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EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

June 4, 1986

MEMORANDUM FOR THE CHAIR, AGENT ORANGE WORKING GROUP SCIENCE PANEL

FROM: ALVIN ~~L.~~ YOUNG, CHAIR, SCIENCE SUBPANEL

SUBJECT: Report of the Science Subpanel on Exposure Assessment

On April 1, 1986, the Acting Assistant Secretary for Health and Vice-Chairman of the Domestic Policy Council's Agent Orange Working Group (AOWG) requested that I chair a Science Subpanel on Exposure Assessment.

Accordingly, I assembled a Science Subpanel of the AOWG and reviewed pertinent information on exposure assessment, examined the additional pilot data which had been developed by the U.S. Army and Joint Services Environmental Support Group, and evaluated the feasibility of a scientifically valid study of the possible long-term health effects which may have been caused by exposure to Agent Orange among combat veterans who served in Vietnam.

It is my pleasure to transmit to you the requested report. To have accomplished the tasks requested, let alone to do so in two months, is due entirely to the superb members of the Subpanel and the tremendous support and cooperation of the Army and Joint Serices Environmental Support Group and the Centers for Disease Control. The dedication of all parties testify to the concerns we all have for resolving issues surrounding the use of Agent Orange in Vietnam and the health of our Vietnam Veterans.

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

May 28, 1986

MEMORANDUM FOR THE CHAIRMAN, AGENT ORANGE WORKING GROUP

THROUGH: CARL KELLER, CHAIR, SCIENCE PANEL

FROM: ALVIN L. YOUNG, SCIENCE SUBPANEL

SUBJECT: Conclusions of the AOWG Science Subpanel on Exposure Assessment

REPORT OF THE AGENT ORANGE WORKING GROUP
SCIENCE SUBPANEL ON EXPOSURE ASSESSMENT

June 3, 1986

At its meeting on January 29, 1986, the Agent Orange Working Group (AOWG) directed the Science Panel "to examine the additional pilot data which are being developed by the U.S. Army and Joint Services Environmental Support Group, and to evaluate the feasibility of a scientifically valid study of the possible long-term health effects which may have been caused by exposure to Agent Orange among combat veterans who served in Vietnam". Accordingly, a Subpanel of the AOWG was assembled to review pertinent information on exposure assessment, to examine the additional pilot data which have been developed by the U.S. Army and Joint Services Environmental Support Group, and to evaluate the feasibility of a scientifically valid study of the possible long-term health effects which may have been caused by exposure to Agent Orange among combat veterans who served in Vietnam.

The Subpanel consisted of the following members:

Alvin L. Young, Ph.D., Chairman
Office of Science and Technology Policy
Executive Office of the President

Donald G. Barnes, Ph.D.
Office of Pesticides and Toxic Substances
Environmental Protection Agency

Aaron Blair, Ph.D.
Occupational Study Section
National Cancer Institute

Jerome G. Bricker, Ph.D.
OASD (Health Affairs)
Department of Defense

Richard S. Christian, C.R.M.
U.S. Army and Joint Services
Environmental Support Group

Marilyn Fingerhut, Ph.D.
Industry Wide Studies Branch
National Institute of Occupational Safety and Health

Han Kang, Dr. P.H.
Office of Environmental Epidemiology
Veterans Administration

Carl Keller, D.V.M., Ph.D.
National Institute of Environmental Health Sciences
National Institutes of Health

John E. Murray
Major General, USA (Retired)
DOD - Appointed Representative
Fairfax, Virginia

Barclay M. Shepard, M.D.
Agent Orange Projects Office
Veterans Administration

Peter Layde, M.D. (Observer)
Center for Environmental Health
Center for Disease Control

The Subpanel met on February 26; March 10; March 28; April 10; April 21; May 2; May 19, and May 27, 1986. This report is the Subpanel's evaluation prepared for the Agent Orange Working Group.

BACKGROUND

Public Law 95-151 (1980) directed the Veterans Administration (VA) to conduct an "epidemiological" study of United States veterans to assess the possible health effects of exposure to herbicides and dioxin during the Vietnam Conflict. Public Law 97-72 (1982) expanded this mandate to include the study of other environmental hazards or conditions which may have occurred in Vietnam. In January 1983, the design, conduct and analyses of health studies responsive to these laws were transferred by an Interagency Agreement from the VA to the Centers for Disease Control (CDC). In November 1983, CDC completed protocols on three complementary studies to address the health concerns of Vietnam veterans: The Vietnam Experience Study, the Agent Orange Study, and the Selected Cancers Study. CDC is currently conducting the Vietnam Experience Study and the Selected Cancers Study.

The Agent Orange Study was designed to look at the influence of Agent Orange applications on the health of Vietnam veterans. Achieving this goal was problematic because a critical component of such a study was that there existed an accurate assessment of exposure to Agent Orange. The hostile environment in Vietnam precluded guantitative assessments of human exposure. The collection of detailed military records were those appropriate to military herbicide operations, but not necessarily appropriate for follow-on health studies. Thus the November 1983 protocol for the Agent Orange Study proposed an approach to estimating

the opportunity for exposure to Agent Orange. At the time it was anticipated that large numbers of Vietnam combat veterans had been heavily and frequently exposed to Agent Orange. There was even concern that unexposed individuals would be very difficult to identify. Thus, the basic approach was to score veterans' opportunity of exposure based on their proximity to known herbicide applications. Veterans' daily locations were to be abstracted from records of the men's units. The protocol noted that changes in methods might be required as new data became available. In addition, certain reviewers of that protocol, including members of the Agent Orange Advisory Panel of the Congressional Office of Technology Assessment (OTA) and the AOWG Science Panel, expressed concern about the validity of the approach to exposure assessment and the extent of opportunity for exposure to Agent Orange in this cohort. Since the November 1983 protocol, CDC has provided OTA and the AOWG Science Panel with two interim reports on the status of the exposure assessment issue. After reviewing these materials, neither the AOWG Science Panel nor OTA believed that sufficient data had been presented on the extent of exposure opportunities among those thought most likely to be exposed nor on the details of revised study methods to warrant proceeding with the Agent Orange Study at this time. Both review groups asked that a new comprehensive protocol for the Agent Orange Study be prepared by CDC in order to address concerns in the areas of 1) exposure assessment, 2) selection of study participants, and 3) data analysis. In addition, the Department of Health and Human Services (HHS) was directed to delay commencement of interviews for the Agent Orange Study, which was scheduled to begin in January 1986, until a revised protocol could be evaluated by appropriate review groups.

DEFINITION OF THE PROBLEM

The original Study Design by CDC provided that a comparison of health outcomes was to be made between a cohort of men who had little or no opportunity for contact with herbicide and a cohort of men who were highly likely to have been exposed to Agent Orange while in Vietnam. Both cohorts were to be selected from among U.S. Army draftees or single tour enlistees with rank E1 through E5 and who were assigned to combat units operating in III Corps in Vietnam during the period October 1966 through March 1969.

It was proposed that in the absence of direct measurements of exposures, the cohorts would be formed based on a combination of the distance (proximity to areas sprayed with Agent Orange) and frequency of encounters (the number of times during a selected period in relation to the proximity to sprayed areas). This required the linkage of records of spray missions with those of troop deployments. The Army and Joint Services Environmental Support Group has performed such a linkage and they have demonstrated that military records are sufficient

to locate the position of the combat battalions by geography and time they served in III Corps. Indeed, daily locations for company sized Army units (150-200 individuals) can be abstracted from military records and the location of virtually all the recorded herbicide applications has been identified and computerized. The number of days that a company was close to a spraying can therefore be accurately determined by computer matching of daily locations. Duty rosters (Morning Reports) for companies are available which identify individuals available for duty each day.

This report is organized around several issues which the Subpanel has reviewed, including how much Agent Orange might cause health effects, how much was present under varying conditions of exposure, possibilities for misclassification of exposure status, and results and evaluation of pilot data. These issues are discussed below in the form of questions, each with a brief summary discussion. Additional and more complete information is provided in the various appendices to this report. The titles/subject matter of the appendices attached to this report are listed below.

APPENDIX	TITLE/SUBJECT
I	Methodology and Results of Pilot Tests for Agent Orange Exposure Among Vietnam Veterans
II	The Evaluation of Vietnam War Records
III	The Assessment of Perimeter Applications of Military Herbicides in Vietnam
IV	Agent Orange Exposure Probability Modeling For Vietnam Field Conditions
V	Review of Epidemiologic Data on Humans Exposed to Dioxin-Contaminated Substances
VI	Toxicity Data, Risk Assessment and Exposure Scenarios For Military Herbicide Applications
VII	Utilization of Biological Samples to Assess Exposure to Agent Orange

DISCUSSIONS AND FINDINGS

1. What explicit and/or implicit criteria have been used to determine study subjects' exposure status in other epidemiological studies of the possible health effects associated with exposure to phenoxy acid herbicides and/or dioxin-contaminated substances?

A review (Appendix V) of several epidemiological studies has not revealed any uniform or suggested definition of exposure, although all exposed individuals have generally been involved with herbicides or other suspect chemicals in an occupational setting or through environmental contamination (e.g., Seveso, Italy and Times Beach, Missouri).

In addition to those studies cited in Appendix V, two studies involving Vietnam veterans have attempted a crude exposure index. The CDC/VA Birth Defects Study (JAMA 252:903-912, 1984) employed an Agent Orange Exposure Opportunity Index based on information derived from military records and from information provided by Vietnam Veterans during the interviews. For the Exposure Opportunity Index the term "exposed at all" essentially meant that the assigned unit of a veteran had been within 2 Kilometers within 3 days of an Agent Orange application, or that the veteran had handled or cleaned-up herbicide while in Vietnam. Two major limitations of this "Exposure Opportunity Index" are that it is easy to mistakingly interpret higher values of the Index as greater exposures and inadvertently ascribe a dose response capability to the index, and the Index was inexorably confounded with combat experience.

In the Air Force Health Study (An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposures to Herbicides, 1984) a crude exposure index was developed that incorporated a TCDD Weighting Factor and the number of gallons of TCDD-containing herbicide sprayed in Vietnam during the subject's tour. The weighting factor essentially separated from the total "at risk" cohort those subjects that served in Vietnam prior to July 1965, a period in which high levels of TCDD were thought to have been present in the herbicide. The Air Force Study is a cohort study examining the health of the men who served in Operation Ranch Hand, the defoliation program, in comparison to a control group of men. While this crude exposure index cannot be an exact measure of actual exposure or body burden it was intended to provide some degree of useful inference when applied to groups of individuals who served in Operation Ranch Hand Units.

The Science Subpanel concluded that no useful model exists from current epidemiologic studies that adequately addresses the problems inherent in identifying an exposed cohort of Vietnam Veterans who had served in ground combat operations in Vietnam.

2. What is the quantity of Agent Orange, as used in Vietnam, which can be expected to induce detectable health effects of the type to be investigated during the Agent Orange Study interview and examination?

As with the case of appropriate exposure indices, the available data on the toxicity of Agent Orange or its constituents to humans is extremely limited. Appendix VI reviews the toxicity and risk assessments of Agent Orange and its components. The majority of experimental data on humans enables a conclusion to be drawn that certain doses constitute less than a threshold dose. The Environmental Protection Agency has established an ADI (Acceptable Daily Intake) value for the herbicides used in Vietnam and for the toxic contaminant 2,3,7,8-TCDD. In the Report (Volume 2: Toxicology and General Health, 1985) of the Royal Commission on the Use and Effects of Chemical Agents on Australian Personnel in Vietnam, the Commission critically reviewed the available data and concluded that a "safe dose application" (doses absorbed by a 70 Kg human) was 350 mg for either 2,4-D or 2,4,5-T, and 8ug (microgram) for TCDD. It is also of interest to note, that in testimony before the Royal Commission of Australia, Professor Olav Axelson of Linkoping University in Sweden, considered an occupational exposure of less than 10 days to phenoxy acids and chlorophenols not to be sufficient to induce either soft tissue sarcomas or lymphomas among Swedish forestry workers. These latter studies have been the only studies so far showing a strong positive association between herbicide exposure and these cancers.

As to the animal data, the Science Subpanel concluded that while available animal data may be of importance in establishing prospective standards for human exposure to Agent Orange and its individual components, it offers a doubtful basis for determining retrospectively whether a particular past exposure was sufficient to produce toxic effects in man.

From the above discussion, it should be apparent that the Science Subpanel was unable to determine what quantity of Agent Orange, as used in Vietnam, could have been expected to induce detectable health effects. The "safe dose levels" reported by the Australian Royal Commission Report are clearly above most of the potential exposure scenarios reported in Appendix VI.

3. What are the quantities of Agent Orange and its components which are expected to be found at the time of and at various times and distances following different methods of application?

Appendix IV of this report (the appendix on modeling of exposure probabilities) is a comprehensive treatise on the equipment used for dissemination of herbicides in Vietnam, the impact of operational conditions in affecting exposures, and a discussion of the likely environmental fate of TCDD in various exposure scenarios. Additional exposure scenarios that were discussed by the Subpanel are provided in Appendix VI. The calculations of the quantities of Agent Orange and its associated TCDD which are expected to be found at the time of and at various times and distances following application <u>depend upon a series of assumptions</u>. We use assumptions because <u>we do not have actual</u>

data collected from the field environment. Any calculation includes numerous assumptions, many of which will significantly (orders of magnitude) alter the outcome. Bricker, in his report (Appendix IV) notes 9 different factors that must be considered in just assessing herbicide spray drift (page 14). Despite all these different assumptions, the most likely scenario for the major application method, namely from the Ranch Hand C-123 (fixed-wing) aircraft, suggest that the expected initial concentration directly in the swath path area (no jungle canopy assumed) would be 3.9 gm/m^2 of herbicide esters and 7.8 $\mu g/m^2$ of TCDD (pg 17). These data are remarkedly close to those discussed by the Australian Royal commission, e.g., for TCDD - 5.8 ug/m^2. The Commission used these estimates in the following manner:

Constituent	Theoretical Dose* Application from Exposure	Safe Dose* Application
2, 4-D	14.16 mg**	350 mg
2, 4, 5-T	14.83 mg**	350 mg
TCDD	0.58 ug***	8 ug

*Dose calculations assume the weight of the exposed person to be 70 kg.

**Gross rate per square meter X 0.01

***Gross rate per square meter X 0.1

The Royal Commission concluded that on the basis of the above material that "even the most extreme theoretical exposure in Vietnam would have subjected a person so exposed to a dose of Agent Orange well within the exposure considered to have been safe".

The Science Subpanel neither agreed nor disagreed with such statements. It is clear, however, that the selection of an exposed cohort cannot depend upon unverifiable exposure scenarios.

4. How many encounters, and of what type, could provide a meaningful exposure to Agent Orange and its associated TCDD?

At the time of spraying, substantial contact with the liquid spray must be considered a potentially meaningful exposure. Therefore, individuals known to have been within 500 meters meters at the time of herbicide application on a least one occasion might be included among the exposed, since they could be exposed by both dermal contact and inhalation. The literature suggests that on subsequent days, the amount of TCDD would be markedly less due to photodegradation and would almost be

completely degraded by the 6th day unless it had penetrated into the ground. Although it is not possible to know with any certainty how much TCDD would be absorbed during any encounter, the Subpanel considered it to be at least theoretically possible to come in contact with a potentially toxic amount in two weeks in an area which has been heavily sprayed. Therefore, in order to include all persons who might have been exposed, 14 encounters within 2 kilometers and within 6 days might be considered to have some real potential for a meaningful exposure (the pilot study (Appendix I) addresses these parameters).

In addition to combat veterans exposed during base camp and field operations, there may be an identifiable group of persons who were directly under an emergency dump of Agent Orange. Such a situation did occur over Ben Hoa Air Base in which several hundred gallons were jettisoned at low altitude directly over the base and a number of non-combat veterans may have been exposed. Such a situation might have provided an opportunity for meaningful exposure to potentially identifiable individuals.

5. What is the accuracy of the recorded locations for herbicide sprays and military units, and, what is the average dispersion of troops around the recorded locations of company sized units? How might this affect the classification of exposure and the estimates in 4 above?

The Science Subpanel conducted a critical review of the records and an assessment of the quality control for the handling, interpretation and abstraction of the data (Appendix II, The Evaluation of Vietnam War Records). The following conclusions were important to the issues before the Subpanel:

- Only about 2% of all military records are placed in permanent storage in the National Archives. (Page 9, Appendix II)

- The Vietnam War records that were kept by the military services are in excellent to poor condition. (Page 9, Appendix II).

- The records available for scientific scrutiny include Daily Journals, Morning Reports, Operational Reports - Lessons Learned, and Situation Reports. (Page 15, Appendix II).

- For the above fundamental reports, there are other authorities which cross check the information. Each Infantry Division in Vietnam had its separate chemical detachment that reported and evaluated the evidence. The Air Force in Vietnam had a regular reporting and evaluating system of its herbicide spraying operations. Additionally, the U.S. Embassy and the Military Assistance Command, Vietnam (MACV) jointly approved each Ranch Hand spray. (Page 16, Appendix II).

- The written Journals are as close to raw, unedited reality as one can get. "Truth is virtually an addiction in a world in close proximity to obliviion. The Journals thus deserve trustworthiness." (Page 16, Appendix II).

- Gaps arise in the records of unit locations when grid locations of companies are not given in the Daily Journal. However, company morning reports and other records are usually available to close the gap. (Page 16, Appendix II).

- Location of troops at fixed places, such as fire bases, where they are static within a protected perimeter and not subject to Ranch Hand sprays does not require the same analytic review involving the possible confluence of two mobile components; friendly aircraft and friendly troops. Time, motion and place are different ingredients in the locations puzzle when place is one of relative confinement. (Page 16, Appendix II).

- Scrutinizing the military records invariably led to what may be termed the "Data Abstraction Procedures for the Agent Orange Study". Over 110,000 personnel files of veterans assigned to specific units for two years (1967-68) and the daily field location of these troops has been required. This has taken a painful scrubbing for abstraction from Morning Reports to match names against computer tapes and social security numbers and coordination between four general agencies: The Environmental Support Group; the Centers for Disease Control; The U.S. Army Records Component Personnel and Administration Center (RCPAC); and the National Archives Records Administration (NARA). (Page 17, Appendix II)

- "The ESG abstraction training, procedures, disciplined supervisors, and quality control of their fundamental record abstractions is an excellent model of the careful performance of dull toil." (Page 18, Appendix II).

- "It is not only the record, but who reads the record to obtain the best professional product. In evaluating the talent within the ESG to read the records, I have found it to be the best." (Page 23, Appendix II).

The Science Subpanel concluded that the U.S. Army's Environmental Group has sought and obtained all military records pertinent to the use of herbicides in Vietnam. The Environmental Support Group staff is trained and qualified to have expertly reviewed and abstracted the records appropriate to exposure assessment.

The issues of frequency of encounters to areas sprayed with Agent Orange and the dispersion of troops within company-sized units were addressed in a Pilot Study conducted by the Subpanel and the Army and Joint Services Support Group.

Military records were examined by the Environmental Support Group in order to estimate the amount of daily troop dispersion and the distribution of encounters with Agent Orange applications during the period from October 1, 1966 through March 31, 1969, in Corps Tactical Zone III, Vietnam. Procedures and results of these tests are described in Appendix I. From the Pilot Study the Subpanel concluded:

- After extensive review of military records during the past two years, it was apparent that the majority of veterans had never been within two kilometers of a sprayed area within a week of herbicide application. Additional pilot data reviewed at this time confirmed this finding, and the paucity of clearly exposed combat veterans makes it questionable whether a sufficient number can be assembled to conduct an epidemiological study of the type originally designed.

  From a thorough review of these military records, it appears that considerable misclassification of the individual's exposure status is possible; i.e., we found no way, based on military records, to verify an individual's exposure to herbicide or dioxin. Two issues were specifically recognized as influencing the degree of misclassification:

  a. Unit Dispersion - On a substantial number of days, personnel in combat units eligible for the Agent Orange Study were not located together as a unit, rather they were dispersed geographically up to 20 kilometers on the same day.

  b. Incomplete Records - The most complete records for herbicide applications in Vietnam are the "HERBS TAPES," records of the msisions of OPERATION RANCH HAND. These tapes, originally computerized by the National Academy of Sciences in the early 1970s, were supplemented recently by the SERVICES HERBS TAPES which provide additional data on perimeter applications (including helicopter and ground application missions). Expert opinion suggested that an unknown, but apparently large proportion of firebase perimeter spray operations were never recorded (Appendix III). The degree to which these "unrecorded" operations may have influenced exposure is unknown.

SUMMARY

Information on level of exposure would provide the strongest possible data to address the issue of health risks associated with herbicide exposure. The members of the Science Subpanel felt that such precise information cannot be assembled either for exposure from Ranch Hand spraying or perimeter spraying of firebases or base camps. Present attempts at exposure classification employ dichotomous categories and are based on the likelihood of having contact with herbicides. They do not, however, include information on levels of exposure experienced by individuals. In such a dichotomous classification scheme the only measures of dose would be the number of exposures, latency, and duration.

Similar problems exist in attempts to assess level of exposure while in the fire bases. The Subpanel members felt that levels of exposure are likely to be higher from exposure in camps than from Ranch Hand spraying, but we see little opportunity for quanitfying the level. Actual exposure levels would depend upon the level of contact directly from sprays and indirectly from contaminated surfaces. We see little opportunity for individual evaluation of either method of contact.

The available military records indicate that companies can be located rather precisely, as can deployment of squads and other units. It is not possible, however, to determine which individuals are in which deployed Subunits. The inability to precisely locate individuals in relation to Ranch Hand spray patterns would lead to exposure misclassification no matter what distance/time criteria were used. For example criteria of within 2 kilometers within 3 days of spraying has been proposed to identify companies that would be considered exposed. All persons from a company within this distance of spray tracks would be considered exposed. Two kilometers would seem to be a considerable distance and present little chance of exposure. Although the number of false positives could be reduced (at the expense of numbers of exposed) by a more restrictive distance criterion, precise exposure classification would never be achieved unless companies were required to be within the spray path. An equally serious problem with this approach, however, is the inability to precisely locate the whereabouts of individuals. The distance factor is based on company location, not on individual location. The dispersion of units within a company may considerably exceed the two kilometer criterion. Thus, individuals deployed far from the spray track would be considered exposed even though they would have had little or no contact with herbicide residues.

Although companies are apparently sometimes deployed as a single unit and exposure assessment could be restricted to such situation, ignoring exposure when deployed in subunits would not eliminate the misclassification associated with the situation. The assumption for such a situation would be that the average exposure for all multi-location deployments of companies are equivalent. An assumption that surely is not correct.

Exposure while in camps presents a different set of problems in developing a scale of probability of exposure. Although we can reasonably conclude that exposures occurred in camps; except for cases where applicators can be identified, we see little opportunity for distinquishing the probability of exposure among individuals while in camp. A cohort of persons spending time in camps where spraying occurred could, however, be compared with persons not in such camps, if such a referent cohort can be identified.

In summary, plans to construct a probability of exposure index based on distance and time from Ranch Hand spray paterns based on company locations would introduce misclassification. This misclassification arises from two sources: 1) Inclusion of companies without actual exposure would occur no matter how small the distance and time criteria, and 2) Members of companies would be assigned identical exposure probabilities even though deployment of some units would place them in locations where exposure was not possible. The combined effect of these two sources of misclassification is unclear, but undoubtedly they would seriously bias measures of effect toward the null and greatly reduce study power.

The Subpanel recognized the social importance of the Agent Orange - health risk issue and the need to provide data that can address concerns raised by veterans. Completion of a study with poor definition of exposure, however, may not resolve the issue. In a strict scientific sense, the misclassification issue must be clearly addressed. The pilot study provided information regarding estimates of misclassification. As a consequence of that information, however, the Subpanel felt that an additional method to verify exposure is required prior to the conduct of a "scientifically valid epidemiology study". Recent advances in analytical chemistry may make it feasible to identify chemical (e.g., 2,3,7,8-TCDD) or biological (DNA adducts) markers that will permit a more reliable exposure assessment. Appendix VII proposes one such possiblity.