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EXPOSURE ASSESSMENT FOR THE AGENT ORANGE STUDY

Interim Report Number 2
Supplemental Information

December 8,1985

AGENT ORANGE PROJECTS
Division of Chronic Disease Control
Center for Environmental Health
Centers for Disease Control

Introduction

Staff from the Agent Orange Projects at the Centers for Disease Control presented material related to Interim Report Number 2 to the Agent Orange Working Group Science Panel at a meeting on 20 November 1985. Members of the Science Panel requested answers to issues arising from modifications to the original protocol for the Agent Orange Study. AOP staff presented additional material to the Science Panel at a meeting on 3 December 1985. This supplementary report contains a summary of that additional material.

The changes made to the original protocol are reviewed in Section A. In particular, we discuss changes in the method of selection of combat veterans and in eligibility criteria. We emphasize that the original two distinct combat cohorts will be combined to yield a single larger combat cohort.

The Science Panel had an extensive discussion of whether an unexposed noncombat cohort should be included in the study, and of analysis problems arising from such a cohort. Section B discusses our reasons for retaining this cohort.

Section C discusses selection of combat veterans. We explain our decision to expand the service period from 1967-1968 and demonstrate that, with this change, we can identify enough eligible combat veterans for the study. We discuss whether to include engineers in the study.

Models for exposure need to incorporate both the known data and the uncertainty in these data. We describe the systems for scoring the likelihood of exposure in Section D. These methods incorporate the three half-lives known to exist for dioxin.

The distributions of exposure scores for units and men currently available are presented in Section E. There is substantial variability in the estimated likelihood of exposure both among units and among men. The data indicate that at least one-third to one-half of the combat veterans have some opportunity for exposure to Agent Orange.

We present an outline of our data analysis strategy in Section F, emphasizing analyses within the combat cohort.

Section G contains estimates of power based on the analysis strategy adopted. We demonstrate that we should have very good power to detect a meaningful association between adverse health effects and exposure to Agent Orange.

Section A. Study Design Changes.

As in any research project, AOP expected modifications of the original protocol as planning continued. It has been necessary to change the manner in which men are selected for possible inclusion in the study and to change the criteria for inclusion of those men selected. In this section we review the protocol study design of the Agent Orange Study (AOS) prepared by CDC in November 1983 and the modifications recommended in the Interim Report on Exposure Assessment of February 1985. On the basis of recent analyses we propose futher minor modifications.

The original AOS protocol divides the study population into three cohorts as illustrated in the following 2x2 table.

		Likely Herbicide Exposure	
		Yes	No
Combat Experience	Yes	Cohort 1	Cohort 2
	No		Cohort 3

CDC proposed selecting the first and second cohorts from units with combat experience to ensure that the cohorts are comparable with respect to other factors which might influence health such as combat intensity, indigenous diseases, socioeconomic status, and type of personnel deployed. Because these two cohorts were to be chosen from combat units all of which may have been exposed to Agent Orange, it was anticipated that there could be overlap with respect to exposure, resulting in possible misclassification. Therefore, CDC recomended selecting a third cohort drawn from units with no combat experience from areas where there is good evidence of little or no herbicide usage. This third cohort would give maximum exposure separation from the "likely exposed" cohort but could lack comparability with respect to other health-influencing factors such as socioeconomic status. The empty cell, representing the combination of herbicide exposure with no combat experience, cannot be filled because herbicide use was inextricably entwined with combat experience, i.e., areas with heavy use of herbicide were generally combat areas.

1. Selection of Study Units.

In the original study design companies were to be ranked according to exposure. Study subjects for the first cohort were to be selected from the top third and for the second cohort from the bottom third of the exposure ranking. By excluding the middle third, we hoped to maximize differences in the likelihood of exposure between the two cohorts.

The selection of men for possible inclusion will not be based on the likelihood of exposure of the unit from which they are identified. Classification of men according to the likelihood that they were exposed to Agent Orange will be done after the cohort has been identified. This change was specified in the February 1985 interim report. This modification means the combat veterans are one cohort of 17,000 men, rather than two separate cohorts. That is, men who served in units with intermediate likelihood of exposure will also be recruited for the study. This decision results from finding a transfer rate among units higher than was expected and the inability to obtain company level locations with which to rank companies according to the likelihood they were exposed to Agent Orange.

2. Selection Criteria

On the basis of power calculations the protocol indicates a sample size of 8,500 men for each cohort. The two combat cohorts were to consist of 17,000 men selected from 65 battalions who served in III corps during the study period (January 1, 1967 to December 31, 1968). The selection of men for the study was to be based on the following criteria:

a. Draftees and single-term enlistees
b. U.S. Army grades E1 through E5
c. Only one tour of duty in Vietnam
d. At least 9 months served in a single unit
e. Entire period of service in Vietnam in 1967-1968

Further work has demonstrated that it will be necessary to change the last two criteria in order to obtain the required 17,000 men from combat units serving in III Corps. The following criteria will be substituted:

d*. At least 6 months in combat units in III Corps during the period of study.

On the basis of information obtained from the abstraction of approximately 10,000 personnel files, the 9 month criterion for inclusion in the study will not yield enough men. We, therefore reduced the criterion for eligibility for the combat cohort to at least 180 days served in combat companies (company A-E).

e*. Entire period of service in Vietnam between October 1, 1966 and March 31, 1968. 1969

This change is necessary in order to assure that enough eligible men are identified and that a large number of men with possible exposure to Agent Orange are not excluded from the study.

We do not believe that these changes seriously effect the ability to ascertain adverse effects due to exposure.

Section B. Unexposed Cohort.

In this section, we address the need to include the "third cohort" in the Agent Orange study. Several rationales for its inclusion, as well as the potential for confounding in comparisons of this cohort have been discussed ("Protocol, 1983; "Responses to Scientific Reviews of the Centers for Disease Control's Draft Protocols for Epidemiologic Studies of the Health of Vietnam Veterans", 1983). These issues are summarized below.

Since the third cohort is to be selected from men who served in areas of Vietnam where there is good evidence of little or no herbicide exposure, this cohort was included to give "maximum separation of exposure from the likely exposed cohort" (Protocol, 1983, p7). The potential lack of comparability of the third cohort with respect to other health influencing factors (e.g. combat, SES, etc.) and the resulting potential for confounding have been discussed (Protocol 1983: pp7, 52, 53; "responses.." 1983:p 12, appendix A, p11). A second possible rationale for inclusion of the third cohort is that comparison with the "likely not exposed" cohort would address the effect on health of service experiences, such as combat, since the third cohort would probably have been engaged in little combat ("responses.." 1983:p14). Again, the difficult issues of comparability, other biases, and associated difficulties in interpretation are recognized ("protocol" 1983: pp 7,52,53).

With the current study design in which the "likely exposed" and "unlikely exposed" cohorts are replaced by a single cohort with a range of exposures, the primary rationale remains the same. The most highly exposed men in the cohort can be compared with the third cohort. Potential problems related to lack of comparability, confounding, bias, and interpretation are recognized. Other possible rationales for inclusion of the third cohort, such as comparison with a "likely not exposed" cohort (for example by comparing the third cohort with men with the lowest exposure scores) are similarly little changed by the current study design.

In summary, inclusion of the third cohort is still recommended. The limitations of analyses involving this cohort are recognized, but the modification in design does not change the rationale for its inclusion.

Section C. Selection of Combat Veterans

We wish to emphasize four points with respect to recruitment of veterans for the Agent Orange Study:

1. It is necessary to extend the service period outside of 1967-1968, in order to increase both the number of eligible men and the number with a relatively high likelihood of exposure.

2. With the service period extended by 6 months, we may be able to identify more than the 17,000 combat veterans specified by the protocol.

3. If many more than 17,000 eligible combat veterans are available, we will try to choose participants to obtain a distribution of exposure scores which increases study power.

4. We shall decide soon whether to include engineers in the study. The locations available for the single battalion abstracted thus far are too sparse to permit assessment of possible exposure to Agent Orange.

These points are discussed briefly in this section.

1. Extension of the service period.

It was specified that any veteran who served time in Vietnam outside the designated study period would be excluded from the study. The period chosen in the original protocol is the two year period 1 January 1967 to 31 December 1968.

This choice substantially reduces both the number of men eligible and the number with relatively high likelihood of exposure compared to a somewhat longer period. Table 1 shows the dates of arrival in Vietnam of the 59 nonengineering battalions to be used in the study. Battalions arrive as a unit. Note that about 30% (17 of 59) arrived between 1 October and 31 December 1966. All of the men who arrived in this period are ineligible unless the service period is extended into late 1966. Therefore, we plan to begin the service period on 1 October 1966.

Table 2 shows the amount of spraying of Agent Orange, by calendar quarter. Some of the heaviest spraying is in the fourth quarter of 1966 and first quarter of 1967. However, many of the men present during the first quarter of 1967 entered Vietnam during 1966 (the usual tour of duty was about 350 days). These potentially exposed men will not be eligible unless the service period is extended into 1966.

2. Recruitment estimates for combat veterans.

We considered three alternative service periods: 1 January 1967 to 31 December 1968 (the period originally proposed), 1 October 1966 to 31 December 1968 (a three-month extension), and 1 October 1966 to 31 March 1969 (a six-month extension). Table 3 contains our projections of the total number of combat veterans who could be recruited for the study (excluding engineers) under these alternatives. Note that, with the current 1967-1968 service period, it might not be possible to recruit 17,000, but that the six-month extension should result in about 24,000 potentially eligible men. Therefore, we plan to extend the service period to ensure that we can recruit enough combat veterans. These projections are based on records of about 10,000 men abstracted by the Environmental Support Group (ESG). These men come primarily from four infantry, four artillery, and two armor or cavalry battalions. The projections assume that these ten battalions are representative of the battalions to be abstracted. The estimated number of eligible combat veterans with the service period extended by six months appears to be enough, however, that we believe we can obtain 17,000 with this extended service period.

We are, therefore, changing the period of veterans' allowable tour in Vietnam to include this period.

3. Choice of participants to increase power.

If substantially more than 17,000 combat vererans are eligible for the study, we will try to choose those recruited to increase the power of the study. For example, battalions with relatively high likelihood of exposure may also provide men with a very slight likelihood of exposure. That is, we will try to select battalions from which veterans are chosen to reduce the proportion of men chosen with intermediate likelihood of exposure.

4. Inclusion of engineers in the study.

Locations for engineering battalions may not be available for enough days to assess exposure to Agent Orange. There are six engineering battalions on the battalion list. Locations have been abstracted for one; for each company, locations are

available for at most ten days. Thus, we cannot estimate likelihood of exposure to Agent Orange for this battalion.

ESG is now abstracting locations for two more engineering battalions. These should indicate whether enough locations are available to estimate proximity to Agent Orange spraying for engineering battalions. We note that engineers often operated in small (less than company-sized) units. Therefore, it may be more difficult to estimate likelihood of exposure for engineers than for other types of troops.

It may be desirable to include engineers in the study since the Austrailian study demonstrated an excess mortality among engineers as compared to other veterans. If so, and if insufficient location information is available, they would be treated as a separate cohort.

Table 1.

Number of Battalions Entering Vietnam, by Type and Period of Entry.

Type	Period		Number
Infantry	1965		9
	1966:	Jan - Apr	6
		Oct	3
		Dec	5
	1967:	Jan	4
	Total		27
Artillery	1965		9
	1966:	Jan - June	4
		Aug	1
		Oct	4
		Dec	2
	1967:	Jan - June	5
	Total		25
Armor, Cavalry	1965		1
	1966:	Mar	1
		Aug - Sept	3
	1967		2
	Total		7

Source: Shelby L. Stanton, Vietnam Order of Battle.

Table 2.

Number of Spray Missions with Data Available, by Quarter

Year	Quarter	N	%
1966	3	70	4
	4	174	9
1967	1	281	14
	2	85	4
	3	121	6
	4	192	10
1968	1	58	3
	2	77	4
	3	44	2
	4	43	2
1969	1	68	4
	2	330	17
	3	172	9
	4	265	13

Table 3.

Estimated Number of Men Eligible for Agent Orange Study, for Alternative Service Periods

Battalion			Service Period					
			1 Jan 67-31 Dec 68		1 Oct 66-31 Dec 68		1 Oct 66-31 Mar 69	
Type	N	No. abstracted per battalion	%	N	%	N	%	N
nfantry	27	1000	35	9,500	40	10,800	50	13,500
rtillery	25	550	40	5,500	50	6,900	55	7,500
avalry, Armor	7	1000	35	2,400	40	2,800	50	3,500
otal	59			17,400 ± 1,500		20,500 ± 1,500		24,500 ± 1,500

= percent of those abstracted estimated to be eligible for study.

rror shown in estimate of total based on error of 25 in estimate of number ligible per battalion (59 x 25 = 1475).

27 November 1985

Section D. Scoring the Likelihood of Exposure

In this section we describe the models we presently propose to use to estimate the likelihood of exposure to Agent Orange for military units, and thus veterans. The models are chosen to incorporate the data available, so far as possible. Should additional relevant information become available prior to data analysis we will attempt to incorporate it into our models. These models reflect the uncertainty in TCDD half-lives, in distances of veterans from and elapsed time since spraying, and what type of exposure to dioxin may be related to adverse health effects.

1. Environmental persistence and dispersion of Agent Orange.

a. Environmental persistence

Disappearance of tetrachloro-dibenzo-p-dioxin (TCDD) from the environment occurs through several processes including photodegradation, volatilization, transport, sorption, and perhaps biodegradation (EPA 1985). Photodegradation is felt to be a major process in the disappearance of TCDD and follows first order kinetics under some conditions (Choudhry 1982). To adequately describe the disappearance of TCDD from the environment, however, an exponential model with multiple compartments, each with its own half life, has been used (Jensen, 1983). Many factors, including amount of sunlight and other climatic conditions, area of the environment in which the dioxin is found, and vehicle in which the dioxin is applied, influence the rate of disappearance of TCDD as well as its initial distribution. Reflecting the dependence on many factors, a wide range of half-lives have been published, some of which are summarized in table 1. The published half lives have been divided into three groups or compartments: a fast compartment with half-lives measured in hours, an intermediate compartment with half lives measured in days, and a slow compartment with half lives measured in years.

Table 1. Estimated TCDD half-lives, grouped by length

half-life	deposition	Reference
fast compartment		
2 hours	leaves	Crosby and Wong,1977
intermediate compartment		
2 days	soil surface	Crosby and Wong, 1977
4-7 days	grass (in silvex)	Nash and Beal (1980)
6 days	grass (in herbicide)	Jensen(1983)
slow compartment		
0.5 yrs	soil,initially	DiDomenico,1980
10 yrs	soil	Wipf and Schmid 1983
5 yrs	pond, predicted	EPA,1985

While other data exist and the relevance of these estimates to the environment in Vietnam can be questioned, the data support the existence of at least three compartments with half-lives differing by one or more orders of magnitude.

b. Dispersion

The dispersion of herbicide following aerial spraying has been evaluated by flying test missions over a sampling grid, under controlled conditions (Harrigan 1970). While many conditions such as the spray system, altitude, and aircraft were similar to those which prevailed in Vietnam for the Ranch Hand missions, other conditions (e.g. the number of aircraft used and vegetative cover) were different, so that results can only be used as rough estimates of herbicide dispersion. In a crosswind, the concentration decreased approximately as a first-order exponential. We estimated the rate parameter to be approximately 8.5 (with distance in kilometers) from linear regression after logarithmic transformation of the concentration.

The above information addresses the environmental persistence and dispersion of herbicides and TCDD, but not the actual amount of TCDD absorbed by subjects, which is of more relevance. Unfortunately, estimates of dose would depend on knowledge of bioavailability, absortion rates, clothing worn, as well as behaviorial factors such as amount of time spent in contact with vegetation, soil, and grasses, and consumption of local food and water. Data are insufficient to estimate dose.

2. Data available for study subjects

For each subject, the primary data available to assess exposure opportunity are troop and spray locations and dates. Troop locations are for entire battalions or individual companies and are recorded to the nearest tenth of a kilometer. These data permit calculation of the distance of each company, and by inference the distance of each subject, from Agent Orange spraying.

Distance estimates are uncertain for the reasons given below. The magnitude of the uncertainty is large compared to the dispersion of Agent Orange from the release of herbicide.

1. There is some uncertainty in the exact location of the spray path.

2. Many company locations represent portions of the company, so that a man may not be at all locations recorded for his company on a given day. In addition, since a company consisted of about 240 men, a single company could be spread out over a region up to several kilometers long.

3. In some battalions, positions were recorded with digit preference.

4. Companies moved about during the day, and not all locations are recorded in the source documents.

5. There was error in estimating location due to field conditions.

6. There are errors in recording locations in the source documents.

The actual distribution of the error in the calculated distances from spray lines is impossible to estimate at this point. However, we believe that the calculated distance may be in error by 2 to 5 km, or perhaps more.

The elapsed time between spraying and possible exposure is also uncertain.

1. The times at which spraying was done are not given on our data tapes. Ranch Hand spraying was conducted at dawn and dusk (an uncertainty of about 12 hours).

2. Although times are given for company coordinates, we do not know the times at which a company arrived at or left reported locations.

The uncertainty in the elapsed time is relatively large compared to the half-life of the fast compartment, and of some importance compared to that of the intermediate compartment. Therefore, we choose the time factor in our scoring system to be constant on each day.

3. Scoring opportunity for exposure.

Subjects may have been exposed to TCDD in any of several ways, corresponding to the components defined above. If present in an area previously sprayed, exposure might have occurred through contact with sprayed soil or through the food or water supply. This might be viewed as "chronic" exposure. In the first few weeks after spraying, the environmental persistence is such

that exposure could also have occurred through contact with TCDD on the forest floor (soil surface or grass). This might be viewed as "intermediate" exposure. On the day of spraying, exposure might have also occurred through contact with TCDD on vegetation or in the air. This might be viewed as "acute" exposure.

The final score for each individual will be the sum of his daily scores, and the daily score will be the sum of the scores for each spray line for each day. The exposure score for each day and spray line will, as proposed in the protocol, be the product of a distance score and a time score.

Unfortunately, available information is insufficient to decide which type of exposure opportunity (acute, intermediate, or chronic) was most important to health. Therefore, we must consider the possibility that each is important, perhaps for different diseases or health outcomes.

a. Dependence of score on time.

To reflect the uncertainty in the elapsed time between spraying and potential exposure, we choose scores which are constant on each day.

To develope a time score, hypothetically suppose that significant TCDD exposure was due to contact with TCDD which disappeared rapidly from the environment, say with a half-life of about 2 hours ("acute" exposure). Then, a reasonable exposure score is 1 for individuals present near a sprayed area on the day of spraying and 0 otherwise, since nearly all the TCDD in this compartment would have disappeared by the second day. On the other hand, significant TCDD exposure may have been due to contact with TCDD which disappeared at an intermediate rate ("intermediate" exposure, reflecting contact with the forest floor, grass, and so forth). Then a reasonable time score, based on a half-life of two days, is 1 on the day of spraying, 1/2 two days later, 1/4 four days after spraying, 1/8 six days after spraying, etc.; the time score for each day is obtained by dividing that for the previous day by the square root of 2. Finally, suppose that significant TCDD exposure was due to contact with TCDD which disappeared very slowly, say with a half life of about 5 years ("chronic" exposure, reflecting contact with TCDD adsorbed to soil and in water). A reasonable choice for the time score for this component is one which decreases very slowly with time, reaching 1/2 after 5 years, consistent with an exponential decay with a half-life of about 5 years.

To develop a single time score would require some sort of selection from, or weighting of, the above three scores. As we stated above, we do not believe that available information is sufficient to develop such a summary score.

In fact, it is possible that the relative importance of the acute, intermediate, and chronic exposures differed for different health outcomes. To avoid making an arbitrary choice, we propose to use all three time scores. The general question as to the association between potential TCDD exposure and adverse health outcomes can then be addressed by a statistical analysis which incorporates all three exposure scores simultaneously (see the next section). The major advantage of this approach is its avoidance of the need to arbitrarily decide which of the acute, intermediate, or chronic exposures were most important.

b. Dependence of score on distance

TCDD after aerial spraying is dispersed (in a moderate crosswind) over an area several hundred meters in width, the concentration decreasing approximately as exp (-8 d) with the distance, d, expressed in kilometers. This model predicts that the concentration at a distance of 1/2 kilometer from the flight line would be only 2% of the concentration near the center of the flight path, and at a distance of 1 kilometer only .03% of the highest concentration. These distances are small compared to uncertainties in our estimates of distance of subjects from spray lines, as described above. As a determinant of exposure opportunity, then, the uncertainty in the actual distance from spraying is probably much greater than the dispersion of TCDD around spray lines. Therefore, we propose to define the distance factor as (approximately) 1 if a subject's company was within K kilometers of a spray line and zero otherwise, with K a parameter to be specified. We believe that a reasonable choice for K is about 2 to 5; the CDC Agent Orange birth defects study used an uncertainty of 8 km in location estimation.

More precisely, we use a step function with a shoulder at K kilometers, the value being 0.5 at K and 0 by K+.5. This form can be justified as follows. Assume that the concentration of TCDD decreases as exp(-8 d), with d the distance in kilometers from the spray line and that the uncertainty in our estimate of distance is K kilometers. For each estimated distance, the concentration of TCDD, <u>averaged</u> over the interval centered at the estimated distance +/- K kilometers, has the form described above.

c. Interpretation of exposure scores

The definitions of the three exposure scores are summarized in table 2.

Table 2
Description of Exposure Scores based on the uncertainty in distance estimation.

E1: acute exposure

1	if within K km, on day of spray
0	otherwise

E2: intermediate exposure (half-life of two days)

1	if within K km, on day of spray
0.5	if within K km, on second day after spray
0.25	if within K km, on fourth day after spray
0.125	if within K km, on sixth day after spray
...	
0	if more than K km from spray

E3: chronic exposure (half-life of 5 years)

1	if within K km, within a few days after spray
0.87	if within K km, one year after spray
0.76	if within K km, two years after spray
0.66	if within K km, three years after spray
...	
0	if more than K km from spray

Subjects who were in the vicinity of a spray line on the day of spraying have a high score for E1 and a greater opportunity for "acute" exposure to TCDD. An association of E1 with disease, after control of confounding, would support the hypothsis that men who were in the vicinity of a spray line on the day of spraying were sufficiently exposed to TCDD to increase risk of adverse health effects. Subjects who were often near a spray line during the first several weeks after a spraying would have a high E2 score and a high opportunity for exposure to that fraction of TCDD which persisted in the environment during this time period ("intermediate" exposure). An association between E2 and disease would support the hypothesis that men who were frequently in the vicinity of a spray line during the first several weeks after a spraying were sufficiently exposed to TCDD to increase risk of adverse health effects. Finally, subjects who were frequently in the vicinity of a spray line at any time after an application would tend to have a high E3 score and would have had a higher opportunity for exposure to that fraction of TCDD which remained in the environment for several years (perhaps in soil). An association between E3 and disease would support the hypothesis that presence in the vicinity of a spray line, even long after application, carried increased risk of adverse health effects.

We do not know whether the acute half-life is 2 hours, rather than 1 or 5 hours. In any case, a half-life in this range would result in relatively little exposure to the fast compartment 24 hours after spraying. Similarly, we do not know whether the true half-life for the "intermediate" compartment is 2 days rather than 1 or 6 days. In any case, this is roughly an order of magnitude greater than the half-life for the fast compartment. Similarly, the half-life for the slow compartment is roughly two or three orders of magnitude greater than that for the intermediate compartment. Therefore, for data analysis the important fact is likely to be the existence of three distinct compartments with half-lives differing by one or more orders of magnitude, not the actual half-lives for each. We discuss how we plan to assess the sensitivity of our analysis to these scoring systems in the next section on data analysis.

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Section E. Distribution of Exposure Scores

Information is presently available on about 2600 combat veterans who would be eligible for the study based on a 1967-1968 service period. This is the period for which we have troop locations. Locations are available for 36 battalions, including 21 infantry, 11 artillery, 3 armor or cavalry, and one engineering. This section describes the distributions of the exposure scores for these battalions and these men. We demonstrate that:

1. There is substantial variability in the exposure scores among units (companies and battalions) for both artillery and infantry.

2. There is substantial variability in the exposure scores among individual veterans.

The results reported here are restricted to the short and intermediate compartments of TCDD exposure (E1 and E2, respectively). Evaluation of the chronic compartment (E3) will require substantial computation and we have not yet been able to obtain this information.

1. Data available

The eligible men come primarily from four infantry battalions, four artillery battalions, and one armor and one cavalry battalion. Very few locations are available for the companies for one armor and two artillery battalions, so we have not evaluated these battalions nor the men who served in them. Company-specific locations are available for about half of the 731 days in 1967-1968 for the remaining battalions, as shown in Table 1.

2. Distribution of exposure scores among units.

Table 2 summarizes the distribution of the mean exposure scores for the intermediate component (E2) for the infantry, artillery, and cavalry battalions. The distance parameter used for this table is $K = 5$. The mean score is obtained by dividing the sum of the daily scores by the number of days for which locations are currently available. Thus, one might estimate the sum of the scores were locations available for all days by multiplying the mean by 731.

Table 2 demonstrates substantial variability in likelihood of exposure among infantry units, and among artillery units.

For infantry units, the maximum mean score (extrapolated to 731 days) is equivalent to being within 5 km of a spray on the day of a spray about 65 times in two years. Similarly, several of the artillery batteries (companies) have substantial likelihood of exposure, but at least half have essentially no opportunity for exposure. We emphasize that the percentiles of these distributions are likely to increase if we obtain location information for the missing days.

3. Distribution of exposure scores for combat troops.

Table 3 describes the distribution of the intermediate compartment (E2) scores for men from four infantry, two artillery, and one cavalry battalions. Scores are shown for distance parameter K = 2 and K = 5 km. It is clear that the scores are typically substantially higher with the larger distance parameter (except for battalion 16), as would be expected. Recall that these scores are based on incomplete location data; they will increase if additional locations for these units are obtained.

Interpreting these results requires knowledge of the ranking of these units among all battalions. Unit-specific scores indicate that infantry battalions 1 and 2 are in the central part of the distribution, battalion 3 may be somewhat below the median, and battalion 4 had relatively little likelihood of exposure. Battalion 6 was one of the most heavily exposed artillery battalions (but also has location data available on unusually many days).

Most men in battalions 4 and 16 have little likelihood for exposure with either distance parameter, based on the currently available locations. However, with distance parameter 5 km, at least half the men in battalion 16 are estimated to have exposure equivalent to being within 5 km of a spray on the day of the spray six times, and at least 25% of the men in battalion 2 have similar proximity to spraying 10 times. Appreciable percentages of the men in battalions 1 and 10 also have relatively high likelihood of exposure. Thus, a substantial proportion of the men eligible for the study thus far have substantial likelihood of exposure, while others in the same battalion or same type of battalion have little likelihood for exposure.

Most men with data available now were never within 2 to 5 km of a spray on the day of spraying. It is possible that this will change if more location data become available.

We conclude that there should be substantial variability in the estimated likelihood of exposure among men recruited for the study. The analysis of outcomes and power for detecting differences in health outcomes are discussed in the final two sections.

Table 1
Number of Days with at Least One Location

Battn	Company A	B	C	D	E	H	Entire battn
			Infantry				
1	293	325	291	238	0	29	527
2	324	415	450	46	22	275	438
3	485	499	494	238	347	505	78
4	578	590	558	80	2	86	416
median (20 battns)	398	398	421	225	1	10	519
			Artillery				
6	719	665	679	572	2	364	2
8	42	28	48	25	1	12	220
16	284	290	296	0	0	217	341
18	29	60	80	0	0	0	306
median (11 battns)	163	137	80	25	1	42	603

Table 2
Distribution of Intermediate Component (E_2) Scores
for Units with Locations for at least 250 days.
Distance Parameter = 5 km.

Battalion type	Unit type	No. units	Mean	Percentiles					
				Min	10	25	50	75	90
Infantry	company	78	.016	.000	.000	.003	.011	.024	.039
	battalion	21	.019	.000	.000	.005	.014	.025	.052
Artillery	company	19	.012	.000	.000	.000	.003	.013	.054
	battalion	10	.012	.000	.000	.000	.000	.030	.041
Cavalry	company	7	.021	.006		.012	.014	.041	
	battalion	2	.026	.023					

Unit = company includes companies A-E and headquarters.

Unit = battalion indicates reference to an entire battalion.

Table 3
Distribution of Sum of E_2 Scores, Individual Men

Battn	N	km	Percentile 25	median	75	90	95	max
1	418	2	0	0	0	.4	1.0	1.0
		5	2.1	4.5	6.2	6.3	6.9	12.6
2	389	2	0	2.0	3.8	4.0	4.6	4.9
		5	0	3.1	10.2	13.6	15.0	17.3
3	268	2	0	0	0	0.7	0.7	2.5
		5	0	0	0.4	8.4	8.4	8.4
4	310	2	0	0	0	0	0	0.5
		5	0	0	0	2.7	2.7	4.2
6	172	2	1.1	1.5	5.4	10.2	15.4	32.0
		5	3.4	6.2	7.3	12.2	20.8	39.3
10	229	2	0	1.2	3.9	6.5	6.5	6.6
		5	0	1.9	6.1	6.6	6.8	7.8
16	141	2	0	0	0	0.2	1.0	1.0
		5	0	0	0	0.5	2.6	5.8

Section F. Data Analysis

In this section we discuss the following points:

1. The formation of groups within the combat cohort based on the relative likelihood of exposure to Agent Orange.

2. Strategies for data analysis within the cohort of combat troops to assess the effects of exposure to Agent Orange and of other important variables.

3. Strategies to analyze differences between the combat troops and the noncombat unexposed cohort.

4. Assessment of the sensitivity of results to the exposure scoring systems used.

1. Division of combat veterans into groups.

Although the inferential analyses of the relation of exposure scores will involve using the actual scores (or their ranks) for individual veterans, it will be necessary to group combat veterans based on their exposure scores in order to present summary statistics. A combination of the three exposure scores (short, intermediate, and chronic) will be used to define groups. It is likely that more than two groups will be defined in presenting descriptive statistics.

2. Analysis of the combat veterans.

We will present descriptive statistics on these men, both for baseline information (such as age at entry, length of Vietnam service, and education) and outcomes (e.g. disease rates and laboratory results). As indicated above, this will be based on groups (probably more than two) defined based on exposure scores.

The association between likelihood of exposure to Agent Orange and outcomes will be assessed by using all three exposure scores defined above in an appropriate statistical model. We expect to enter these measures linearly. As a result, the data will determine the appropriate linear combination in assessing the strength of the potential association between exposure and a particular outcome. We will test the significance of the association using all three measures jointly, and using a two-sided significance test.

Mortality will be analyzed using survival analysis methods, including the proportional hazards model. Dichotomous responses, such as prevalence rates of diseases, will be modeled using logistic regression. Potential follow-up time will be quite uniform for all participants since follow-up time will begin only on discharge from the Army. Continuous measurements, such as laboratory results, will be modeled using regression relationships. Appropriate transformations of the dependent and predictor variables will be used as necessary in these models.

Other risk factors and potential confounders and effect modifiers will be included in the models. These include both pre-service characteristics and descriptors of military experience. The former include basic demographic information and indicators of socioeconomic status, such as test scores. The latter are predictors of future outcomes since, as stated above, only outcomes after military service are being considered. They include year of entry into Vietnam, type of battalion in which the veteran served, length of service, and severity of combat to which the veteran was exposed.

Thus, for logistic regression, the model is

$$\text{logit}(p) = \log(p/(1-p))$$

$$= b0 + (b1E1 + b2E2 + b3E3) + \text{other terms}$$

where p is, e.g., the prevalence of disease. As noted above, an advantage of this method is that, if exposure is a linear combination of these scores, the data can dictate the coefficients, rather than our specifying them. This is a substantial advantage. First, the components of exposure may vary in their importance for different diseases or conditions. Second, it would be extremely difficult to estimate the relative importance of these components, as partitioning in the environment seems hard to determine, and bioavailability seems even more difficult. We recognize the possible difficulties in interpreting individual coefficients, therefore, our emphasis will be on the association between mortality or disease and the overall measure of exposure, rather than the association with individual components of exposure.

3. Analyses of the unexposed noncombat veterans.

Similar techniques will be used to compare the unexposed noncombat cohort with the combat veterans. That is, the same types of models will be used, with the noncombat veterans assigned an exposure score based on the same procedures used to score the combat veterans (we expect most of the noncombat men

to have zero scores) and an indicator variable for cohort. We will compare the noncombat cohort with the entire combat cohort, to look for overall differences. To analyze the effect of combat, removing the effect of Agent Orange as much as possible, we will also compare the noncombat cohort with the combat veterans with relatively low likelihood of exposure to Agent Orange.

4. Sensitivity of results to the exposure models chosen.

We will assess the sensitivity of our results to the models chosen by examining the correlations obtained for scores from alternative models and by repeating key analyses with alternative models varying the half-life and distance parameters used. We also intend to compare the results obtained from the simple scoring system that assigns a score of 1 if a company is within K kilometers of a spray within D days after spraying, and 0 otherwise. Such a system is called a sum of "encounters" in Interim Report Number 2.

Section G. Power Estimates

The sample size statements in the original protocol were based on a comparison of distinct cohorts for the interview phase of the study. 6,000 men per cohort were needed to obtain 95% power for detecting a "2-fold increase in the risk for health outcomes normally occurring at the rate of about 5 per 1,000 in comparisons of two cohorts (if there is little or no misclassification...)", using a one-tailed test at level alpha = .05. Based on an estimated 70'% interview rate, about 8,500 men per cohort were needed. For the medical examination, 2,000 men per cohort gives 95% power for detecting such an increase in risk for health outcomes with a prevalence of 1.5 to 2.0%

As discussed in Section A, the original two combat cohorts will be combined into one larger cohort. We provide power calculations for the analysis within this cohort, as that is the primary objective of the study. The calculations are restricted to dichotomous outcomes, such as death or the development of disease. With our proposed analysis by logistic regression, we should have good power for detecting effects with this design.

If health outcomes are related to exposure, power depends on the distribution of exposure. The distributions of exposure scores presented in Section E suggest that a monotonic transformation of these scores (roughly square root or logarithm) may be approximately normal: there is a substantial proportion veterans with scores near zero and a long right tail. We recognize that the ranking of participants' scores may be somewhat different from the ranking of actual (but unmeasurable) exposure. Thus, our power calculations are intended to serve only as a rough guide to the ability of the study components to detect meaningful differences.

1. Methods

We use the logistic regression model presented in the previous section. In particular, we assume that logit(p) is linear in some transformation of the combined exposure scores. For the sake of convenience, we assume that the model is

$$\text{logit}(p) = b0 + b1E$$

where E is a transformation of an overall exposure score. Then the odds of an outcome for a man with score E=a compared to the odds of this outcome for a man with score E=b depends only on a-b. In particular, if a = b + 1, then the ratio of the odds for a and b is the odds ratio (OR), and

OR = exp(bl).

For example, odds ratios of 2 and 1.5 indicate 100% and 50% increases, respectively, in the risk of developing disease (or dying) associated with an increase of one unit in E.

The relation between sample size and power can be computed from a method due to Whittemore (Journal of the American Statistical Association, 1981). She tabulates the sample size needed to obtain given power to detect a given odds ratio associated with an increase of one standard deviation in a risk factor (here, the exposure score), for given alpha (probability of a type I error) and probability of outcome (assumed small). Tables are provided for a risk factor with a normal, exponential, and Poisson distribution. For odds ratios not too much larger than 1.0, the sample size does not depend very much on the distribution.

For comparison with the power calculations in the original protocol, it should be noted that one and two standard deviations contain about the central 40% and 70%, respectively, of the normal distribution. Thus, if a monotone transformation of the scores are roughly normal, the increase in risk associated with an increase of one or two standard deviations in the transformed score corresponds roughly to the increase in risk in going from the 30th to the 70th percentile, or 15th to 85th percentile, respectively, in the score distribution.

2. Results

Tables 1 and 2 contain estimates of the odds ratio for the 70th percentile vs. the 30th percentile of exposure score detectable with given power for the Agent Orange mortality, and interview and medical examination components, respectively. Estimates are given for mortality rates of 0.25 to 2.0 %, and for prevalences of 0.5 to 2.0%. All tables are based on tests with a two-sided alternative at alpha = .01 and .05, with powers of 90% and 99%. The odds ratio for the 85th vs. 15th percentile of the exposure score detectable with the same power is the square root of the odds ratio given.

Table 1 is applicable to the mortality study. We expect the overall mortality rate to be somewhat greater than 2.0%. Thus, we should have about 90% power to detect an increased risk of 20% for total mortality associated with the 70th percentile of exposure score compared to the 30th percentile. The remaining mortality rates pertain to cause-specific analyses.

For example, we should have about 90% power to detect an increased risk of 50% for a cause with a prevalence of 0.5%, associated with this same increase in exposure score.

Table 2 is applicable to the interview and medical components. Once again there is very good power for detecting a 50% increase in risk associated with this increase in exposure scores for prevalences as low as 0.5% and 2% in the interview and medical components, respectively. Power is estimated to be better than for a simple comparison of proportions in separate cohorts as in the original design.

The validity of these power estimates depends on the validity of the logistic model and the extent to which our exposure scores correctly rank participants' exposures. Even if these assumptions are not completely valid, these estimates indicate to us that these studies should be able to detect meaningful increases in risk associated with exposure to Agent Orange.

Table 1

Estimated Odds Ratio Detectable for the 70th vs. 30th Percentile.
of Exposure Score with Given Type I Error Rate and Power, for
Various Mortality Rates.
Agent Orange Mortality Study, Combat Veterans (N = 17,000).

Mortality rate	Alpha	Power	Odds Ratio
.0025	.01	.99	2.0
		.90	1.8
	.05	.99	1.7
		.90	1.6
.005	.01	.99	1.7
		.90	1.5
	.05	.99	1.6
		.90	1.5
.01	.01	.99	1.5
		.90	1.3
	.05	.99	1.4
		.90	1.3
.02	.01	.99	1.3
		.90	1.2
	.05	.99	1.3
		.90	1.2

omputation based on a logistic regression model for the mortality rate; see
ext.

Table 2

Estimated Odds Ratio Detectable for the 70th vs. 30th Percentile of Exposure Score with Given Type I Error Rate and Power, for Various Morbidity Rates. Agent Orange Study Interview and Medical Examination.

Prevalence rate	Alpha	Power	Odds ratio
Interview (N = 12,000)			
.0025	.01	.90	2.0
	.05	.90	1.8
.005	.01	.90	1.6
	.05	.90	1.5
.01	.01	.99	1.6
		.90	1.4
	.05	.99	1.5
		.90	1.3
.02	.01	.99	1.4
		.90	1.3
	.05	.99	1.3
		.90	1.2
Medical Examination (N = 4,000)			
.005	.05	.90	2.0
.01	.01	.90	1.8
	.05	.90	1.7
.02	.01	.99	1.7
		.90	1.6
	.05	.99	1.6
		.90	1.5