finally, TCDD was a highly variable constituent of the herbicides used in Vietnam, and some herbicides did not contain TCDD; therefore, TCDD may not be a good marker for all types of herbicide exposure. Additional information on biomarkers is provided in the Appendix.

VALIDATION OF EXPOSURE ASSESSMENT APPROACHES

Validation of the exposure assessment approach developed will be a critical part of the proposal. The committee recognizes that retrospective exposure assessment of herbicide exposures among Vietnam War veterans may, at best, be semiquantitative or rank ordered. Because we have a generally poor understanding of the sources and magnitudes of exposures to herbicides that occurred in Vietnam more than 25 years ago, the predicted levels of exposure to individual veterans are likely to be imprecise. Thus, applicants should discuss the anticipated sources and magnitudes of uncertainty in their model predictions. Attention should also be paid to the role that quantitative or semiquantitative data might play in the validation of exposure predictions in a pilot study.

The best method for validation is not obvious and is left to the researchers to propose, critique, and defend. The limitations and uncertainties associated with the validation method—such as those discussed previously for serum TCDD levels—should be addressed.

Respondents are encouraged to consider other alternative approaches to the validation process.

EVALUATION CRITERIA

The purpose of the research to be sponsored under the RFP is to develop exposure assessment models for use in epidemiologic studies of Vietnam veterans. Proposals of models for which the relevance to Vietnam veterans is unclear will not be further evaluated. The proposals will be assessed based on

five criteria: (1) context, (2) technical merit, (3) feasibility and validation, (4) personnel and experience, and (5) cost and timeline. A discussion of these criteria and the weighting they will be assigned. follows.

Context (10%)

Proposals should be specific about how the intended assessment approach could be used in epidemiologic studies and should briefly describe the types of studies envisioned. Such descriptions should provide enough detail to allow an evaluation of their potential for successful completion. A strong proposal will describe feasible epidemiologic studies that have a high likelihood of detecting whether or not particular health effects (e.g., cancer) are related to veterans' exposure to herbicides in Vietnam.

Technical Merit (35%)

The proposal should describe the following:

- How the proposed method may improve upon other available methods for Vietnam veterans and provide a better basis for exposure assessment.
- The degree to which the overall herbicide exposure in Vietnam of individuals or groups can be described by the proposed exposure assessment approach.
- The likelihood of discriminating levels of herbicide exposure among the individuals or groups and of identifying high-exposure subgroups or individuals.
- How critical sources of uncertainty will be identified and characterized.
- The characteristics of the groups or individuals studied that need to be controlled for in the analysis and, for the validation study, important confounding exposures and other factors.
- Explicit justification for any proposed biomarker (e.g., TCDD) studies.
- The weaknesses of the chosen approach and the means that will be used to minimize their impact, including a discussion of the critical sources of uncertainty and how they may affect the validation study being proposed.

Feasibility and Validation (25%)

The proposal should describe in detail the study designed to demonstrate the feasibility and validity of implementing the exposure assessment approach, as well as the accuracy, biases, and uncertainties of the approach. The proposal should also describe how this approach could be applied to achieve meaningful

results in a possible future epidemiologic study of herbicide-related health effects in Vietnam veterans.

Personnel and Experience (20%)

A list of the proposed management and investigators should be submitted, along with a description of activities to be performed by the individual investigators and their curriculum vitae. The research team must have expertise in performing exposure assessments for epidemiologic studies and should include an experienced epidemiologist, as well as individuals experienced in handling military records.

It is recognized that specific expertise in different types of exposure models (i.e., records based vs. biomarker based) may not be available within the same research group or organization. Collaborations between scientific researchers and individuals or organizations familiar with military records and combat operations are encouraged.

Cost and Timeline (10%)

The costs and schedule of proposed activities must be delineated. Proposals will be evaluated in terms of cost-effectiveness, as well as the capacity to perform the proposed work within the schedule provided, using the resources described.

RESEARCH PRODUCTS

Research sponsored under the RFP should include the following products:

- Scientific progress reports should be submitted every 6 months and presentations of research progress every 12 months, beginning 6 months from the start of the subcontract. The progress reports should include a description of the overall progress; descriptions of the specific work accomplished, including problems encountered and corrective actions; pertinent data or other information in sufficient detail to explain significant results achieved and any preliminary conclusions resulting from analysis and scientific evaluation of data accumulated to date; and a description of the work to be accomplished over the following 6 months. Presentations of research progress are intended to facilitate interaction between the committee and the researchers. Presentations should be made in front of the committee or its designated representatives and should include all of the information requested for progress reports.
- At the completion of the research, a report should be submitted including full details on the proposed exposure assessment methodology; the

degree to which exposure can be determined, both qualitatively and quantitatively, by this methodology; the details of the validation studies performed, including both methods and results; and a description of how important confounding variables will be evaluated.

The committee encourages the dissemination of scholarly findings resulting from conduct of the research and encourages investigators to disseminate their findings through publication in peer-reviewed journals.

REFERENCES

Institute of Medicine. 1994. Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam. Washington, DC: National Academy Press.

Institute of Medicine. 1996. Veterans and Agent Orange: Update 1996. Washington, DC: National Academy Press.

Midwest Research Institute (MRI). 1967. Assessment of Ecological Effects of Extensive or Repeated Use of Herbicides. MRI Project No. 3103-B. Kansas City, MO: MRI. (NTIS AD-824-314.)

National Research Council, Assembly of Life Sciences. 1974. The Effects of Herbicides in South Vietnam. Washington, DC: National Academy of Sciences.

Young AL, Reggiani GM, eds. 1988. Agent Orange and Its Associated Dioxin: Assessment of a Controversy. Amsterdam: Elsevier.

APPENDIX

The Assessment of Exposure to Herbicides Among Vietnam Veterans: A Review and Recommendations for Future Studies

David Kriebel, Michael Stoto, Clifford Weisel, and Susan Rogers

ABSTRACT

In 1991, the U.S. Congress enacted P.L. 102-4, The Agent Orange Act of 1991, which among its provisions mandated a study commissioned by the Department of Veterans Affairs and conducted by the National Academy of Sciences' Institute of Medicine (IOM) to review the existing literature on the human health effects of the herbicides used in Vietnam. A second charge was to review the existing efforts at the assessment of herbicide exposures among Vietnam veterans and make recommendations for future exposure studies. This paper summarizes the investigations conducted by an IOM committee (referred to here as the Agent Orange, or AO, committee) into the problems and prospects for herbicide exposure assessment studies among Vietnam veterans.

The AO committee found that although different approaches have been used to estimate exposure in Vietnam veterans, each of the approaches is limited in its ability to determine precisely the degree and level of individual exposure. The measurement of the dioxin 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in the blood many years after exposure may be useful, especially for detecting *group* differences. However, because of common background exposures to TCDD, poorly understood variations among individuals in TCDD metabolism, and analytic uncertainty of the analysis, *individual* TCDD serum levels are usually not meaningful. Furthermore, because not all of the herbicides used in Vietnam contained TCDD, serum TCDD levels are not good indicators of overall exposure to herbicides.

Although definitive data are lacking, the available quantitative and qualitative evidence about herbicide exposure suggests that Vietnam veterans as a group had substantially lower exposure to herbicides and TCDD than the subjects in many occupational studies of herbicide exposure. The participants in "Operation Ranch Hand"—the U.S. Air Force program of aerial spraying of herbicides in South Vietnam—are an exception to this pattern, and it is likely that others among the approximately 3 million men and woman who served in

Vietnam were exposed to herbicides at levels associated with health effects. The difficulty (from the perspective of epidemiologic studies) is that the available data do not readily permit precise quantification of exposure. None of the measures that has been proposed to date would be free of nondifferential misclassification bias. The effect of this bias on risk estimates would likely be to underestimate true effects if they existed, possibly to such an extent that these effects could be missed entirely by future studies.

However, it may be possible to develop a valid exposure reconstruction model for epidemiologic studies based on existing records and structured interview data, using principles of historic exposure reconstruction developed by industrial hygienists. Such a model would estimate the likelihood that each veteran was exposed to herbicides in Vietnam, and could possibly quantify the likely degree of exposure. This model would incorporate information in existing military records about herbicide spraying and troop movements. It would also include less formal sources of information on ground and perimeter spraying.

INTRODUCTION

In 1991, the U.S. Congress enacted P.L. 102-4, The Agent Orange Act of 1991, which attempted to address several of the long-standing concerns of Vietnam veterans concerned with the possibility of lingering health effects from exposure to herbicides during the Vietnam War. One provision of the act required the Department of Veterans Affairs to contract with the National Academy of Sciences' Institute of Medicine (IOM) to conduct a review of the existing literature on the human health effects of the herbicides used in Vietnam. The most prominent of these was Agent Orange (so named because of orange stripes on the barrels used to store and ship the chemical), a 50-50 mixture of the herbicides 2,4,5-T and 2,4-D. The former was contaminated with varying concentrations of numerous dioxins including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). The purpose of the review was to assess the strength of the evidence for association between exposure to these herbicides and human disease. The secretary of veterans affairs was then directed by the act to use these findings and other relevant scientific information in making determinations of which, if any, diseases should be considered "service related," and hence compensable for Vietnam veterans. The results of the AO committee's review were published in *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (IOM, 1994). In 1996, the first biannual update, also mandated by P.L. 102–4, was published as *Veterans and Agent Orange: Update 1996* (IOM, 1996).

Another provision of P.L. 102–4 requested that the IOM assess the feasibility of further epidemiologic studies of Vietnam veterans. In preparing to respond to this mandate, the IOM committee formed to conduct the review found

that exposure assessment was the weakest aspect of existing data on health effects of the herbicides used in Vietnam, and developed a series of recommendations aimed at improving this situation with respect to Vietnam veterans. This paper represents a summary of the findings of the AO committee with regard to exposure assessment of herbicide exposure for Vietnam veterans. After a brief review of the history of herbicide exposures in Vietnam, the article presents an evaluation of the various approaches to exposure assessment that have been used in studies of Vietnam veterans and some of the problems of inaccurate exposure measurement in these studies. Drawing upon the AO committee's evaluation of the available literature and upon information on the military use of herbicides, the paper then summarizes what is known about exposure to herbicides in Vietnam in comparison to other populations with widely different types of exposure (e.g., in factories, of professional herbicide sprayers, from environmental accidents). Finally, proposals for the reconstruction of past exposures to herbicides are discussed and evaluated. This paper draws on and summarizes material published in chapters 3, 6, and 12 of *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* and chapter 5 of *Veterans and Agent Orange: Update 1996*.

HERBICIDE USE IN VIETNAM

As background for the consideration of measures of exposure to herbicides in Vietnam that can be used in epidemiologic studies of veterans, both the deployment of troops and the military use of herbicides must be considered.

The Military Experience in Vietnam

As one historian notes in his account of the Vietnam conflict, "there was no 'typical' U.S. soldier in Vietnam ... the three million Americans who served there went through many varied experiences—partly because the quality of the war varied in different areas of the country, and partly because its nature changed over time" (Karnow, 1991:479). Individual experiences (and potential for exposure to herbicides) also varied according to job assignment, military unit of service, rank, and branch of service. Artillery units, for example, tended to be less mobile than cavalry because of the heavy equipment involved. An individual assigned to base headquarters with an Army personnel position experienced a different tour of duty than an infantry commander, a field engineer, or an officer stationed aboard a Navy vessel off the coast. Personnel assigned to units in the Mekong Delta might slog week after week across paddy fields, while others patrolling the perimeters of major U.S. installations at Danang, Bien Hoa, and Camranh were often targets for sniper attacks (Karnow,

1991). Individuals and units also varied in their consumption of locally grown foods and water from local supplies, as well as in their personal hygiene practices.

Estimates of the number of U.S. military personnel who served in Vietnam during this period of herbicide use vary from 2.6 to 3.8 million. The total number of U.S. servicemen and women exposed to herbicides is also not known, although some individuals, such as those of the Air Force Operation Ranch Hand and the Army Chemical Corps (groups that are discussed below), were more likely to have been exposed by the nature of their job assignments.

Approximately 50 percent of Vietnam-era veterans served in the Army, 20 percent in the Navy, 20 percent in the Air Force, and the remaining 10 percent in the Marines or Coast Guard (Kulka et al., 1988). Ground forces—the Army and Marines—were likely to experience more of the day-to-day fighting than Navy or Air Force personnel (Card, 1983). Sociological assessments of the American soldier in Vietnam suggest that no one factor is more important in understanding the experiences of the individual veteran than the degree of exposure to combat (Moskos, 1975; Fischer et al., 1980; Martin, 1986; Shafer, 1990). Twenty percent of soldiers sent to Vietnam were assigned to combat units (Shafer, 1990), although surveys of veterans indicate much higher percentages who reported having experienced combat. A survey published by the Veterans Administration indicated that 70 percent of those sampled reported exposure to combat, which meant that they had come under some kind of attack (U.S. Department of Labor, 1990; Karnow, 1991). The CDC Vietnam Experience Study found that 57 percent of Army veterans had served in combat units (i.e., infantry, artillery, armor, cavalry, and engineer; CDC, 1989).

Military Use of Herbicides in Vietnam

From 1962 to 1971, the U.S. Air Force sprayed nearly 19 million gallons of herbicides in Vietnam, of which at least 11 million gallons was Agent Orange, in a military project called Operation Ranch Hand. An additional quantity (1.6 million gallons has been documented) of herbicides was applied to base perimeters, roadways, and communication lines by helicopter and surface sprayings from riverboats, trucks, or backpacks. Special forces troops also performed an unknown, but relatively small, amount of spraying in support of their operations.

Military documents report the use of herbicides over areas of Laos, particularly near the Vietnam border and along the Ho Chi Minh Trail. The purpose of the operation in Laos was to expose foot trails, roads, and other lines of communication that led into Vietnam. Herbicide operations began in December 1965; within a 6-month period, more than 200,000 gallons of

herbicide had been sprayed over approximately 1,500 km of roads and trails in Laos (Collins, 1967).

Operation Ranch Hand

The major defoliation program in Vietnam—Operation Ranch Hand—began on December 4, 1961, when President Kennedy authorized the secretary of defense to test the military effectiveness of the defoliation of several lines of communication (MACV, 1968). The first major operation, to clear enemy infiltration routes, was carried out over the mangrove forests in the Ca Mau peninsula in the southernmost region of the Mekong Delta in September 1962 (Dux and Young, 1980).

Operation Ranch Hand had two primary objectives: (1) defoliation of trees and plants to improve visibility for military operations, and (2) destruction of essential enemy food supplies. Targets for defoliation by Ranch Hand included base camps and fire support bases (specifically constructed sites for storage of artillery in support of combat operations), lines of communication, enemy infiltration routes, and enemy base camps. Clearance of these areas improved aerial observation, opened roads to free travel, and hindered enemy ambushes.

All large-area defoliation missions were flown exclusively by Ranch Hand crews (Collins, 1967). According to Department of Defense (DoD) records, the aerial application of herbicides was accomplished by spraying from C-123 fixed-wing aircraft and helicopters (UH-1 and H-34). During 1967–1968, requirements for herbicide missions increased to the point that the number of available C-123 aircraft was not sufficient to complete all approved targets within the desired time frame (MACV, 1968). In order to permit a more timely response to defoliation requirements, helicopter operations were recommended for smaller targets, such as in support of local base defense, maintenance of deforested areas, and the uncovering of known small ambush sites along lines of communication (MACV, 1968). As Ranch Hand operations declined in 1970–1971, the number of helicopter herbicide operations increased and gradually became the only aerial means of herbicide delivery.

With the buildup of American troops in 1965, Operation Ranch Hand also intensified: the number of C-123 aircraft assigned to the operation increased from 3 to 12 (36 aircraft were assigned to the program from 1967 until it was phased out in 1971); permanent personnel were assigned to the team (Dux and Young, 1980); and the number of missions increased nearly 16-fold from 107 in 1962 to more than 1,600 in 1967 (Huddle, 1969; NAS, 1974). Typical missions early in the conflict included 3 to 4 aircraft, increasing to as many as 19 in the later years. The operation of a single aircraft was termed a sortie. In the period from 1966 through 1968, more than one sortie per day was often common. During the first 6 months of 1968, the 24 C-123 aircraft assigned to Ranch Hand averaged nearly 39 sorties per day (Young et al., 1978). All missions within a

target area formed a project (Young and Reggiani, 1988). Ranch Hand missions were also frequent targets of ground fire due to the low altitude and slow speed of the aircraft, and flights required fighter cover for protection (Collins, 1967; Warren, 1968; Spey, 1993). As early as 1963, fighter cover was used in conjunction with defoliation missions to provide mission protection. In 1966, it was reported that nearly one-third (29 percent) of all C-123 defoliation sorties received "hits" from ground fire. The ratio of hits per sortie decreased in later years with improved fighter tactics (Warren, 1968). The helicopter delivery system was also particularly vulnerable to ground fire because of the slow delivery speed (Collins, 1967).

The normal altitude of the C-123 for spray application was 150 feet, flying at a speed of 130 to 150 knots, and producing a swath width of 80 in per aircraft (MRI, 1967; NAS, 1974). Under these ideal conditions, a 1,000-gallon tank permitted a 3-to 4-minute spray time at a total distance of about 8.7 statute miles, or about 340 acres treated per aircraft, with a deposition rate of 3 gallons per acre (Young et al., 1978).

In addition to aircraft altitude and speed, distribution of the spray was also affected by climate, wind, terrain, and turbulence from the aircraft. Although missions generally were flown in the early morning when the wind was calm, to minimize spray drift, the NAS (1974) study showed that crop damage resulting from drift on defoliation missions was greater than that caused by crop destruction missions—indicating that widespread crop damage resulted from drift. Tschirley (1967) estimated that in a moist, tropical, triple-canopy forest, approximately 80 percent of the spray droplets were intercepted by the uppermost canopy, 14 percent fell to the inner level, and only 6 percent reached ground-level vegetation. Air turbulence from the aircraft also helped to distribute spray droplets throughout the foliage and was an important factor in the dispersal of the spray (MRI, 1967).

Four major herbicide compounds were used in the Ranch Hand herbicide formulations—2,4-D (2,4-dichlorophenoxyacetic acid), 2,4,5-T (2,4,5-trichlorophenoxyacetic acid), picloram, and cacodylic acid. Which of these four major chemicals was chosen for a specific application depended on the desired effects. 2,4-D and 2,4,5-T are chlorinated phenoxy acids, and each is effective against a wide array of broadleaf plant species (Irish et al., 1969). They persist in soil only a few weeks (Buckingham, 1982). Picloram, like 2,4-D and 2,4,5-T, regulates plant growth. Compared to 2,4-D, picloram is more mobile, and therefore better able to penetrate the plant's roots and be transported throughout the plant's tissues. Unlike the phenoxy herbicides, picloram is extremely persistent in soils. The fourth compound, cacodylic acid, contains an organic form of arsenic. Cacodylic acid is a desiccant, causing a plant's tissues to lose their moisture and eventually killing the plant. It is a contact herbicide that is rapidly rendered ineffective in soil.

These compounds have been used worldwide for the control of weeds and unwanted vegetation, although the application of 2,4,5-T is no longer permitted in the United States following a series of Environmental Protection Agency directives in the 1970s. 2,3,7,8-TCDD is a contaminant of 2,4,5-T, but not of 2,4-D, and is a very toxic material. Of all the herbicides used in South Vietnam, only Agent Orange was formulated differently from the materials for commercial application that were readily available in the United States (Young et al., 1978).

The levels of TCDD found in any given lot of 2,4,5-T depend on the manufacturing process (Young et al., 1976), and different manufacturers produced 2,4,5-T with various concentrations of TCDD. The primary source of 2,4,5-T in the herbicides used in Vietnam was Agent Orange. It is the unknown concentration of TCDD in Agent Orange that is of particular concern. TCDD concentrations in individual shipments were not recorded, and levels of TCDD varied in sampled inventories of herbicides containing 2,4,5-T. Analysis of the TCDD concentration in stocks of Agent Orange remaining after the conflict, which had either been returned from South Vietnam or had been procured but not shipped, ranged from less than 0.05 to almost 50 parts per million (ppm), averaging 1.98 and 2.99 ppm in two sets of samples (NAS, 1974; Young et al., 1978). Comparable manufacturing standards for domestic use of 2,4,5-T in 1974 required that TCDD levels be less than 0.05 ppm (NAS, 1974). Therefore, depending on which stocks were sampled, the level of dioxin contamination in Agent Orange could have been up to 1,000 times higher than the level of dioxin found in phenoxy herbicides domestically available at the time.

For each herbicide mission, the date, number of gallons sprayed, and type of herbicide, NAS produced maps showing how many times any hectare had been sprayed due to repetition or overlapping of herbicide applications. Figure A-1, for instance, depicts the extent of spraying conducted in the Rung Sat Special Zone during 1966 and 1967 using data from the HERBS tapes—a digitally stored log of spraying missions created by DoD. Areas designated as defoliation targets were much more likely to be sprayed repeatedly than targets of crop destruction missions. Less than 10 percent of the targets for crop destruction missions were sprayed more than once, and the intervals were usually 6 to 12 months; one-third of the areas classified as defoliation were resprayed, and approximately 70 percent received the second spray within 6 months of the initial spray (NAS, 1974).

One limitation of the HERBS tapes, and the maps generated from them, is that the plotted lines represent the center of each mission. The assumed swath width for a sortie was 80 m. Typical missions consisted of three aircraft, and some as many as 12 to 16; these differences in effective spray area are not reflected by the maps.

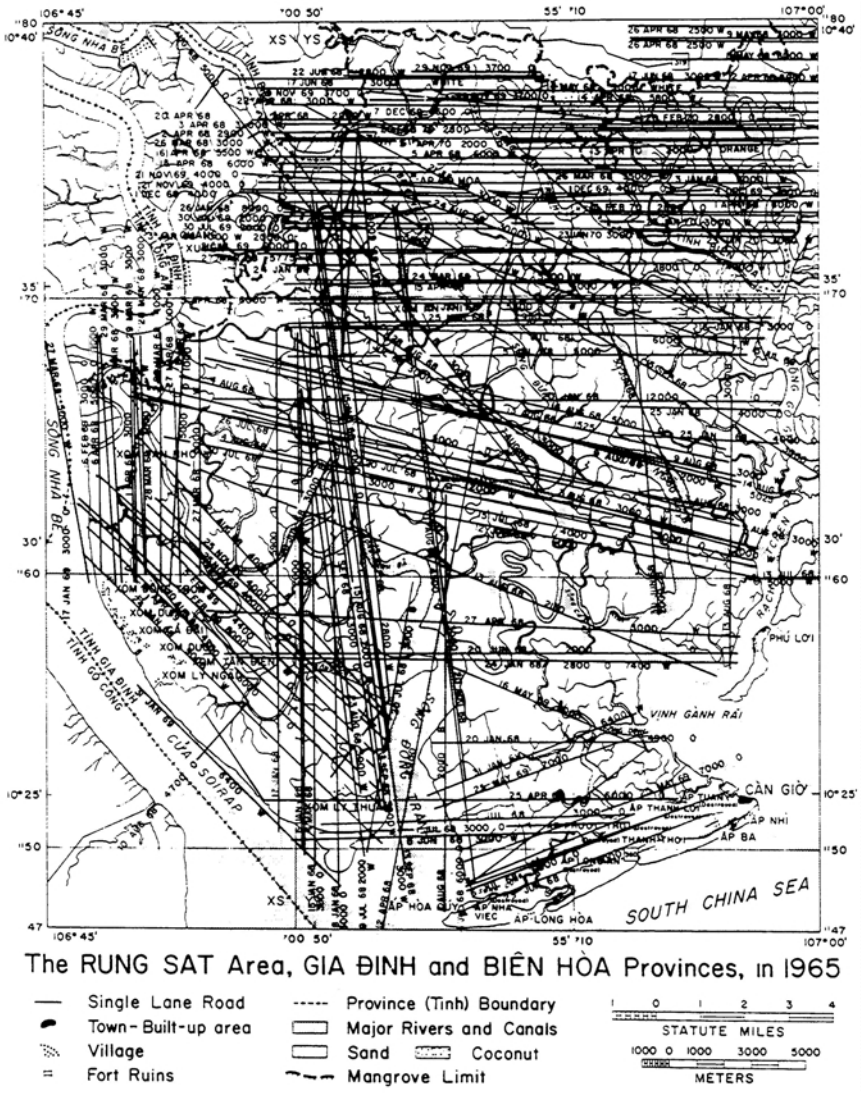

Figure A-1.
Herbicide spray missions (1966–1967) in the Rung Sat Special Zone. Data from HERBS tape include date of mission, number of gallons, and type of herbi cide agent.
SOURCE: NAS, 1974.

Much of the currently available information on the military use of herbicides in South Vietnam during the period 1962 to 1971—the chemical formulations used, the quantities applied, the operational procedures for aerial spray missions, and the aircraft used—was compiled in the 1970s and early 1980s from military records kept during the conflict, DoD technical reports, and procurement records. In 1974, the National Academy of Sciences' Committee to Review the Ecological Consequences of Herbicides in Vietnam evaluated the available DoD records of herbicide spray missions conducted from 1965 to 1971. During the Vietnam era, thousands of pieces of information on fixed-wing herbicide spray missions were compiled and recorded on the HERBS data tapes. The HERBS tapes are considered to contain the most complete, accurate, and authoritative compilation of data available on *aerial fixed-wing* herbicide operations conducted in Vietnam (Dashiell, 1973).

Non-Ranch Hand Spraying of Herbicides

Herbicides were applied by a variety of methods other than fixed-wing aerial spraying. An unknown, but smaller, quantity of herbicides was applied around base perimeters and lines of communication to improve visibility and reduce the likelihood of enemy ambush. Records of these smaller-scale uses of herbicides were not systematically logged and do not appear on the HERBS tapes. A review of various Army records and military reports identified the use of an additional 1.6 million gallons of herbicides, and information on these sprays was subsequently recorded on the Services HERBS tapes. Together these tapes of herbicide sprays account for approximately 20 million gallons of herbicides used in Vietnam from 1962 to 1971.

The U.S. Army Chemical Corps, using hand equipment and H-34-type helicopters, conducted smaller spray operations, such as defoliation around Special Forces camps; clearance of perimeters surrounding airfields, depots, and other bases; and small-scale crop destruction (Warren, 1968; Thomas and Kang, 1990). Twenty-two Army Chemical Corps units were assigned to South Vietnam between 1966 and 1971. Approximately 2,900 veterans who served in the Army Chemical Corps in Vietnam between 1966 and 1971 have been identified from unit morning reports. Men serving in these units were trained in the preparation and application of chemicals, as well as in the cleaning and maintenance of the spray equipment (Thomas and Kang, 1990, Dalager and Kang, 1995).

Units and individuals other than the members of the Air Force Ranch Hand and Army Chemical Corps were also likely to have handled or sprayed herbicides around bases or lines of communication. For example, Navy riverine patrols were reported to have used herbicides for clearance of inland waterways. Engineering personnel required the use of herbicides for removal of underbrush

and dense growth in constructing fire support bases. It is estimated that 10 to 12 percent of the total volume of herbicides was dispensed from the ground by spraying from backpacks, boats, trucks, and buffalo turbines (NAS, 1974). The buffalo turbine was a trailer-mounted spray system used for roadside spraying and perimeter applications, which essentially "shot" the herbicide with a velocity up to 240 km/hour and a volume of 280 m3 /min (Young and Reggiani, 1988). Hand spray units consisted of a backpack type of dispenser with a capacity of 3 gallons (Collins, 1967).

Although the Air Force maintained complete records of its Operation Ranch Hand fixed-wing herbicide missions, documentation of spraying conducted on the ground by boat, truck, or backpack and authorized at the unit level was less systematic. Authorization for herbicide missions by helicopter or surface spraying from riverboats, trucks, and hand-operated backpacks was delegated to the Republic of Vietnam and U.S. authorities at the Corps level; these operations required only the approval of the unit commanders or senior advisors. "Free-spraying" areas, including the Demilitarized Zone (DMZ) at the seventeenth parallel and the first 100 meters outside base camps, were also exempt from Ranch Hand regulations (NAS, 1974). This delegation of authority for spraying to the Corps level reduced the lag time that existed from proposal to completion of small defoliation projects, such as around depots, airfields, and outposts (Collins, 1967). However, because these helicopter and ground sprays were less rigidly controlled than fixed-wing aerial sprayings, the recording of such sprays was not as systematic as those of Operation Ranch Hand.

According to official documents, the "small-scale use of herbicides, for example around friendly base perimeters, was at the discretion of area commanders. Such uses seemed so obvious and so uncontroversial at the time that little thought was given to any detailed or permanent record of the uses or results" (U.S. Army, 1972). DoD took few precautions to prevent troops' exposure to herbicides since they were considered to be a low-level health hazard. Precautions prescribed were consistent with those applied in the domestic use of herbicides existing before the Vietnam conflict (U.S. GAO, 1979). The Army added that exposure of ground troops was very unlikely since DoD personnel did not enter a Ranch Hand-sprayed area until approximately 4 to 6 weeks after the mission, when defoliation was complete and the herbicide had biodegraded or photodegraded (U.S. Army, 1972). The restriction placed on troops' entering a previously sprayed area was primarily for operational reasons, to prevent troops from being injured by the fighter aircraft that often accompanied the herbicide-spraying aircraft (U.S. GAO, 1979).

Although some information is documented in military records, it is impossible to determine accurately from military records alone the extent of spraying conducted on the ground or the number of personnel involved in these operations with potential herbicide exposure. An unknown number of non-Ranch Hand personnel likely received various degrees of exposure to herbicides.

Young and Reggiani (1988) report that the actual number "may be in the thousands since at least 100 helicopter spray equipment units were used in South Vietnam, and most military bases had vehicle-mounted and backpack spray units available for use in routine vegetation control programs." The dregs of the 55-gallon drums were pumped into smaller drums and sent to military camps for local defoliation of crops and control of perimeter foliage (Dux and Young, 1980).

A 1979 study by the U.S. General Accounting Office (U.S. GAO, 1979) examined the military defoliation operation in the Con Thieu province of I Corps between January 1966 and December 1969. During this period, more than 2 million gallons of herbicides were sprayed in I Corps. By using average troop strength and turnover figures, an estimated 218,000 Marine infantry personnel were determined to have been assigned to I Corps between 1966 and 1969. By randomly selecting 276 of 976 Marine monthly battalion reports, the GAO tracked troop movement and compared troop locations with herbicide mission data. Nearly 26,000 U.S. Marines and Navy medical personnel were identified who entered within a radius of 2.5 km of the defoliated target areas within I day of spraying; 4,300 troops were identified as being within 0.5 km of the flight path; 11,700 were within 2.5 km within 4 weeks. In the Khe Sanh-Thon Son Lam area, an estimated 4,300–8,000 troops were within 0.5 km of the sprayed area within I day of spraying; within 28 days, 33,600–45,300 troops were determined to have been within 2.5 km of the defoliation target. Army records were found to lack sufficient information, so that estimates of the number of Army personnel close to sprayed areas could not be calculated. The GAO report concluded that "the chances that ground troops were exposed to herbicide Orange are higher than the DoD previously acknowledged ... the group of personnel most likely to have been exposed could include ground troops as well as herbicide handlers and aircraft crew members" (U.S. GAO, 1979).

Geographical Distribution of Herbicide Sprays

South Vietnam was divided into four combat tactical zones, from I Corps lying south of the DMZ to IV Corps in the Mekong Delta region (Figure A-2). Although spraying occurred in most provinces of Vietnam, certain areas of the country were subject to more intensive spraying. The herbicide mission maps (Figure A-3) indicate that defoliation missions were not uniformly distributed but were concentrated in certain geographical areas—along transportation routes, in occupied areas around Saigon, and on infiltration routes along the Laotian and Cambodian borders and the DMZ where enemy attacks were likely (U.S. Army, 1972). Primary target areas for crop destruction missions were in I Corps and along the upland and mountain valleys of II Corps (NAS, 1974). The military purposes of these missions were to deny food to the enemy, to redirect enemy

manpower to crop production, and to weaken enemy strength in these areas (Warren, 1968).

According to a 1972 Department of the Army report, *Herbicides and Military Operations*, the dense forest along many of the key marine and land transportation routes served as effective cover for enemy ambushes (U.S. Army, 1972). In particular, the Rung-Sat Special Zone, an area of dense mangrove forests, afforded enemy concealment along the main shipping route to Saigon. Defoliation of the area began in the mid-1960s, and by the late 1960s, most of the mangrove forests adjacent to the shipping routes were defoliated. The defoliation operation was so complete that it eliminated enemy attacks on shipping in the Rung Sat area (U.S. Army, 1972).

Infiltration of the enemy and their supplies into Vietnam was also a major problem for military operations. The predominant points of entry were in densely forested areas, where U.S. patrols were subject to enemy ambush, and the forest cover concealed the enemy and its supplies. The Ca Mau peninsula was a temporary staging area for infiltration into the Mekong Delta and for attacks on local shipping and Navy patrol craft along the peninsula's streams and canals. Defoliation operations in 1967 and early 1968 aided military operations by improving observation of formerly heavily forested jungle areas (U.S. Army, 1972).

The enemy infiltration terminated in base camps within South Vietnam; several were located near the Cambodian border, and others were located near Saigon. These enemy camps were the source of raids on and harassment of friendly forces, terrorist attacks on local inhabitants, and attempted infiltration into cities. War Zone C (an area in III Corps on the Cambodian border), and War Zone D and Bear Cat (both near Saigon), were three such enemy base camp areas noted by the Army that were sprayed repeatedly to reach all levels of the canopy forest and restrict regrowth.

Perimeter spraying by hand or helicopter at base camps and other installations was required to control the growth of tall grasses and brush. In areas where bamboo or tall grass surrounded a base, it was necessary to respray every 2 or 3 months to keep the vegetation low; however, the Army notes that in most locations, the topography, hazardous conditions, minefields, and limited work force and equipment precluded the use of hand sprays for clearing base perimeters (U.S. Army, 1972).

Crop destruction targets were primarily located in I Corps and the western region of II Corps. Rice was the main target for destruction, and Agent Blue was found to be most effective. Although the immediate effect of the herbicides was to destroy the rice crop, the Army reported that new crops could be planted during the next growing season due to the lack of residuals in the soil that would restrict subsequent plant growth.

Figure A-2.
South Vietnam during the Vietnam conflict. SOURCE: IOM, 1994.

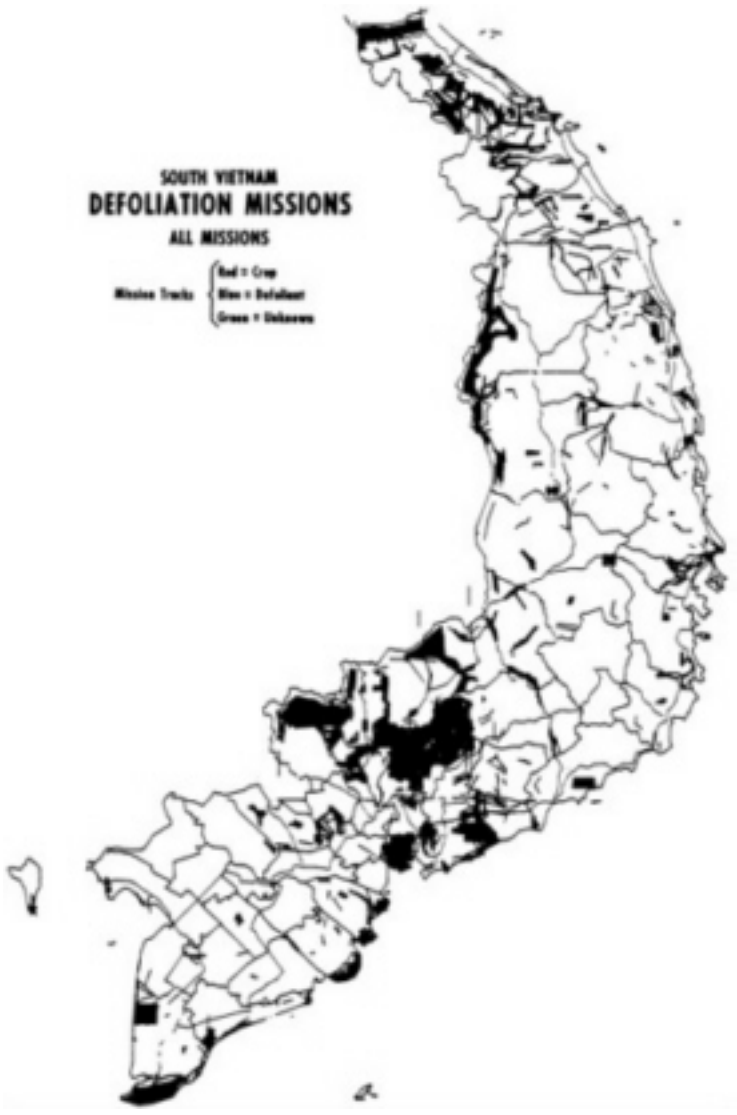

Figure A-3.
Herbicide defoliation missions in Vietnam as recorded on HERBS tapes.
NOTE: Lines indicate mission tracks. SOURCE: NAS, 1974.

Assuming a flight swath width of 80 m, the NAS estimated that from 1965 to 1971, 3.6 million acres, or nearly 10 percent of the land area of South Vietnam, had been sprayed at least once with herbicides (NAS, 1974). About 1.2 million acres, or roughly 34 percent of the sprayed area, was sprayed more than one time. These calculations are based on figures for the spraying missions by the C-123s and do not take into account unrecorded helicopter or ground sprays, or the effects of wind drift, aircraft speed, and rates of delivery. III Corps was the most heavily sprayed area of Vietnam, receiving about 53 percent of all herbicide sprays from 1965 to 1971. Thirty percent of III Corps was sprayed at least once (Westing, 1984). War Zones C and D, and the Iron Triangle in III Corps, can also be identified as heavily sprayed areas in maps of herbicide defoliation missions. The Rung Sat Special Zone in III Corps near Saigon, where the Saigon and Dong Nai Rivers linked together, was the most heavily sprayed region in Vietnam, as well as a site of frequent U.S. Navy operations. In 42 missions, the C-123s sprayed thousands of gallons of herbicides on the mangrove swamps to flush out Vietcong from hidden strongholds, from which they attacked supply ships and instituted offensives in the Delta region and surrounding provinces (Dux and Young, 1980). The area was sprayed consistently until 1970; the NAS (1974) estimated that 57 percent of the Rung Sat Special zone had been sprayed.

Another heavily sprayed area, the Ca Mau Peninsula at the southern tip of South Vietnam, was almost entirely covered with dense mangrove forests up to 1968. However, after extensive spraying of the peninsula in 1967 and 1968, the NAS (1974) concluded that nearly half of the mangrove trees had been destroyed. Mangrove forests were more heavily affected by herbicide spraying than any other vegetation type in South Vietnam. One spray usually killed all the mangrove trees (NAS, 1974).

EXPOSURE ASSESSMENT IN STUDIES OF VIETNAM VETERANS

Different approaches have been used in estimating exposure to herbicides in studies of Vietnam veterans. These studies generally rely on self-reported exposures, records-based exposure estimates, or biomarkers. Each of these approaches is limited in its ability to determine precisely the intensity and duration of individual exposure.

Self-Reports

Self-reported data are a common epidemiologic too for assessing exposure, but they have a number of drawbacks when applied to studies of Vietnam veterans to determine herbicide and TCDD exposures. These include the general problem of recall and, in particular, the possible confusion of herbicide spraying

with the spraying of insecticides, and underreporting by individuals who unknowingly entered an area that had previously been sprayed and still contained residual herbicides or TCDD. On the other hand, some veterans who believe they were exposed to herbicides may not actually have been exposed.

Records-Based Measures

Vietnam Service

The advantage of using Vietnam service as an exposure measure is the simplicity of study design and analysis. The major limitation of Vietnam service as a measure of exposure is that not all men and women who served in Vietnam were actually exposed to herbicides or TCDD above global background levels, and therefore, any epidemiologic study examining adverse health outcomes associated with herbicides or TCDD exposures would be diluted by the misclassification as exposed of individuals who served in Vietnam but were not exposed.

Branch of Service

The rationale for using branch of service in classifying exposure is that the activities and locations of service of the Air Force, Army, Marines, and Navy varied, and therefore the potential for exposure to herbicides may also have varied. Among the factors that could have differed among the four branches of service and could potentially be related to the extent of exposure were troop mobility, the percentage of time spent outside of base camps, the availability of hygienic facilities, and the degree of reliance on local water and food. For example, it might be assumed that more mobile troops, by spending more time in the field, having less access to hygienic facilities, and consuming more local food and water, would have greater potential exposures. However, those who operated primarily in the field cannot all be considered exposed because herbicide spraying was not distributed uniformly throughout the country. Also, support troops that operated from major bases might have been exposed because herbicides were used extensively around some base camps to remove tall grasses and heavy growth that obscured visibility. Since herbicides were used around base camps, military personnel could have received exposures in areas where no records of Operation Ranch Hand spraying exist. The violations of the simplifying assumptions would result in both false-positive and false-negative exposure assignments when "job classification" by branch of service is used.

Combat Experience

Classification using combat experience is based on the assumption that troops who had more frequent encounters with the enemy, and therefore engaged in combat more frequently, were more likely to enter areas that had been sprayed with herbicides. But since this was true only for some troops or regions in Vietnam, in certain periods, combat experience is a poor surrogate for herbicide exposure.

Military Occupation

Military occupation has been shown to be a valid exposure classification for two specific occupations that involved the direct handling and distribution of herbicides: the Air Force Ranch Hands, who were responsible for aerial spraying of herbicides and, the Army Chemical Corps, which performed ground and helicopter chemical operations. Biomarker studies of the Ranch Hands are consistent with their exposure to TCDD as a group. When the Ranch Hand cohort was further classified by military occupation, a general increase in serum TCDD levels was detected with jobs that involved more frequent handling of herbicides. The median TCDD level for enlisted ground crew (24 ppt, range 0–618 ppt) was higher than the median level for enlisted flyers (18 ppt, range 0–196 ppt), and three times greater than the median level for officers (8 ppt, range 0–43 ppt) (AFHS, 1991).

The number of military personnel involved in these two units is small, however—approximately 1,000 for the Ranch Hands and 750 for the Chemical Corps (Thomas and Kang, 1990) at the last follow-up. Individuals serving in the Army Chemical Corps were also likely to be exposed to a number of chemicals other than herbicides, which can contribute to confounding in epidemiologic studies. Other classifications of general Vietnam veterans by military occupations are unlikely to improve the ability to predict exposure above what might be obtained from a category such as combat experience.

NEW APPROACHES TO EXPOSURE ASSESSMENT FROM OCCUPATIONAL EPIDEMIOLOGY AND INDUSTRIAL HYGIENE

In recent years, considerable research has been done to develop systematic methods of historic reconstruction of exposure—the broad term covering all of the various strategies discussed above (Gamble and Spirtas, 1976; Smith, 1987; Bond et al., 1991; Rice, 1991; Smith et al., 1991; Stewart and Herrick, 1991; Tankersley et al., 1991). Three international symposia have been held on the subject (Rappaport and Smith, 1991; Stewart and Herrick, 1991; Axelson and Westberg, 1992). The essential features of historic exposure reconstruction applied to each member of a study cohort are (1) the use of surrogates of past

exposure to toxic chemicals (if no measurements are available) to estimate the likely intensity of exposure an individual would have experienced in a particular location (often a job or industrial department) at a particular time; (2) the use of either work records, individual recollections, or a combination of the two to determine which locations or jobs the subject was in for which periods—this information can then be combined with the job/location exposure estimates to build up for each subject an estimated exposure history covering years to decades of past exposure; and (3) summation of individual exposure histories in parameters that can then be used in epidemiologic models to assess exposure-risk associations.

Historic exposure reconstruction is a lengthy and expensive process, and the field is still developing. There are, however, some recent examples of occupational epidemiologic studies in which exposure estimates derived from historic reconstruction have proven superior to those relying on simpler measures such as the total duration of exposure (Dement et al., 1983; Stewart et al., 1986; Rinsky et al., 1987; Kriebel, 1988a,b; Seixas, 1990; Blair and Stewart, 1992).

Exposure assessment was the weakest aspect in most of the epidemiologic studies that the IOM AO committee has reviewed of people exposed to herbicides used in Vietnam and TCDD. Rarely is there precise information on the intensity and duration of individual exposure. Rather, surrogates such as the length of employment and job location in the workplace are measured. In some cases, not even the specific chemicals to which a cohort has been exposed are specified. Many studies use overall membership in a group to assign exposure. Exceptions are studies conducted by Fingerhut et al. (1991) and Saracci et al. (1991), which involve chemical production workers and evaluate subgroups with presumed higher, longer, or better-characterized exposure. The types of occupational and environmental exposure situations studied, and the likely intensity and duration of the exposures to herbicides and TCDD, are diverse. In principle, this provides an opportunity to compare results between studies in order to determine whether certain diseases are more common in populations likely to have higher exposures. However, because of the complex pattern of exposures to the various herbicides and TCDD in the available epidemiologic studies, the AO committee was generally not able to differentiate among multiple chemical exposures to determine whether specific health effects were associated with a particular herbicide or TCDD in the mixed exposure setting.

Two recent publications examined the development of exposure indices for cohorts exposed to herbicides, dioxins, or related compounds during chemical manufacture (Kauppinen et al., 1994; Ott et al., 1993). Both illustrate methods of exposure reconstruction for cohorts with past exposures to chemicals for which no actual exposure monitoring data exist. In both cases, an indirect validation or evaluation of the model was accomplished.

Kauppinen et al. (1994) estimated past exposures to phenoxy herbicides, chlorophenols, and dioxins for workers engaged in the manufacture or spraying

of phenoxy herbicides and related compounds. The procedure was carried out for two diseases (soft-tissue sarcoma and non-Hodgkin's lymphoma), using controls chosen from the multicountry IARC cohort (Saracci, 1991). A team of three industrial hygienists, blind to case-control status, evaluated the exposure histories of each subject using a standardized procedure. The main steps of the reconstruction procedure were qualitative exposure assessment; determination of the duration of exposure; estimation of the intensity, or level, of exposure; calculation of cumulative exposure; and the ranking of the subjects. The procedure was performed separately for more than a dozen agents, including the principal phenoxy herbicides (2,4-D, 2,4,5-T), several chlorophenols, dioxins, and dibenzofurans.

Kauppinen's procedure could not be directly validated because almost no quantitative exposure data existed. However, in a separate paper Kogevinas et al. (1995) used the exposure estimates to study the association with soft-tissue sarcoma (STS) and non-Hodgkin's lymphoma (NHL) in nested case-control studies. The authors report considerably stronger associations between estimated exposure and risk of STS than was seen with the simpler exposure classification used in the full cohort study (Saracci, 1991). The relationship between estimated exposure and NHL was equivocal, although some evidence of increasing risk with increasing estimated exposure to some agents was observed.

A follow-up report on exposure reconstruction for an occupational cohort has been produced by Ott and colleagues (1993). Workers at a German chemical plant involved in a 1953 industrial accident resulting in TCDD exposure and those who took part in the subsequent cleanup operations have been followed to study potential health effects (Zober et al., 1990). Of the 254 workers followed, serum TCDD data were available on 138. Ott et al. (1993) have constructed a model to characterize the relationships between current (1988–1992) serum TCDD levels and information on the workers' activities during and after the accident for those members with measured serum TCDD levels. The model was then used to estimate TCDD levels for those cohort members without measurements. The investigators also used a simple back-extrapolation procedure to estimate serum TCDD levels for all cohort members during the time of the accident and cleanup.

Using such factors as the period of exposure (varying from the first few days after the accident to 15 years later), physical location of the worker during exposure, type of work performed, use of protective equipment, and duration of exposure, the authors could explain 65 percent of the variability in the measured serum TCDD levels. The authors found that estimated back-extrapolated serum TCDD levels were higher in those who experienced severe chloracne (geometric mean = 1,008 ppt, $n = 56$) than in workers with moderate chloracne (geometric mean = 421 ppt, $n = 59$) and those with no chloracne (geometric mean = 38 ppt, $n = 139$).

Studies of occupational and environmental exposures to air contaminants often observe that although most exposures occur at lower levels, a few people are exposed to much higher concentrations. Those with the highest exposures are at the highest risk for disease, and their risks are not well represented by the average or median exposure of the group. The importance of the "tail" of the exposure distribution can be illustrated by examining the serum TCDD concentrations among the sample of Ranch Hand ground crews studied by Michalek et al. (1995). Although the geometric mean (approximately the median) serum TCDD concentration for 397 ground crew was 26 ppt, a quarter of these men had serum TCDD levels above 150 ppt, and some were above 500 ppt. Note that those with the highest exposures had serum TCDD concentrations 20 times greater than the geometric mean. Thus, the mean or median exposure of Vietnam veterans, either as a whole or as members of any military occupation group, will not adequately represent the exposure of maximally exposed veterans. In *Veterans and Agent Orange* (1994), the AO committee estimated that some unknown, but likely small, fraction of Vietnam veterans may have had phenoxy herbicide exposures comparable in intensity to members of the occupational cohorts (the NIOSH and IARC cohorts, for example). It is not currently possible to identify this heavily exposed fraction of Vietnam veterans (outside the Ranch Hand and Chemical Corps groups), although the AO committee recommended testing exposure reconstruction methods that might have this capability.

RECONSTRUCTING ESTIMATED EXPOSURE FROM TROOP LOCATION AND HERBICIDESPRAY DATA

Another approach, a more detailed records-based classification scheme, matches troop location data with information on herbicide spraying from the HERBS and Services HERBS tapes to assign exposure categories based on the number of times a unit was within a defined time and distance from a documented herbicide spray. This strategy is similar to reconstructing occupational exposure based on the location of an employee within a plant during different time intervals and estimating the cumulative exposure associated with being in each location and performing specific job activities.

Data on herbicide sprays from the HERBS and Services HERBS tapes can then be matched to information on troop location gathered either from self-reports of locations of military service or from military records. Military records, including morning reports, operational reports, and daily journals have been abstracted by the DoD Environmental Services Group for a subset of Army personnel to determine the location of their military units for a specified period. Once individuals have been identified, information on their period of service can

be verified from military personnel files archived at the National Personnel Records Center in St. Louis, Missouri.

Thus, at least in principle, one should be able to estimate the likelihood of herbicide exposure for a veteran or a military unit that served in Vietnam. This general approach has been tested, and different conclusions have been drawn as to the feasibility and utility of the estimates that result. Like other exposure estimation strategies for retrospective studies, all of these strategies may be valid; however, they vary in their precision and in the degree to which they contribute to assessing a particular exposure-disease association.

Records-Based Measures

The CDC Exposure Opportunity Index

The CDC (Erickson et al., 1984a,b) conducted a case-control study to determine if there was an increased risk of birth defects among the offspring of Vietnam veterans. The potential for an individual Vietnam veteran's exposure to Agent Orange ("exposure opportunity") was estimated by military records specialists of the Army Agent Orange Task Force without knowledge of case or control status. The exposure opportunity index (EOI) scores ranged from a value of I (minimum opportunities for exposure) to a value of 5 (most numerous opportunities for exposure). Higher values signify a greater likelihood of exposure but do not necessarily indicate a higher degree (duration or intensity) of exposure. Table A-1 gives some examples of the EOI.

All individual veterans were given two index scores: one was derived from self-reported information on dates and location of service, and military duties, obtained during the interview; the second was developed based on a review of military records. The records-based EOI used unit location data determined from the Operational Report Lessons Learned. The proximity of these general unit locations was compared to Agent Orange and other herbicide spray data by using the HERBS tapes and other data available on base perimeter sprays to construct the index scores.

Approximately 25 percent of interviewed Vietnam veterans reported that they had been exposed to Agent Orange. Fifty-two percent received the same score in both the index score and the self-reported Agent Orange exposure. A higher proportion of subjects who thought they had been exposed received scores of 4 or 5 than did subjects who thought they had not been exposed.

The EOI developed for this contributed to the 1996 IOM AO committee's finding of limited/suggestive evidence of an association between veterans' exposure to herbicides and the occurrence of the birth defect spina bifida in their offspring; for the highest estimated level of exposure (EOI-5) the odds ratio for spina bifida was 2.7 (CI 1.2–6.2). Neither Vietnam service nor self-reported

herbicide exposure were significantly associated with spina bifida or other birth defects.

The CDC Agent Orange Study

In 1983, the CDC was assigned to conduct a study of the possible long-term health effects of Vietnam veterans' exposure to Agent Orange. The original design of the CDC Agent Orange Study (AOS) attempted to classify veterans' exposure to herbicides that occurred during military service. This was to be accomplished by determining the proximity of troops to Agent Orange spraying using military records to track troop movement and the HERBS tapes to locate herbicide spraying patterns. The original study was to involve three cohorts, each containing approximately 8,500 men.

The DoD Environmental Services Group assisted CDC in the abstraction of military records on troop locations. According to the CDC protocol, 65 battalions were to be selected from III Corps. Herbicide exposure "scores" were calculated at the company level (about 250 men), based on a reported unit location occurring within a specified time and distance from a known herbicide application. Three exposure scores were proposed—short, intermediate, and chronic—to estimate an individual's likelihood of exposure. These scores attempted to account for variations in TCDD half-life, dispersion of herbicides, error in the calculated distances from spray lines, and uncertainties regarding the time between spraying and possible exposure, as well as whether the exposure could be viewed as acute, chronic, or intermediate. The CDC initially concluded that "many veterans were in close enough proximity to applications of Agent Orange to be classified as highly likely to have been exposed to the herbicide," and that there was substantial variability in exposure scores among units and among individual veterans (CDC, 1985).

The abstraction of military records is very labor intensive, and a number of potential problems may arise. Some of the difficulties encountered by the Environmental Services Group during its work for the AOS involved filling in gaps in the daily records of a unit's location, assigning a location to an individual who was not with the unit at the time of the recording, and tracking geographical dispersion among troops within any individual unit. There continues to be disagreement regarding how and whether these problems can be resolved. Some participants in this research estimate, based on a 30-month study period for 35 different Army companies, that the location of company-sized units is available 85–90 percent of the time (Christian, 1992).

TABLE A-1. Examples of Agent Orange Exposure Opportunity Index Scores[a]

Index Score = 1 (minimum opportunities for exposure)

1. Service in selected locations at specific times (any job description except handling Agent Orange), e.g., Cam Ranh Bay (1966), Qui Nhon (1968–1969), Nha Trang (1967–1968)

2. Non-Ranch Hand pilots and aircrew (1966–1967)

3. Specified controlled environments, e.g., battalion surgeon (1968)

Index Score = 2

1. Service in selected locations at specific times, e.g., Gia Le (1969–1970), Phan Rang (other than September–December 1968, March–September 1970), Qui Nhon (1968–1969)

2. Selected noninfantry occupations at specified places and times, e.g., company clerk—Duc Pho (1968–1969), radio repairman—Chu Lai (1966–1967), truck driver—Cu Lam Nam (1968)

3. Noninfantry stationed at selected bases with perimeter spraying, e.g., wireman—Chu Lai (1968–1969)

Index Score = 3

1. Service at bases with perimeter spray operations, specified times, e.g., Chu Lai (1968–1969), Camp Eagle (1968–1969), LZ English (1967–1968)

2. Selected noninfantry occupations at specified locations and times, e.g., salvage specialist—Danang (1969–1970), M.P.—Danang (1968–1969), wheeled vehicle mechanic—Long Binh (1966–1967)

Index Score = 4

1. Infantry/combat arms at specified locations and times, e.g., An Khe (1966–1967), Tam Ky (1967–1968), Tay Ninh (1969–1970)

2. Selected noninfantry at specified locations and times, e.g., Helicopter pilot—Cu Chi (1966–1967), M.P.—Long Binh (1967–1968)

3. Advisors of Army, Republic of Vietnam Divisions (1968–1969)

4. Special Forces Camps (field personnel), e.g., Nha Trang (1969–1970)

Index Score = 5 (most numerous opportunities for exposure)

1. Infantry/combat arms at specified locations and times, e.g., A Shau Valley (1969). Tay Ninh (1968), Phuoc Vinh (1967)

2. Service at specified locations and times with aborted Ranch Hand missions or other herbicide mishaps, e.g., Bien Hoa AFB (July 1967, November 1968), Long Binh Post (1967–1969), Phu Cat AFB (1969–70)

[a] See text for description.
SOURCE: Erickson et al., 1984a.

In January 1986, a Science Panel of the White House Agent Orange Working Group was convened to evaluate the feasibility of the AOS. A subpanel was formed to review the records and information related to exposure assessment. The subpanel concluded that misclassification of an individual's exposure status was serious enough to warrant cancellation of the study. Two issues were specifically noted as influencing the degree of misclassification:

1. Unit dispersion—On a substantial number of days, personnel in combat units eligible for the AOS were not located together as a unit; rather they were dispersed geographically up to 20 km apart on any given day.
2. Incomplete records—An unknown, but apparently large, proportion of fire base perimeter spray operations were never recorded. The degree to which these "unrecorded" operations may have influenced exposure is unknown.

The panel recommended that "any study of ground troops, which is dependent on military records for the assessment of exposure to herbicides, not be conducted *without an additional method to verify exposure*" (emphasis added; Young et al., 1986).

The Stellmans' Study

Drs. Steven and Jeanne Stellman (1986) developed and published a similar but independent method for assessing veterans' exposure to herbicides in 1986. Because they did not have access to military troop location data, they relied on self-reports of locations and dates of service, but used the same HERBS tapes to identify spray missions. Like the CDC, they used these data to derive a series of exposure scores based on geographic and temporal proximity of a soldier to known spray missions. Several probabilistic exposure indices were developed to estimate exposure to herbicides for individual veterans. Three indices provided counts of the number of times a veteran was located within a specified radius 5, 10, or 15 km from a recorded herbicide spray (there were no time restrictions). Three continuous exposure indices accounted for the actual distance from each spray and for concurrent exposures plus potential exposures from residual herbicides from all previous spray missions that occurred nearby (Stellman and Stellman, 1993). Self-reported Agent Orange exposure was also determined based on a number of questions regarding whether subjects had sprayed, loaded, or handled herbicides, or had entered a sprayed area.

To test the method, the Stellmans selected a sample of 478 veterans participating in an outreach program sponsored by the Veterans Education Project of American University (Stellman and Stellman, 1986). They concluded that the approach was feasible and yielded estimates of exposure likelihood that would be useful in epidemiologic studies. Once again, no direct validation of the

estimates was possible, but the indices appeared consistent with other measures or proxies of exposure.

The indices were also applied to an epidemiologic study of various health effects among a sample of 6,810 American Legionnaires (Stellman et al., 1988). Those in the American Legion survey reporting a military occupation likely to involve heavy exposure (e.g., spraying herbicides from a helicopter, or loading or handling herbicides) had a higher mean exposure score than those reporting no direct exposure. Those who reported heavy combat experience were also more likely to have a higher estimated herbicide exposure. Because the exposure score was based on veterans' recall of dates and locations of service, rather than on recall of exposure per se, recall error was probably reduced.

Ranch Hand Exposure Index

The exposure index initially proposed in the Air Force Ranch Hand study relied upon military records of TCDD-containing herbicides (Agents Orange, Purple, Pink, and Green) sprayed as reported in the HERBS tapes for the period after July 1965, and military procurement records and dissemination information for the period prior to July 1965. A TCDD weighting factor (based on the concentration of TCDD in the herbicide and the time of spraying) was applied to the number of gallons of herbicides sprayed during each subject's tour of duty in Vietnam. The dates of each subject's tour(s) in Vietnam were determined by a manual review of military records. The HERBS tapes were used with quarterly operations reports to construct a table of gallons of TCDD-containing herbicides sprayed for each month during the Ranch Hand operation.

The exposure index for a Ranch Hand was defined as the product of the TCDD weighting factor and the number of gallons of TCDD herbicides sprayed during an individual's tour of duty, divided by the number of Ranch Hands sharing such duties during his tour. Each Ranch Hand was placed in an exposure category (high, medium, or low) based on the value of the individual's exposure index. The index included exposure from recorded Ranch Hand sprays only—the measure did not allow for other unrecorded herbicide exposures, such as chemical dumps or perimeter sprays, or other non-Ranch Hand herbicide applications. In 1991, the exposure index was compared to the results of the Ranch Hand serum TCDD analysis. The exposure index and the TCDD body burden were weakly correlated.

More recently, Michalek and colleagues (1995) developed several indices of herbicide exposure for members of the Ranch Hand cohort and tried to relate these to the levels of serum TCDD (see the "Biomarkers" section, below) measured between 1987 and 1992. Self-administered questionnaires completed by veterans of Operation Ranch Hand were used to develop three indices for herbicide or TCDD exposure: the number of days of skin exposure; the

percentage of skin area exposed; and the number of days of skin exposure, times the percentage of skin exposed, times a factor for the concentration of TCDD in the herbicide. A fourth index used no information gathered from individual subjects. It was calculated as the volume of herbicide sprayed during a specific individual's tour of duty, times the concentration of TCDD in herbicides sprayed in that period, divided by the number of crew members at that time in each job specialty.

Each of the four models tested was significantly related to the serum TCDD level, although each explained only between 19 and 27 percent of the variability in serum TCDD. Days of skin exposure had the highest correlation. Military job classification (non-Ranch Hand combat troops, Ranch Hand administrators, Ranch Hand flight engineers, and Ranch Hand ground crew), which is separate from the four indices, explained 60 percent of the variance in serum TCDD concentrations. When the questionnaire-derived indices were applied within each job classification, days of skin exposure added significantly, but not substantially, to the variability explained by job alone.

Biomarkers of Exposure in Vietnam

Biomarkers for TCDD

TCDD and other chlorinated dibenzo-*p*-dioxins and dibenzofurans are found in tissues of non-occupationally exposed humans at part-per-trillion (nanogram-per-kilogram) levels. Following absorption, TCDD is distributed to tissues with high lipid content. Adipose tissue appears to be the main site of accumulation, although TCDD has been found in all tissue samples that have been examined from autopsy (Ryan et al., 1986).

Although exposure to TCDD from environmental sources, primarily food (Geyer et al., 1986; Byard, 1987), occurs on a continuing basis, both serum and fat biopsy samples taken from individuals with unusually high exposures indicate that TCDD may remain in the body for many years after exposure. For example, fat biopsy samples taken from three Vietnam veterans believed to have been exposed through herbicide use showed levels of TCDD up to 99 ppt approximately 10 years after the exposure occurred. By comparison, veterans with no unusual herbicide exposure had TCDD levels between 3 and 15 ppt (Gross et al., 1984). A number of other studies, including the Ranch Hand half-life study, the Missouri civilian study, and the NIOSH study, suggest that current serum TCDD levels are useful for distinguishing between groups of individuals that were exposed to TCDD 15 to 20 years ago (CDC, 1989a). For example, Sweeney and colleagues (1990) measured TCDD levels in serum lipids of 143 workers at two chemical plants in New Jersey and Missouri. The median TCDD level in a group of 103 production workers at the New Jersey plant was 84 ppt compared to 11 ppt for a group of 8 office workers. A study in which both

serum and fat TCDD levels were compared in 50 individuals showed a very high correlation between the two, suggesting that TCDD levels in serum provide a valid measure of TCDD levels in the body (Patterson et al., 1988). The Pointman Project (Kahn et al., 1988), conducted by the New Jersey Agent Orange Commission, confirmed this result.

The pharmacokinetics of TCDD in humans—its distribution and passage through the body—are not fully understood, which makes individual serum TCDD levels difficult to interpret and also complicates the interpretation of epidemiologic studies relying on these measures of exposure. A complex, poorly understood process distributes dioxins among body tissues and slowly clears it from the body. There is evidence that this process is quite variable among humans, so it is difficult to model its behavior and thereby extrapolate backward to estimate the likely concentration of TCDD in fat or blood in the past. It is also often assumed that TCDD is removed from the body according to first-order kinetics—that is, for a given period of time, a constant fraction of the TCDD body burden is eliminated—but some evidence suggests the process may be more complicated and may vary as conditions in the body change. Furthermore, the metabolic processes governing this movement and disposition may not be relevant to the determination of the dose of TCDD to the brain or reproductive organs, for example. In the epidemiologist's view, the "causal pathways" linking exposure to the biomarker (serum or fat TCDD) may be different from that linking exposure to disease.

By measuring TCDD levels in 1982 and 1987 from serum samples of 36 Ranch Hand veterans, the median half-life of TCDD in humans was estimated to be 7.1 years, adjusted for background TCDD levels (with a 95 percent confidence interval of 5.8 to 9.6 years) (Pirkle et al., 1989). In this study, the background exposure level of TCDD in serum was taken to be 4 ppt on the basis of data from the Agent Orange Validation Study. Background levels appear to be log-normally distributed and to increase with age (Sielken, 1987). An expanded study of 337 Ranch Hand veterans, including the 36 from the previous study, estimated a median half-life between 11.5 and 12 years. The analytical measurement error (coefficient of variation) in these studies was about 22 percent (Pirkle et al., 1989). These data suggest that the half-life of TCDD is independent of its initial serum concentration, thereby supporting a first-order kinetics process for TCDD elimination.

The Air Force-CDC study was further extended with an additional 5 years of follow-up for 213 of the subjects (Michalek et al., 1995). Excluded from study were about 23 percent of the population who had serum TCDD levels below a set level, in order to avoid a biased estimate of decay rate because of serum levels that approach the background level. Using a repeated-measures regression analysis, the investigators estimated a mean half-life of 8.7 years, with a 95 percent confidence interval around the mean half-life that ranged from 8.0 to 9.5 years. However, half-life was found to increase with increasing body fat, and the

mean half-life does not address individual variability in half-life that would derive from differences in body fat among an exposed population. For example, for a high but plausible percent body fat (35 percent), the predicted mean half-life is about 20 years, while for a low percent body fat (15 percent), the predicted mean half-life is about 7 years.

Other recently published studies find similar mean serum TCDD half-life estimates. A study of 27 persons exposed during a 1976 TCDD release in Seveso, Italy, and followed for 15.9 years yielded a half-life estimate of 8.2 years (Needham et al., 1994). A study of 48 German workers in a plant producing herbicides showed a half-life of 10.3 years (Flesch-Janys et al., 1994). In this case, however, the time between the first and last analysis was only 6.3 years. These studies did not investigate possible heterogeneity in half-life due to such variables as body fat. A later paper by Flesch-Janys and colleagues (1996)—which examined the same cohort as the 1994 study—reported a median half-life of 7.2 years and noted that increasing age and percent body fat were associated with increasing half-life.

Variations in TCDD half-life estimates are likely to result from changes in weight and percent body fat, such as those that normally occur with aging. For example, an average 5 foot 10 inch male aged 20–24 years weighs approximately 70 kg, of which 15 to 18 percent is fat. If at age 40–49, this male weighs approximately 80 kg, fat content may almost double. Thus, there may be an expected reduction in serum TCDD levels in Vietnam veterans just from the mechanisms of change in body composition with age (Albanese, 1991). It is therefore possible that a small or moderate intake of dioxin among Vietnam veterans may no longer be detectable by using current serum TCDD level as a biomarker (Schlatter, 1991).

Still other confounding factors may complicate exposure assessment. In a study of 640 Vietnam veterans, researchers found that serum TCDD levels varied with several personal characteristics, including age, race, body mass, and region of residence (Devine et al., 1990). It has also been suggested that disease may affect serum TCDD levels (Michalek and Tripathi, 1992). Flanders and colleagues (1992) have shown, for instance, that reverse causality, in which health outcomes affect the measured serum TCDD level years after exposure, can better explain some relationships between serum TCDD and health outcomes in the Ranch Hand study than a direct model in which TCDD causes the outcome.

Based on these data, the AO committee concluded that serum TCDD measures are helpful in epidemiologic studies, but should not be taken as a "gold standard" of exposure. If there are *group* differences in serum TCDD levels, that probably does indicate a difference in exposure to TCDD between the two groups. However, even if there is a difference in TCDD exposure between two groups, it may disappear as subsequent serum levels fade to background levels with the passage of time between exposure and measurement. In particular,

because of poorly understood variation among individuals in TCDD metabolism and analytic uncertainty of the analysis, *individual* TCDD levels are usually not meaningful. It should be noted that the per-individual cost of determining serum TCDD concentrations is high for the number of individuals typically sampled in epidemiologic studies. For the studies described in this section, CDC charged around $1,000 per sample.

Although quantitative measures of exposure are highly desirable, it may still be quite valid to use approximate measures of exposures or even surrogates such as the amount of time spent in a military occupation or location in which the toxin was likely to have been used. Thus a biomarker, especially one gathered years after exposure, is not necessarily better than qualitative exposure measures based on spraying records. Group differences in serum TCDD levels can be useful in confirming that occupational exposure measures reflect true differences in exposure, as has been done in the NIOSH study (Fingerhut et al., 1989, 1991; Sweeney et al., 1990) and other studies (see below).

Bearing in mind the limitation of current serum TCDD levels in Vietnam veterans, the AO committee concluded that, with the exception of measured levels in Ranch Hand veterans, exposure to TCDD in Vietnam was substantially less, on average, than that of occupationally exposed workers or of persons exposed as a result of the industrial explosion in Seveso, Italy. The measures are summarized in Figure A-4.

Other Dioxin Congeners

In addition to 2,3,7,8-TCDD, other congeners of dioxin and dibenzofuran contaminated the herbicides sprayed in Vietnam as well as the products used and manufactured by the occupational cohorts whose health experience forms the basis for many of the AO committee's conclusions. Because these may contribute to cancer risk, "dioxin toxic-equivalent factors" (Teq factors) have been estimated for the various other congeners of dioxin and dibenzofuran (U.S. EPA, 1989). A Teq factor for each dioxin or furan congener is estimated by comparing its toxicity to that of 2,3,7,8-TCDD, which is arbitrarily assigned a Teq factor of 1.0. Other congeners have lower Teq factors, some as much as 1,000 times lower. In principle, it is possible to measure each congener and calculate a toxic equivalent for the entire mixture, but this is costly. Most studies of dioxin-exposed individuals have related health effects only to TCDD levels and have not considered the other associated dioxins or furans.

The use of 2,3,7,8-TCDD alone as a measure of risk when exposure includes many congeners must be considered cautiously. Different sources of dioxin contamination may have different distributions of congeners. Also, the stability of the different congeners in the environment differs, so that human exposures occurring long after spraying may differ from those at the time of spraying. Finally, the half-lives of the different congeners in the body differ, so that an

exposed individual will have different and varying patterns of exposure to each congener over time.

The degree to which these differences may be of importance is seen in some measured distributions of the various congeners in human tissue. While having lower Teq factors, some of the other dioxins or furans may be present in the body at concentrations hundreds of times greater than TCDD. For example, in a study by Verger et al. (1994) of dioxin levels in adipose tissue of Vietnamese civilians, the geometric mean concentration of TCDD was 7.8 ppt, that of 2,3,7,8-dibenzofuran was 1.7 ppt, and those of other congeners of dioxin ranged up to 384 ppt. By explicitly considering Teqs, Schecter et al. (1995) have shown that the total potential toxicities of all dioxins and furans measured in pooled serum samples of 433 southern, 183 central, and 82 northern Vietnamese civilians during 1991 and 1992 were, respectively, 2.4, 3.8, and 7.0 times the potential toxicity of TCDD alone. Other studies provide similar data (Schecter, 1994). Such Teq studies of Vietnam veterans and occupational cohorts would be valuable.

In summary, the magnitude of the effect of other congeners may be large and may vary among exposure settings. While it is probably not feasible to conduct a total congener analysis in every study, the use of TCDD measurements alone may represent an oversimplification of the full exposure picture.

Chloracne as a Biomarker

There is strong evidence indicating that chloracne develops in at least some individuals heavily exposed to TCDD. Some researchers have used chloracne as a clinical marker of TCDD exposure. As a biomarker, however, chloracne has several serious drawbacks.

Numerous studies of heavily exposed individuals have demonstrated that chloracne is neither a specific nor an exclusive indicator of TCDD exposure at the individual level (Suskind and Hertzberg, 1984; Bond et al., 1989; Zober et al., 1990; Mocarelli et al., 1991). Individual susceptibility to the activity of TCDD seems to vary, especially with respect to the seriousness of the manifestation (Del Como et al., 1985). In Seveso, Italy, for instance, after the TCDD release in 1976, approximately half of the adults with the highest serum TCDD levels developed chloracne whereas the other half did not. Some of the individuals who did not develop chloracne had serum TCDD levels higher than those who did (Mocarelli et al., 1991). There are other causes of chloracne and chloracne-like conditions besides TCDD, so its presence does not indicate certain exposure. The etiology of chloracne can be attributed to a rather wide range of chemical compounds, and lesions mimicking chloracne, such as acne vulgaris, may also appear in subjects who have not been exposed to TCDD.

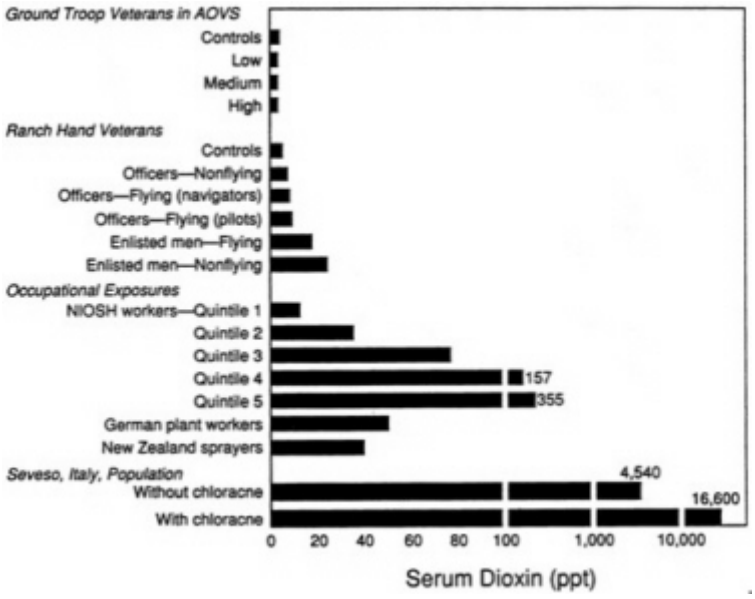

Figure A-4.
Median serum dioxin levels in selected populations. Reprinted in IOM 1994 with permission from Pirkle, 1993.

Although chloracne has been used in epidemiologic studies as a biomarker for TCDD exposure, the data indicate that it is neither a sensitive nor exclusive indicator. It is usually not long lasting, is difficult to diagnose, and is not at all sensitive to exposure to herbicides that are not contaminated with TCDD.

CDC Agent Orange Validation Study

To test the validity of several indirect methods for estimating exposure of ground troops to Agent Orange in Vietnam, in 1987 the CDC measured serum TCDD levels in a nonrandom sample of Vietnam veterans and Vietnam-era veterans who did not serve in Vietnam (CDC, 1988b). Participants were chosen from a pool of 65 Army battalions that operated 18 months or longer in III Corps, a heavily sprayed region around Saigon, during 1967 and 1968. Men in the Vietnam cohort were chosen from among those who had served in a unit for which the ESG had locational data (as determined for the Agent Orange Study). Vietnam veterans were selected for further study based on their estimated Agent Orange exposure; the "low" exposure group included 298 veterans, the

"medium" exposure group included 157 veterans, and included 191 veterans in the "high" exposure group. Blood samples were obtained from 66 percent of Vietnam veterans (n = 646) and 49 percent of the eligible comparison group of veterans (n = 97). Five indirect exposure scores based on military records and two scores based on self-reports were used to rank veterans according to their likelihood of exposure to Agent Orange. The median TCDD level in Vietnam veterans was 4 ppt, with a range from less than 1 to 45 ppt and two having levels greater than 20 ppt; the distributions of these measurements were nearly identical to those for the control group of 97 non-Vietnam veterans (Figure A-5). None of the records-derived estimates of exposure, and neither type of self-reported exposure to herbicides, identified Vietnam veterans who were likely to have currently elevated serum TCDD levels (CDC, 1988b). The study concluded it is unlikely that military records can be used to identify a large number of U.S. Army veterans who might have been heavily exposed to TCDD in Vietnam.

A draft of the Agent Orange Validation Study was reviewed by an IOM committee in 1987 (IOM, 1987). The committee raised the concern that current serum levels (for this study, obtained in 1987) may not be related to an actual exposure that occurred some 20 years previously. Four possible scenarios for observing "background" levels in three hypothetical groups of Vietnam veterans (high, medium, and low exposure) who served in Vietnam in 1967 were suggested: (1) All three veteran groups in the study could have been similarly exposed during the war, but their levels were not sufficiently high in the late 1960s to prevent them from decaying to background level in 1987. (2) All three exposed veteran groups could have had significantly higher blood levels than background before they were potentially exposed in Vietnam, but with the passage of time, all TCDD concentrations had decayed to similar levels. (3) The three groups could have been differentially exposed in Vietnam, and if their serum had been sampled then, variation in TCDD levels would have been detected. However, differences in decay rates and initial concentrations could result in all demonstrating current levels at background. (4) None of the veterans ever had serum TCDD concentrations above background.

Without adequate knowledge of the decay rate and pharmacokinetics of TCDD in humans, it is not possible to distinguish among these alternative explanations. If initial concentrations of TCDD differed but then over the years fell to background levels, estimates based on reconstruction of troop locations and herbicide spraying activities might be more reliable indicators of exposure than current serum TCDD levels.

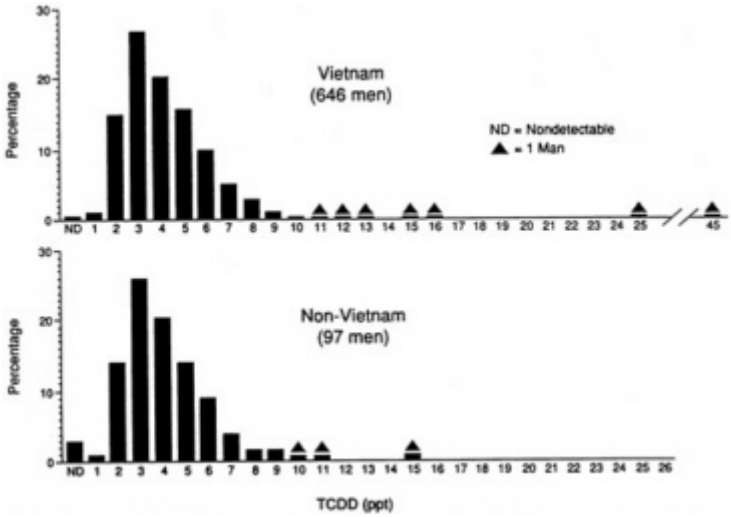

Figure A-5.
Distribution of serum dioxin levels in Vietnam veterans and non-Vietnam (Vietnam era) veterans. SOURCE: Agent Orange Validation Study (CDC, 1989 a). Reprinted in IOM, 1994, with permission.

CONCLUSIONS AND RECOMMENDATIONS

As the AO committee's review of the literature indicates, exposure assessment has been a weak aspect of epidemiologic studies of Vietnam veterans. Different approaches have been used in estimating the exposure of Vietnam veterans, and these studies generally rely on self-reported exposures, records-based exposure estimates, or biomarkers of TCDD exposure. Each of these approaches is limited in its ability to determine precisely the degree of individual exposure. Some studies rely on gross markers such as service in Vietnam, perhaps enhanced by branch of service, military region, military specialty, or exposure to combat as proxies for exposure to herbicides. This approach almost surely dilutes whatever health effects of herbicides exist. At the other extreme, some studies rely on fine details of military records on troop movements and herbicide spraying, perhaps combined with self-reported retrospective data, for individuals or small units on a daily basis. The Stellmans' study and the proposed but not completed CDC AOS are examples of this sort. Even though measures of this type may be accurate for many individuals, such

fine detail *may* exceed the accuracy of a record system not designed for this purpose, and the accuracy of the resulting exposure measure cannot be guaranteed for all potential subjects.

Serum TCDD measurements are difficult to interpret with current knowledge, yet they may provide valuable information in some situations. They are most useful in defining differences in exposure levels among groups rather than among individuals, and particularly between more highly exposed groups and less exposed or unexposed groups. The groups must be of sufficient size to provide the statistical power to make meaningful assessments. In general, group differences in serum levels are likely to be reflective of differences in true past exposure to TCDD, but the failure to detect mean differences does not necessarily indicate that there were no differences in past exposure.

Oral and written testimony presented before the AO committee suggests that substantial numbers of veterans were exposed to Agent Orange and other herbicides. Results from a survey of U.S. military officers in Vietnam, across all branches of service (Army battalion commanders and advisors, Navy personnel and advisors involved in riverine operations, Air Force Ranch Hand personnel, chemical officers, Marine ground and air personnel, and advisors) indicated the utility of herbicides to their military operations. In addition, surveys of veterans indicate that 25 to 55 percent believe they were exposed to herbicides while serving in Vietnam (Erickson et al., 1984a,b; Stellman and Stellman, 1986; CDC, 1989b). It appears that groups of veterans, other than those involved in Operation Ranch Hand, were likely to have been exposed to herbicides during their service in Vietnam.

It is clear that the military use of herbicides in Vietnam was not uniform either spatially or temporally, and that the movement and behavior of troops also varied, so one cannot assume that all troops were equally exposed to herbicides. In the IOM AO committee's judgment, a sufficiently large range of exposures may exist among Vietnam veterans to conduct a valid epidemiologic study for certain health outcomes. The difficulty (from the perspective of epidemiologic studies) is that the available data do not precisely quantify individual exposure. None of the measures that the AO committee has reviewed would be free of nondifferential misclassification bias. The result of this bias on risk estimates would likely be to underestimate true effects if they existed, possibly to such an extent that these effects could be missed entirely by future studies.

The AO committee believed that it might be possible to develop a valid exposure reconstruction model for epidemiologic studies based on existing records and structured interview data. Such a model would estimate the likelihood that each individual veteran was exposed to herbicides in Vietnam and could possibly quantify the likely degree of exposure. This model would incorporate information in existing military records about herbicide spraying (the HERBS and Services HERBS tapes) and troop movements. It would also include less formal sources of information on ground and perimeter spraying

from records of herbicide shipments to various military bases, and would consider the type of terrain, typical foliage of the locations, and military mission of the bases and troops located there. Surveys and interviews of Vietnam veterans, stratified by location and period of service, might also provide useful information on situations in which herbicide spraying was prevalent and, if validated, may be incorporated into the exposure reconstruction model.

Development of the Exposure Reconstruction Model

As conceptualized by the AO committee, this new effort would model the conditions under which herbicides were used in Vietnam and would consider the following information:

1. *troop location*—based on all available military records, including morning reports, daily journals, situation reports, intelligence summaries, Operational Report Lessons Learned, and combat operations after-action reports;
2. *aerial spray mission data*—from the HERBS and Services HERBS tapes;
3. *estimated ground spraying activity*—not based solely on existing records (discussed in more detail below);
4. *estimated exposure opportunity factors*—including the identification of occupations involving the handling of herbicides, and considerations of how likely troops were to have heavier exposure through eating local food, bathing or drinking local water, contact with contaminated soil, and so on.;
5. *military indications for herbicide use*—systematic, historic reviews of the conditions under which military use of herbicides was warranted, including information on typical use patterns in those situations such as the Army survey of military commanders conducted in 1971 (U.S. Army, 1972); and.
6. *considerations of the composition and environmental fate of herbicides* —including changes in the TCDD content of herbicides over time, the persistence of TCDD and herbicides in the environment, and the degree of likely penetration of the herbicides into the ground.

Once an exposure reconstruction model has been developed, it should be possible to estimate an exposure score for the large numbers of veterans needed for epidemiologic studies.

Ground spraying, although probably representing a smaller quantity of herbicide than aerial spraying, may actually have resulted in heavier human exposures since it probably was done in closer proximity to ground troops, at higher application rates (i.e., number of gallons per acre), and potentially by less well-trained individuals than Ranch Hand spraying. This spraying was often performed around camp perimeters and along communication routes in response

to enemy attack or during relocation to a new fire base. Thus, troops may often have remained in the area during spraying or passed through it soon afterward. Ground spraying could reportedly be approved by unit commanders at the Corps level, and the spraying does not appear to have been documented as carefully as the aerial missions of Air Force Ranch Hands. To incorporate estimates of exposure from ground spraying, the AO committee suggested the development of a subsidiary estimation model for this source of exposure. Because ground spraying data are incomplete, this model would be based on a series of factors likely to determine the extent of ground spraying in Vietnam. From testimony presented to the AO committee, it appears that the following factors might have been important determinants of this activity: region and date of military service, terrain, type of vegetation, intensity of enemy activity, any existing data on shipment of herbicides to different regions, and size of military base. Through structured interviews with military personnel who served in various regions and various military units, data would be gathered to permit the development of a model predicting the likelihood and intensity of ground spraying around base perimeters, fire camps, and along roads for different areas and times. A partial check on the utility of this model could be accomplished by comparing its predictions to the limited ground spraying data that do exist in the Services HERBS tapes. This proposal incorporates ideas for exposure reconstruction previously described by others (Bricker, 1981; Erickson et al., 1984a; Stanton, 1989; Lewis, 1993).

Evaluation of the Exposure Reconstruction Model

The overall exposure reconstruction model could be evaluated in several ways. First, model developers would determine whether the data used in the exposure reconstruction model are internally consistent. This involves checking whether existing spraying records indicate more spraying in areas where it was likely to have been militarily useful from the point of view of terrain, foliage, and military mission. It would also be possible to cross-check the estimated spraying intensity data with a systematic survey of the recollections of veterans who served in particular areas.

In a second method of evaluation, exposure estimates based on the reconstruction model would be compared with serum TCDD measurements for a random sample of veterans, stratified according to records-based measures. Although the AO committee concluded that group differences can be useful in confirming that exposure measures reflect the differences in prior exposure, the absence of group differences cannot be interpreted to indicate that groups were not exposed earlier. Serum TCDD measurements should not, therefore, be regarded as a gold standard—a perfect measure of herbicide exposure. In addition to the problems with interpreting serum TCDD measures discussed

above, some of the herbicides used in Vietnam, such as Agent White, did not contain TCDD, so it is possible for a veteran to have been exposed to a large amount of Agent White without having an elevated serum TCDD level at any time.

A third evaluation of the exposure estimation strategy would be to assess the association between the exposure reconstruction estimates and the incidence of health outcomes that are believed to be associated with herbicides. One would expect a positive association between the exposure reconstruction measure and those outcomes found by the AO committee to have sufficient evidence for a statistical association. Because there are sufficient data from occupational studies to suggest an association between herbicides and/or TCDD and non-Hodgkin's lymphoma, one would expect to see a positive association between this cancer and the new exposure reconstruction model data. It might be possible to reanalyze the CDC Selected Cancers Study (CDC, 1990) data, for instance, with data from the proposed exposure reconstruction model rather than with the simple exposure measures that were used in the original study. If such an association were found, it could be interpreted as positive evidence for the validity of the new exposure model. If no association were found, it would not be clear whether this was due to problems in the new exposure measure, to small sample sizes or low average herbicide exposure even in those exposed, or to the lack of a real association between herbicides and non-Hodgkin's lymphoma.

The task of exposure estimation for a diffuse class of agents to which up to 3 million persons may have been exposed nearly 30 years ago in wartime is inherently difficult. The AO committee recommended that any exposure reconstruction model be thoroughly evaluated before it is used in epidemiologic studies. Because of the complexity of this task, and the political sensitivity of any studies of Vietnam veterans, the AO committee further recommended that this evaluation be conducted by an independent, nongovernmental scientific panel with expertise in historic exposure reconstruction and epidemiology.

REFERENCES

Air Force Health Study (AFHS). 1991. An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides. Serum Dioxin Analysis of 1987 Examination Results. Brooks AFB, TX: USAF School of Aerospace Medicine.

Albanese RA. 1991. The chemical 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and U.S. Army Vietnam-era veterans. Chemosphere 22:597–603.

Axelson O, Westberg H, eds. 1992. First seminar on occupational exposure assessment: on the concepts of exposure and dose. American Journal of Industrial Medicine 21:1–132.

Blair A, Stewart P. 1992. Do quantitative exposure assessments improve risk estimates in occupational studies of cancer? American Journal of Industrial Medicine 21:53–63.

Bond GG, Bodner KM, Olsen, GW, Burchfiel CM, Cook RR. 1991. Validation of work histories for the purpose of epidemiological studies. Applied Occupational and Environmental Hygiene 6:521–527.

Bond GG, McLaren EA, Brenner FE, Cook RR. 1989. Incidence of chloracne among chemical workers potentially exposed to chlorinated dioxins. Journal of Occupational Medicine 31:771–774.

Bricker JG. 1981. Proposed Agent Orange Troop Exposure and Non-Exposure Cohort Selection Concept Paper. Memorandum to the Chairman, AOWG Science Panel. December 4, 1981. Washington, DC: Office of the Assistant Secretary of Defense, Health Affairs.

Buckingham WA. 1982. Operation Ranch Hand: The Air Force and Herbicides in Southeast Asia 1961–1971. Washington, DC: U.S. Air Force Office of Air Force History.

Byard JL. 1987. The toxicological significance of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and related compounds in human adipose tissue. Journal of Toxicology and Environmental Health 22:381–403.

Card JJ. 1983. Lives After Vietnam: The Personal Impact of Military Service. Toronto: Lexington Books.

Centers for Disease Control (CDC). 1985. Agent Orange Projects Interim Report Number 2: Exposure Assessment for the Agent Orange Study. Atlanta: CDC, Center for Environmental Health, Division of Chronic Disease Control, Agent Orange Projects .

CDC. 1988. Serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin levels in U.S. Army Vietnam-era veterans. The Centers for Disease Control Veterans Health Studies [see comments]. Journal of the American Medical Association 260:1249–1254.

CDC. 1989a. Health Status of Vietnam Veterans. Vietnam Experience Study. Vols. I–V, Supplements A–C. Atlanta: U.S. Department of Health and Human Services.

CDC. 1989b. Health Status of Vietnam Veterans. Vietnam Experience Study. Vols. I–V, Supplements A–C. Atlanta: U.S. Department of Health and Human Services.

CDC. 1990. The association of selected cancers with service in the U.S. military in Vietnam. 1. Non-Hodgkin's lymphoma. Archives of Internal Medicine 150:2473–2492.

Christian R. 1992. Records-Based Measures of Exposure to Herbicides in Vietnam Veterans. Statement to the Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. December 8, 1992.

Collins CV. 1967. Herbicide Operations in Southeast Asia, July 1961–June 1967. San Francisco: Headquarters, Pacific Air Forces. NTIS AD-779 796.

Dalager NA, Kang, HK. 1995. Mortality among chemical operations personnel who served in Vietnam (abstract). December 1995 American Public Health Association Annual Meeting , San Diego, CA.

Dashiell TR. Office of the Director of Defense Research and Engineering. 1973. Comments to Dr. Peter Kunstadter's Comparison of HERBS and 202 Records. Memorandum to Dr. Philip Ross, National Academy of Sciences. July 11, 1973.

Del Corno G, Montesarchio E, Fara GM. 1985. Problems in the assessment of human exposure to tetrachlorodibenzodioxin (TCDD): the marker chloracne. European Journal of Epidemiology 1: 139–144.

Dement JM, Harris RL, Symons MJ, Shy CM. 1983. Exposures and mortality among chrysotile asbestos workers. Part II, Mortality. American Journal of Industrial Medicine 4:421–433.

Devine OJ, Karon JM, Flanders WD, Needham LL, Patterson DG Jr. 1990. Relationships between concentrations of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin serum and personal characteristics in U.S. Army Vietnam veterans. Chemosphere 20:681–691.

Dux J, Young PJ. 1980. Agent Orange: The Bitter Harvest. Sydney: Hodder and Stoughton.

Erickson JD, Mulinare J, McClain PW. 1984a. Vietnam veterans' risks for fathering babies with birth defects. Journal of the American Medical Association 252:903–912.

Erickson JD, Mulinare J, McClain PW, Fitch TG, James LM, McClearn AB, Adams MJ. 1984b. Vietnam Veterans' Risks for Fathering Babies with Birth Defects. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control.

Fingerhut MA, Halperin WE, Marlow DA, Piacitelli LA, Honchar PA, Sweeney MH, Greife AL, Dill PA, Steenland K, Suruda AJ. 1991. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. New England Journal of Medicine 324:212–218.

Fingerhut MA, Sweeney MH, Patterson DG Jr., Piacitelli LA, Morris JA, Marlow DA, Hornung RW, Cameron LW, Connally LB, Needham LL, Halperin WE. 1989. Levels of 2,3,7,8-TCDD in the serum of U.S. chemical workers exposed to dioxin contaminated products: Interim results. Chemosphere 19:835–840.

Fischer V, Boyle JM, Bucuvalas M. 1980. Myths and Realities: A Study of Attitudes Toward Vietnam-Era Veterans. Submitted by the Veterans' Administration to the Committee on Veterans' Affairs, U.S. House of Representatives. House Committee Print No. 89.

Flanders WD, Lin L, Pirkle JL, Caudill SP. 1992. Assessing the direction of causality in cross-sectional studies. American Journal of Epidemiology 135:926–935.

Flesch-Janys D, Becher H, Gum P, Jung D, Konietzko J, Manz A, Päpke O. 1996. Elimination of polychlorinated dibenzo-*p*-dioxins and dibenzofurans in occupationally exposed persons. Journal of Toxicology and Environmental Health 47:363–378.

Flesch-Janys D, Gum P, Jung D, Konietzko J, Päpke O. 1994. First results of an investigation of the elimination of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/F) in occupationally exposed persons. Organohalogen Compounds 21:93–99.

Gamble J, Spirtas R. 1976. Job classification and utilization of complete work histories in occupational epidemiology. Journal of Occupational Medicine 18:399–404.

Geyer H, Scheunert I, Korte F. 1986. Bioconcentration potential of organic environmental chemicals in humans. Regulatory Toxicology and Pharmacology 6:313–347.

Gross ML, Lay JO, Lippstreu D, Lyon PA, Kangas N, Harless RL, Taylor SE. 1984. 2,3,7,8-tetrachlorodibenzo-*p*-dioxin levels in adipose tissue of Vietnam veterans. Environmental Research 33:261.

Huddle FP. 1969. A Technology Assessment of the Vietnam Defoliant Matter. Report to the Subcommittee on Science, Research, and Development of the Committee on Science and Astronautics, U.S. House of Representatives. 91st Cong., 1st Sess. August 8, 1969.

Institute of Medicine (IOM), Advisory Committee on the CDC Study of the Health of Vietnam Veterans. 1987. Review of Comparison of Serum Levels of 2,3,7,8-TCDD with Indirect Estimates of Agent Orange Exposure in Vietnam Veterans. Fifth Letter Report. Washington, DC: IOM.

IOM. 1994. Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam. Washington, DC: National Academy Press.

IOM. 1996. Veterans and Agent Orange: Update 1996. Washington, DC: National Academy Press.

Irish KR, Darrow RA, Minarik CE. 1969. Information Manual for Vegetation Control in Southeast Asia. Misc. Publication 33. Fort Detrick, MD: Department of the Army, Plant Sciences Laboratories, Plant Physiology Division. NTIS AD-864-443.

Kahn PC, Gochfeld M, Nygren M, Hansson M, Rappe C, Velez H, Ghent-Guenther T, Wilson WP. 1988. Dioxins and dibenzofurans in blood and adipose tissue of Agent Orange-exposed Vietnam veterans and matched controls. Journal of the American Medical Association 259:1661–1667.

Karnow S. 1991. Vietnam: A History. New York: Penguin.

Kauppinen TP, Pannett B, Marlow DA, Kogevinas M. 1994. Retrospective assessment of exposure through modeling in a study on cancer risks among

workers exposed to phenoxy herbicides, chlorophenols and dioxins. Scandinavian Journal of Work, Environment, and Health 20:262–271.

Kogevinas M, Kauppinen T, Winkelmann R, Becher H, Bertazzi PA, Bueno de Mesquita HB, Coggon D, Green L, Johnson E, Littorin M, Lynge E, Marlow DA, Mathews JD, Neuberger M, Benn T, Pannett B, Pearce N, Saracci R. 1995. Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-control studies. Epidemiology 6:396–402.

Kriebel D, Sprince N, Eisen E, Greaves I. 1988a. Pulmonary function in beryllium workers: assessment of exposure. British Journal of Industrial Medicine 45:83–92.

Kriebel D, Sprince N, Eisen E, Greaves I, Feldman H, Greene R. 1988b. Beryllium exposure and pulmonary function: a cross-sectional study of beryllium workers. British Journal of Industrial Medicine 45:167–173.

Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jordan BK, Marmar CR, Weiss DS. 1988. Contractual Report of Findings from the National Vietnam Veterans Readjustment Study. Research Triangle Park, NC: Research Triangle Institute.

Lewis W. 1993. The Vietnam Experience. Presentation to the Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. February 8, 1993.

Martin R. 1986. Who went to war. In: Boulanger G, Kadushin C, eds. The Vietnam Veteran Redefined: Fact and Fiction. Hillsdale, NJ: Lawrence Erlbaum.

Michalek JE, Pirkle JL, Caudill SP, Tripathi RC, Patterson G, Needham LL. 1995. Pharmacokinetics of TCDD in veterans of Operation Ranch Hand: 10-year follow-up. Journal of Toxicology and Environmental Health 47(3):209–220.

Michalek JE, Tripathi RC. 1992. Predicting Checkmark Patterns in the Air Force Health Study. Brooks AFB, TX: Armstrong Laboratory.

Michalek JE, Wolfe WH, Miner JC, Papa TM, Pirkle JL. 1995. Indices of TCDD exposure and TCDD body burden in veterans of Operation Ranch Hand. Journal of Exposure Analysis and Environmental Epidemiology, 5:209–223.

Midwest Research Institute (MRI). 1967. Assessment of Ecological Effects of Extensive or Repeated Use of Herbicides. MRI Project No. 3103-B. Kansas City, MO: MRI. NTIS AD-824-314.

Military Assistance Command, Vietnam (MACV). 1968. The Herbicide Policy Review. Report for March–May 1968. APO San Francisco: MACV. NTIS AD-779-794/7.

Mocarelli P, Needham LL, Marocchi A, Patterson DG Jr., Brambilla P, Gerthoux PM, Meazza L, Carreri V. 1991. Serum concentrations of 2,3,7,8-

tetrachlorodibenzo-*p*-dioxin and test results from selected residents of Seveso, Italy. Journal of Toxicology and Environmental Health 32:357–366.

Moskos CC Jr. 1975. The American combat soldier in Vietnam. Journal of Social Issues 31:25–37.

National Academy of Sciences. 1974. The Effects of Herbicides in South Vietnam. Washington, DC: National Academy Press.

Needham LL, Gerthoux PM, Patterson DG, Brambilla P, Pirkle JL, Tramacere PI, Turner WE, Beretta C, Sampson EJ, Mocarelli P. 1994. Half-life of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in serum of Seveso adults: interim report. Organohalogen Compounds 21:81–85.

Ott MG, Messerer P, Zober A. 1993. Assessment of past occupational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin using blood lipid analyses. International Archives of Occupational and Environmental Health 65:1–8.

Patterson DG Jr., Needham LL, Pirkle JL, Roberts DW, Bagby J, Garrett WA, Andrews JS Jr., Falk H, Bernert JT, Sampson EJ, Houk VN. 1988. Correlation between serum and adipose tissue levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in 50 persons from Missouri. Archives of Environmental Contamination and Toxicology 17:139–143.

Pirkle, JL. 1993. Document submitted to the Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. April 14.

Pirkle JL, Wolfe WH, Patterson DG, Needham LL, Michalek JE, Miner JC, Peterson MR, Phillips DL. 1989. Estimates of the half-life of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in Vietnam veterans of Operation Ranch Hand. Journal of Toxicology and Environmental Health 27:165–171.

Rappaport SM, Smith TJ, eds. 1991. Exposure Assessment for Epidemiology and Hazard Control. Chelsea, MI: Lewis Publishers.

Rice C. 1991. Retrospective exposure assessment: a review of approaches and directions for the future . In: Rappaport SM, Smith TJ, eds. Exposure Assessment for Epidemiology and Hazard Control. Chelsea, MI: Lewis Publishers. Pp. 185–198.

Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ. 1987. Benzene and leukemia: an epidemiologic risk assessment. New England Journal of Medicine 316:1044–1050.

Ryan JJ, Schecter A, Sun W-F, Lizotte R. 1986. Distribution of chlorinated dibenzo-*p*-dioxins and chlorinated dibenzofurans in human tissues from the general population. In: Rappe C, Choudhary G, Keith L, eds. Chlorinated Dioxins and Dibenzofurans in Perspective. Chelsea, MI: Lewis Publishers. Pp. 3–16.

Saracci R, Kogevinas M, Bertazzi PA, Bueno De Mesquita BH, Coggon D, Green LM, Kauppinen T, L'Abbe KA, Littorin M, Lynge E, Mathews JD, Neuberger M, Osman J, Pearce N, Winkelmann R. 1991. Cancer mortality

in workers exposed to chlorophenoxy herbicides and chlorophenols. Lancet 338:1027–1032.

Schecter A. 1994. Exposure Assessment: Measurement of Dioxins and Related Chemicals in Human Tissues. In Schecter A, ed.: Dioxins and Health. New York: Plenum Press. Pp. 449–485.

Schecter A, Le CD, Le TBT, Hoang TQ. 1995. Agent Orange and the Vietnamese: the persistence of elevated dioxin levels in human tissues. American Journal of Public Health 85:516–522.

Schlatter C. 1991. Data on kinetics of PCDDs and PCDFs as a prerequisite for human risk assessment. In: Gallo MA, Scheuplein RJ, van der Heijden KA, eds. Biological Basis for Risk Assessment of Dioxins and Related Compounds. Plainview, NY: Cold Spring Harbor Laboratory Press. Banbury Report 35. Pp. 215–227.

Seixas NS. 1990. Estimation of cumulative exposure for a cohort of coal miners with "post-MSHA" exposures. Presented at the American Industrial Hygiene Conference, 17 May, 1990, Orlando, FL.

Shafer DM. 1990. The Legacy: The Vietnam War in the American Imagination. Boston: Beacon Press.

Sielken RL Jr. 1987. Statistical evaluations reflecting the skewness in the distribution of TCDD levels in human adipose tissue. Chemosphere 16:2135–2140.

Smith TJ. 1987. Exposure assessment for occupational epidemiology. American Journal of Industrial Medicine 126:249–268.

Smith TJ, Hammond SK, Hallock M, Woskie SR. 1991. Exposure assessment for epidemiology: characteristics of exposure. Applied Occupational and Environmental Hygiene 6:441–447.

Solet D, Zoloth SR, Sullivan C, Jewett J, Michaels DM. 1989. Patterns of mortality in pulp and paper workers. Journal of Occupational Medicine 31:627–630.

Spey J. 1993. Presentation to the Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. February 8, 1993.

Stanton SL. 1989. Area-scoring methodology for estimating Agent Orange exposure status of U.S. Army personnel in the Republic of Vietnam. In: Centers for Disease Control, Veterans Health Study. Comparison of Serum Levels of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin with Indirect Estimates of Agent Orange Exposure Among Vietnam Veterans. Atlanta: Centers for Disease Control. Appendix A.

Stellman JM, Stellman SD. 1993. An Appraisal of Military Records Available for Research on the Health Effects of Herbicides Used During the Vietnam War . Prepared for the Institute of Medicine Committee to Survey the Health Effects in Vietnam Veterans of Exposure to Herbicides. February 4, 1993.

Stellman SD, Stellman JM. 1986. Estimation of exposure to Agent Orange and other defoliants among American troops in Vietnam: a methodological approach. American Journal of Industrial Medicine 9:305–321.

Stellman SD, Mager-Stellman J, Sommer JF Jr. 1988. Combat and herbicide exposures in Vietnam among a sample of American Legionnaires. Environmental Research 47:112–128.

Stewart PA, Blair A, Cubit D, et al. 1986. Estimating historical exposures to formaldehyde in a retrospective mortality study. Applied Industrial Hygiene 1:34–41.

Stewart PA, Herrick RF, eds. 1991. International workshop on retrospective exposure assessment for occupational epidemiologic studies. Applied Occupational and Environmental Hygiene 6:417–559.

Suskind RR, Hertzberg VS. 1984. Human health effects of 2,4,5-T and its toxic contaminants. Journal of the American Medical Association 251:2372–2380.

Sweeney MH, Fingerhut MA, Patterson DG, Connally LB, Piacitelli L, Morris JA, Greife AL. 1990. Comparison of serum levels of 2,3,7,8-TCDD in TCP production workers and in an unexposed comparison group. Chemosphere 20:993–1000.

Tankersley WG, Ingle J, West C, Watson J, Crawford-Brown D. 1991. Guidelines for systematic assessment of occupational exposures in absence of monitoring data. Presented at Eighth International Symposium on Epidemiology in Occupational Health, Paris

Thomas TL, Kang HK. 1990. Mortality and morbidity among Army Chemical Corps Vietnam veterans: a preliminary report. American Journal of Industrial Medicine 18:665–673.

Tschirley FH. 1967. Herbicide application. In: Responses of Tropical. and Subtropical Woody Plants to Chemical Treatments. ARPA Order 424 (draft). Agricultural Research Service. As cited in: Midwest Research Institute. 1967. Assessment of Ecological Effects of Extensive or Repeated Use of Herbicides. MRI Project No. 3103-B. Kansas City, MO: MRI. NTIS AD-824.

U.S. Army. 1972. Herbicides and Military Operations. Vols. I and II. Washington, DC: Department of the Army, Engineer Strategic Studies Group, Office, Chief of Engineers.

U.S. Department of Labor, Bureau of Labor Statistics. 1990. Employment Situation of Vietnam-Era Veterans . Washington, DC: BLS. USDL 90–347.

U.S. Environmental Protection Agency. 1989. Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-*p*-dioxins and Dibenzofurans (CDDs and CDFs) and 1989 Update. Springfield: U.S. Department of Commerce, National Technical Information Service. PB90-145756.

U.S. General Accounting Office. 1979. U.S. Ground Troops in South Vietnam Were in Areas Sprayed with Herbicide Orange. Report by the Comptroller General of the United States, FPCD 80–23. Washington, DC: GAO.

Verger P, Cordier S, Thuy LT, Bard D, Dai LC, Phiet PH, Gonnord MF, Abenhaim L. May 1994. Correlation between dioxin levels in adipose tissue and estimated exposure to Agent Orange in South Vietnamese residents. Environmental Research 65:226–242.

Warren WF. 1968. A Review of the Herbicide Program in South Vietnam. San Francisco: Scientific Advisory Group. Working Paper No. 10–68. NTIS AD-779-797.

Westing AD, ed. 1984. Herbicides in War: The Long-Term Ecological and Human Consequences. London: Taylor and Francis.

Young AL, Barnes DG, Blair A, Bricker JG, Christian RS, Fingerhut M, Kang H, Keller C, Muray JE, Shepard BM. 1986. Report of the Agent Orange Working Group Science Subpanel on Exposure Assessment. Submitted to the Chairman, Agent Orange Working Group. Washington, DC: Executive Office of the President, Office of Science and Technology Policy.

Young AL, Calcagni JA, Thalken CE, Tremblay JW. 1978. The Toxicology, Environmental Fate, and Human Risk of Herbicide Orange and Its Associated Dioxin. Brooks AFB, TX: Air Force Occupational and Environmental Health Lab. USAF OEHL-TR-78-92.

Young AL, Reggiani GM, eds. 1988. Agent Orange and Its Associated Dioxin: Assessment of A Controversy. Amsterdam: Elsevier.

Young AL, Thalken CE, Arnold EL, Cupello JM, Cockerham LG. 1976. Fate of 2,3,7,9,-Tetrachlorodibenzo-*p*-dioxin (TCDD) in the Environment: Summary and Decontamination Recommendations. Colorado Springs: U.S. Air Force Academy. USAFA TR-76-18.

Zober A, Messerer P, Huber P. 1990. Thirty-four-year mortality follow-up of BASF employees exposed to 2,3,7,8-TCDD after the 1953 accident. International Archives of Occupational and Environmental Health 62:139–157.