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SUBJECT: Review of the Draft Protocol for Epidemiological Studies of Agent Orange

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Attached please find the individual comments of members of the Science Panel of the Agent Orange Working Group. Basically, every member expressed concern about the lack of details in the protocol to the point that it is not possible to constructively review the proposal.

The following paragraphs taken from comments submitted by individual members highlight these concerns:

General Comments

1. "While we certainly appreciate Dr. Spivey's concern that release of certain specifics of his anticipated protocol might induce bias in the eventual study, we cannot provide an effective analysis of a protocol without such information. We suggest that at least a small subcommittee of the Science Panel be supplied with all of the details of the protocol and that the report of this subcommittee be held in confidence and not be released to the general public. We believe that an informed evaluation is absolutely essential before any further action is undertaken to initiate any subsequent studies."

2. "The section on proposed outcome measures is particularly weak. The statement that an examination will be done because '...the veterans will expect a physical exam' is inappropriate. The inclusion of special examinations for individuals with recognized disease unrelated to Agent Orange, for example, an examination of the eye backgrounds and peripheral pulses in subjects with a history of diabetes mellitus is of questionable value in such a protocol. At the same time the protocol ignores entirely the neurological examination, which both animal and human data suggest may be of importance.

"Statements such as the one included on page 9 which opines that chloracne is a 'self-limiting skin condition' raise further questions about the authors' full understanding of the potential health effects of dioxins. Chloracne can be a severe skin condition that in some individuals is persistent for years even following discontinuation of exposure. The statement on page 18 that 'Chloracne is the only established health outcome associated with dioxin exposure' is not justified."

3. "It is clear that the current UCLA protocol is inadequate. Therefore, a study is yet to be designed and conducted. Overall, it is our opinion that two important factors must be present for the design and conduct of

a study. First, it is critical that adequate epidemiologic expertise be available within the Group or Agency which assumes responsibility, and second, there must be continuous interface with and cooperation from the DOD and VA so that details of records and activities during the Vietnam War are accessible to the researchers.

"Finally, any delay dependent upon further review of this UCLA protocol should be avoided due to its incomplete nature. Any further review should be postponed until an appropriate scientific protocol based upon a complete iteration of exposure data and veterans' data is available."

4. "In summary, prior to any further attempts to design a study on Vietnam veterans, it is recommended that the Veterans Administration review the morbidity data they have collected thus far, that the Department of Defense establish information on exposure data and determine what the sizes of prospective cohorts might be, and that the Veterans Administration embark on a mortality study. Since any outside group is unfamiliar with the record keeping system of the military, it would be redundant, wasteful, and time-consuming to have outside groups do this preliminary work for the military."

Specific Comments

Exposure

1. "I am deeply troubled by this aspect of the report. On page 43, the authors correctly surmise, 'We have not identified a mechanism which would document actual exposure.' Over the past year in our Committee, as well as the Agent Orange Working Group in the White House, we have wrestled, frankly unsuccessfully, with trying to establish some mechanism for documenting exposure. I recall clearly our meeting with the members of the National Academy of Sciences and their comments regarding any proposed epidemiological study on Agent Orange exposure in Vietnam. The take-home message was, 'If we cannot scientifically validate and document exposure, we cannot do a scientific epidemiological study.' Although Spivey's approach suggests a mechanism by which we might overcome this problem, I suspect we are justifiably due some criticism for the grouping approach. I am now persuaded that we will never be able to do an epidemiology study on individual veterans per se, but must examine military units serving in specific spray areas. There is now some hope from recent DOD activities that we might be able to document some segments of the military population in Vietnam exposed to Agent Orange. Every effort then must be made to work closely with Mr. Christian and his associates in DOD in meticulously reviewing records and films to establish some case for exposure. I recommend we do not fund any additional feasibility studies until a thorough and comprehensive search and cataloging of available DOD records, films, and reports are completed."
2. "In conclusion, I am not convinced that significant ground troop exposure to 2,4,5-T containing herbicide occurred as a result of aerial application. Other uses of the herbicide most likely represented a greater exposure. Additionally, the study must address the question of did the Vietnam

conflict participant incur a health decrement risk over and beyond that which was expected and secondly, if a risk was incurred, is it service connected? This protocol requires greater examination of the exposure criteria and further discussion and refinement."

Use of Terminology

"Definition of Antipersonnel gas: Riot agents such as CS and CN used in Vietnam were not antipersonnel gases since they do not kill or incapacitate for an extended period of time. Both CS and CN have been used throughout the world by civilian police to control riots of civilians and in prisons without causing fatalities. This improper definition should be corrected.

"The substitution of 'riot control agents' in place of 'antipersonnel gases' is suggested."

Conclusion

The members of the Panel had many other specific comments and only some of their major concerns were quoted here. It appears that the present proposal is inadequate and it is recommended that a course of action be developed that will not cause any further unnecessary delays in attempting to answer questions about health issues of Vietnam veterans. A specific protocol should be ~~developed~~ *developed* in which the size of the cohorts and their perceived exposures are characterized and which will serve as the basis for the studies.

The major concern we have with this draft document is the lack of detail provided by the authors in describing the protocol itself. This lack of detail makes an informed critical review impossible. The investigators state that a detailed protocol is not provided due to their inability to examine all relevant military records on which the studies would be based and also because of potential bias they fear might result from premature public release of a detailed study design.

The quality, scope, and availability of military records on Vietnam veterans in addition to the ability to locate individuals in a time - space frame in Vietnam have previously been major issues with regard to developing an epidemiologic protocol. In our view, an adequate protocol requires a clear and detailed evaluation of those military records that are available. While a preliminary feasibility study might be indicated to evaluate the procedure of establishing cohorts with differing exposure levels, a detailed and clear understanding of what records are available may make this unnecessary. A thorough evaluation of those records that exist, what the records contain, and how they might be used in establishing appropriate cohorts must be performed before any protocol can be properly reviewed.

We also strongly disagree that the full protocol should be withheld due to potential bias. It is important that the full protocol receive adequate peer review due to the importance of the investigation. The publicity which currently surrounds the study has already influenced those individuals who will eventually be included. A full presentation of the protocol in our view would have little further adverse impact. To withhold pertinent details may cause far more harm by seriously damaging public confidence in the credibility and independence of the study.

We do not agree that the "historical cohort study" should be limited to draftees and one term enlisted men. Excluding individuals with longer service will undoubtedly exclude some individuals with the greatest potential exposures.

Inadequate detail is provided about cohort selection by the authors. Full and extensive discussion of the HERBS data, of the nature of troop movements through Vietnam, and the pattern of likely exposures are critical in evaluating the protocol. There is a fair amount of information offered on environmental persistence of agent orange, but no assessment of how the data affects presumed exposure to ground troops. The concept of establishing low to high exposure groups based on a "time - place - company exposure grid" is too vague as presented and it is not clear that the authors have a fundamental understanding of the core issues which need to be addressed in establishing such cohorts.

The sections in the protocol on potential confounding variables and control groups are both non-specific and short on detail.

The section on proposed outcome measures is particularly weak. The physical examination in our view can be a significant factor in this study in determining ill health, since the potential end organ toxicity for a number of organ systems can be identified and specifically evaluated through a physical examination. The statement that an examination will be done because "...the veterans will expect a physical exam" is inappropriate. The inclusion of special examinations for individuals with recognized disease unrelated to agent orange, for example an examination of the eye grounds and peripheral pulses in subjects with a history of diabetes mellitus is of questionable value in such a protocol. At the same time the protocol ignores entirely the neurological examination, which both animal and human data suggest may be of importance.

Statements such as the one included on page 9 which opines that chloracne is a "self-limiting skin condition" raise further questions about the authors' full understanding of the potential health effects of dioxins. Chloracne can be a severe skin condition that in some individuals is persistent for years even following discontinuation of exposure. The statement on page 18 that "chloracne is the only established health outcome associated with dioxin exposure" is not justified.

The authors have devoted considerable effort to giving a review of basic epidemiologic principles and a superficial review of toxicity information. While this information may be of interest as introductory material, the critical task of the contract was to establish a thorough, detailed, and scientifically defensible protocol.

It is our opinion that the current draft protocol is inadequate as presented and that a major effort will be required to develop the protocol to a point where further peer review can be meaningful.

We look forward to working with the Science Panel in responding to the VA on this important proposed study.

B

1. While we certainly appreciate Dr. Spivey's concern that release of certain specifics of his anticipated protocol might induce bias in the eventual study, we can not provide an effective analysis of a protocol without such information. We do not support blind trust in the correctness of Dr. Spivey's deductions and selections. We suggest that at least a small subcommittee of the Science Panel be supplied with all of the details of the protocol and that the report of this subcommittee be held in confidence and not be released to the general public. We believe that an informed evaluation is absolutely essential before any further action is undertaken to initiate any subsequent studies.

2. The following comments are provided with references to paragraphs and stamped page numbers at the bottom of each page:

a. Pg. 007, Para. B, Method: Calls for Computer mapping of HERBS data. This has already been accomplished for both crop and defoliation missions with separate map overlays by year. The Veterans Administration has such a set of overlays.

b. Pg. 011, Last paragraph: Our records show that all fixed wing missions using herbicides blue and white were not stopped until 31 October 1971. The last helicopter mission with Herbicide Orange was recorded on 9 June 1970. All fixed wing defoliation missions with Orange ceased on 16 April 1970. The same paragraph neglects to mention that herbicides were also sprayed along the sides of rivers, roads, and communication lines to prevent cover to the enemy.

c. Pg. 020, 1st Para.: For possibly highly exposed personnel he might also wish to include chemical unit personnel at battalion level charged with spraying base camp perimeters, riverine personnel who sprayed the edges of rivers, and other personnel involved in cleaning up herbicide spills after accidental releases.

d. Pg. 040, Ques. 1 posed: The discussion here is extremely limited and does not mention the fact that many personnel both Orange and non-Orange exposed may have had prior exposures to TCDD through agricultural or home use during childhood and adolescence. There is no reason to believe that commercially available herbicides did not also contain TCDD. In fact, during the period when these young men were children the TCDD concentrations in such compounds may have been higher due to lack of perfection in the manufacturing process. We believe this should be looked into and also considered. If such is the case then an "unexposed" guaranteed population of young adult males of that period may be impossible to find. We are now researching the use of 2, 4, 5-T at posts and stations here in the United States and overseas. Because of the long latent period for carcinogenic effects, perhaps those persons claiming effects such as testicular cancer may be reaping exposures which took place while in childhood here in the United States and having nothing to do with Vietnam service. Similarly, prior exposures to other toxic environmental hazards may now be showing up as diseases in the Vietnam veteran population. No mention is made of possible other exposures to dioxin containing substances such as pentachlorophenol wood preservatives and hexachlorophene used in surgical germicidal soaps. Thus unexposed Orange troops may have gained dioxin exposure from other sources. Likewise, a veteran who served in Vietnam say from 1967 to 1968 has had 12 years in which (depending upon his civilian work environment) he may have been exposed to several other toxic and hazardous compounds that are now producing disease symptoms and which have no relation to Herbicide Orange in any way.

e. Pg. 041, Ques. 2, Other Exposure: Attachment 1 to these comments lists possible other exposures encountered by military members serving in Vietnam. It is by no means an exhaustive list. We agree that these additional sources of exposure to various substances and disease entities may be very important confounding factors in relation to sorting out primary effects caused by exposure to Herbicide Orange.

f. Pg. 043, Ques. 5: Comparison to veterans who served in Korea and World War II may be exceptionally difficult since many if not most of the personnel records were destroyed in the St. Louis Records Center fire.

g. Pg. 047, 1st line, 1st paragraph: Suggest substitution of "riot control agents" in place of "antipersonnel gases."

h. Pg. 049, Para. E.1.: Why will the study be limited to draftees and one term enlisted men? Why not include young troop commander officers and senior enlisted personnel who were in the field? Follow-up physical examination records for career enlisted and officer personnel would probably be much more extensive and easily obtainable than from civilians who left the service at the end of one enlistment.

i. Pg. 052, Para. 3, Estimation of Exposure: We see no reason to construct a second exposure index involving a long term environmental persistence as many studies have been already directed at herbicide persistence, especially considering the high mobility of the troop populations while in Vietnam and decay studies of herbicides and TCDD such as Seveso. Also supporting this contention would be the long term studies conducted at Englin Air Force Base at the loading hardstands where there was exceptionally high concentrations of Herbicide Orange spilled and trapped in the ground.

j. Pg. 052, last para.: What is proposed in this last paragraph and on the following page can amount to millions of dollars of labor time to locate a defined population with respect to the HERB tapes. The already accomplished Battalion studies conducted by the Army and the Marine Corps have pointed out how laborious and time consuming such a massive effort would be. The major fallacy of such a study would be that the major source of contamination and/or exposure to ground troops may not be from fixed wing Ranch Hand spraying. This is because of entrapment of the herbicide in triple layer tree canopies, rapid absorption of the herbicide into plant leaf tissue, vaporization of the spray above the jungle canopy, rapid decay of dioxin due to photo degradation (less than 6hr. half-life), and low or non-existent volatility and very low solubility of dioxin in water. A probable source of much higher contamination would be from spraying of herbicides around the perimeters of camps and fire bases through the use of helicopters, truck mounted decontamination spray units, backpack hand sprayers, and Buffalo turbines. These types of perimeter spraying are very poorly documented at best and only a tiny fraction of all helicopter spray missions are documented in the HERBS tapes. Couple this lack of data as to amounts, type and dates of perimeter spraying with the already proven difficult task of placing troops with respect to physical location by each day of the year at a specific grid location and we have a very "iffy" situation at best. What the author advocates in no way seems to be a solution. Finally after 18 months neither the Science Panel nor anyone else has been able to establish just what constitutes an "Exposure" to Herbicide Orange.

k. Pg. 053, Para. 4, Establishing Cohorts: In this discussion we assume the author is referring to single or multiple exposures from Ranch Hand flights over or near the selected company. There are many problems to this method of counting on a company and its personnel being at a certain place at a certain time with respect to an overflight by Ranch Hand aircraft. To name a few, we have the following:

(1) In the case of Marine records the troops were carried on the Morning Reports (MR) as either Killed in Action (KIA), Wounded in Action (WIA), Missing in Action (MIA), present for duty, or transferred. Hence minor disabilities were not entered in the MR and consequently a Marine may have remained in base camp while his platoon was out on patrol.

(2) Companies did not necessarily operate all together and stay together. Marine units very frequently operated in small patrols and platoon size units. Documentation as to their day-to-day locations are very poor. In one Marine battalion study for a two month period only 4 exact unit locations could be determined for an operational area of 10km long along route 9 and width of 6.5km back from each side of this road. We know that patrols roamed all over this area to protect the security of the route from enemy ambushes but it is impossible to fix company, platoon, or squad locations during this time.

(3) In the case of the 1st. Cav. units, platoons would be detached from a company for a period of time and assigned to another infantry battalion far from the operating location of this 1st. Cav. parent company.

(4) In air mobile operations, it was not uncommon to have helicopters drop a platoon of men into a landing zone and then the platoon would go into a search mission through the jungle with no documentation as to their day-to-day location. Finally one or more days later the platoon would reassemble at the landing zone and be airlifted out. In the mean time the rest of the Company would be at the base camp or operating in other areas.

(5) We have also found that there are errors in the morning reports regarding the duty status of individuals. It has been observed that as long as six months elapsed before a correction was made to pick-up or drop an individual. Similarly some people may have been detached from the units for short periods of time (several days) without this showing up in the Morning Report. We know of one case of an individual whose body was in the mortuary in Tan San Nhut and his unit was unknown for quite a while. When his unit was contacted they thought he was still with them until they made a detailed search. He was, of course, being carried on the Morning Report as present for duty although he had been dead for several days. We cannot trust the validity of these combat records in all cases.

(6) There was also a very high thruput of personnel in the Army battalions studied. For a battalion of about 971 persons over 2,300 personnel served for varying periods of time in the one year period which was studied.

1. Pg. 063, last para.: It seems wise to mention that a preliminary review cost for pulling a record at the St. Louis Records Center and determining minimum locator information will be \$5.17 per record. More detailed research could run the bill up and overall costs of a major search could be very very expensive.

m. Pg. 069, HERBS Tape Mapping: The National Academy of Sciences report "The Effects of Herbicides in South Vietnam" Part A, Summary on page IV-104 shows just such a mapping as is desired to be accomplished. We understand that it took the computer at least 5 twelve hour runs to produce these maps. Why should they be done over as they were made directly from the HERBS hard copy reports and should be available. This is a very costly process to duplicate. As may be seen from the referenced page, each spray track is shown on the map with the date of the mission, number of gallons sprayed and the type of herbicide. (Attachment 2 enclosed)

n. Pg. 070, Major portion of page: This is an idealized approach and is not at all typical to many units operating over there, especially those which were air mobile, or to Marine units. We determined this when we looked at the same Marine battalion that GAO had said was right under a spray track. In one of the battalion studies no detailed unit records were found for an entire six month period.

o. Pg. 089, 1st new para.: As mentioned earlier detailed personnel records for Korean veterans may not be available because of the St. Louis records center fire. We understand reconstruction (costly) of about 35% might be possible. One major factor has been overlooked in a possible comparison between Vietnam and Korean veterans and that is Korea was not in a jungle environment and units operated as units. Winter fighting was common in portions of the Korean war while Vietnam was in a jungle environment with many different types of disease exposures and small unit operations involving living off the land. Korea was not as unpopular as Vietnam.

p. Pg. 249, Definition of Antipersonnel gas: Riot agents such as CS and CN such as used in Vietnam were not antipersonnel gases since they do not kill or incapacitate for an extended period of time. Both CS and CN have been used throughout the world by civilian police to control riots of civilians and in prisons without causing fatalities. This improper definition should be corrected.

q. Pg. 249, Definition of Battalion: An idealized definition, not necessarily true in Vietnam type combat operations.

As you requested, we have reviewed the "Draft Protocol for Epidemiologic Studies of Agent Orange", G.H. Spivey and R. Detels, U.C.L.A., submitted to the Veterans Administration (contract V101 (93) P-842).

It is our understanding that the purpose of the contract was to procure an epidemiologic protocol outlining specific plans for the study of Vietnam Veterans exposed to Agent Orange. The protocol submitted, if it is a final product, does not fulfill this goal. It is diffuse and nonspecific and does not outline an approach particular to the problem being addressed. In fact, numerous epidemiologic approaches to the study of veterans are outlined, as are numerous hypotheses which could be tested. Not included, however, is a clear discussion of benefits and drawbacks of various approaches, and a clear recommendation for a study addressing this issue.

The authors of the protocol note a number of problems which they encountered including access to military data and the issue of bias if specific plans for a study of Veterans are publicly discussed. To these problems should be added the very limited time which the contractor had to fulfill the assignment. The question of scientific bias, however, should not continue to be a deterrent to the development and outline of specific plans for a study of the Vietnam Veterans. In fact, any protocol for such a study should be specific and receive the widest review possible before a study is initiated.

In response to Senator Cranston's letter, it is clear that the current UCLA protocol is inadequate. Therefore, a study is yet to be designed, and conducted. Overall, it is our opinion that two important factors must be present for the design and conduct of a study, regardless of what Group or Agency specifically carries out these tasks. First, it is critical that adequate epidemiologic expertise be available within the Group or Agency which assumes responsibility, and second, there must be continuous interface with and cooperation from the DOD and VA so that details of records and activities during the Vietnam War are accessible to the researchers.

Finally, any delay dependent upon further review of this UCLA protocol should be avoided due to its incomplete nature. In particular, review by the National Academy of Sciences should be postponed until an appropriate scientific protocol based upon a complete iteration of exposure data and veterans' records is available.

This review represents my own personal assessment of the protocol and does not represent necessarily a Department position. Several fundamental comments are provided in the way of general criticism. More specific, perhaps less important, thoughts are then attached, Atch 1.

a. Confidentiality of Protocol Design

Since premature public disclosure could potentially jeopardize the validity of the study, it is agreed that certain specific details of the protocol design requires restricted public access. However, this scientific panel must obtain a more detailed discussion of the study design. The Veterans Administration must develop a mechanism which preserves the validity of the study while providing adequate scientific peer review. Functionally it would be preferable to have the detailed protocol made available to this panel with a follow on discussion with Dr Sprivey and the other principal designers some weeks later.

b. Definition of the Fundamental Question to Be Answered.

The Vietnam veteran through some form of "collective wisdom" perceives himself to have suffered an abnormal, unexpected health decrement either in himself or his progeny following his participation in the Vietnam conflict. One cannot determine why this "collective wisdom" has singled out Agent Orange as the causative factor. However, the "collective wisdom" of a group of persons occupationally exposed has often times proved correct. Subsequently, the scientific community has then through rigorous examination determined the cause of the observed decrement. I have not come to a conclusion regarding Herbicide Orange, the "collective wisdom" of the veteran may prove to be correct on both counts i.e. health decrement and cause. However, close examination of the "occupational environment" of the Vietnam conflict does not easily reduce to a single factor of exposure but rather reveals a multiplicity of exposures which singularly or in combination could produce the decrements described. The fundamental question to be answered by the VA study is: Did the Vietnam conflict participant incur a health decrement risk over and beyond that which was expected and secondly if a risk was incurred is it service connected? The Congress, perhaps naively, tried to address this question by directing the VA to conduct an epidemiology study. Approximately a year later the Congress had gathered additional information on the Vietnam experience. While not yet an act of Congress, the newly proposed legislation has enjoyed wide acceptance and support. The so called broadening of the VA study to include other possible causitive factors was supported by this scientific panel.

Dr Spivey has concluded that "the original Agent Orange question, # 1 page 30, addressed with suitable safeguards for confounding by other exposures and factors, would seem to be the most appropriate for this study". His discussion of this narrowly defined question leaves the impression that a true decrement may go unrecognized and that sequential study of other narrowly defined exposures may be necessary to determine the existence of a health risk. The Government and the veteran wants an answer to the broader question in terms of what diseases and health decrements are in excess of the norm and is the excess, if it exist, service connected. For the purpose of prevention of future disease the identification of the causative factor becomes useful.

Dr Spivey's discussion of the broader question, #no. 4, page 33, implies that the discrimination of an effect would not be discernable. A properly designed study could examine the existence of disease excess in both broad categories of impacted systems and specific disease end points. Identification of exposure factors could be examined by use of a regression matrix. The use of multivariate statistics may be ideal in this study design instance. Further, a group of reasonably informed individuals could develop a list of major independent variables (occupational and environmental exposures) which given present state of the art knowledge represent potential risks to human health singularly or in combination.

c. Exposure Criteria

The Spivey design if adopted would be largely dependent on an exposure which at this reading admittedly lacked definitive objective criteria. Sole reliance on the Herbs tape and troop headquarters location assumes that the aerial spraying of herbicide was the principal route of exposure to 2,4,5-T containing herbicides. This method functionally ignores the application of herbicide by means other than aircraft and helicopter. Additionally, it fails to observe the possible presence of other 2,4,5-T containing herbicides which may have been used by local commanders. The various agencies were free to procure these herbicides through the Federal supply system; the General Services Administration (GSA) regularly negotiated contracts with private companies. Only the tactical herbicides were controlled and even then local commanders obtained these herbicides probably by barter. A list of commercially available 2,4-D and 2,4,5-T herbicides is attached, Atch 2. It is not known how many of these were procured by the GSA. Attachment 3 lists some Federal Stock Numbers (FSN's) which were 2,4-D and 2,4,5-T containing herbicides other than Herbicide Orange. If Herbicide Orange is the causative factor for the health decrements claimed, the aerial application was not necessarily the significant route of exposure. While the quantities applied aurally were massive, the ground troop proximity was not sufficiently close to represent a significant exposure. A more likely exposure would have been the local application of herbicide to base perimeters and associated undesirable vegetation. Here some ground troops were immediately adjacent to the spray. This is not to say that in certain instances that the Ranch Hand aircraft application of herbicide to base perimeters didn't occur. There is reason to believe that base perimeter spraying by Ranch Hand did occur.

Lastly, if the Herbs tapes are to be used to establish exposure then a consistent objective exposure model needs to be developed. Such a model must consider wind direction, altitude of dispersal, air temperature, particle size, volatility of the herbicide and the type of vegetation targeted. If ground troops were not directly below the spray path, then the above parameters become important in determining what residual material may have been inhaled by personnel located some distance away from the spray path. Obviously the greater the distance the less the concentration of exposure. However, a simple plume dispersion model may not be appropriate since local vegetation would intercept the mist/vapors and incident radiation may degrade the level of TCDD. It is suggested that local weather information be used if available. Failing that, simplifying assumptions could be made using seasonal information. Development of this methodology may not prove definitive but would most likely describe reasonable bounds for exposure.

d. Proportionate mortality study

This short term study proposed by Dr Spivey's group has merit. The proportionate mortality study should be undertaken even though the results may be less than definitive.

In conclusion, I am not convinced that significant ground troop exposure to 2,4,5-T containing herbicide occurred as a result of aerial application. Other uses of the herbicide most likely represented a greater exposure. Additionally the exposure to other occupational and environmental factors present in Vietnam represent equivalent in greater risks of chronic disease. The study must address the question of did the Vietnam conflict participant incur a health decrement risk over and beyond that which was expected and secondly, if a risk was incurred, is it service connected? This protocol requires greater examination of the exposure criteria and the further discussion and refinement of question number four, page 33.

3 Attachments

1. Specific Comments
2. Formulations Containing 2,4,5-T

Specific Comments

1. Design of a Study Using Vietnam as the Exposure Criteria

The concept of a factorial experimental design could be used to establish an independent variable matrix. This matrix could have incorporated within it the Agent Orange exposure as well as exposure to such factors as Dapsone, pentachlorophenol, other 2,4-D and 2,4,5-T herbicides, Malithion, illicit drugs, alcohol consumption, riot control agents, DEET and smoking. Variables which are not quantitative or quantifiable could have digital descriptors applied as indicators of exposure.

The dependent variable matrix could access categories of disease or specific disease end points. The independent matrix could then be used to predict disease outcome via multivariate regression. If significant relationships were found, examination would be required to determine plausibility before causation could be assigned.

The control group of non Vietnam veterans would have similar independent and dependent matrices developed. A comparison of the two dependent matrices would examine the question of health decrement over and beyond what was expected.

All persons in the study matrix would receive a study questionnaire and have their military and private medical records examined. A random number of personnel in the large matrix cells would be selected for physical examination. The objective physical examination findings would flesh out and validate the independent and dependent matrices. Should significant health decrements be found in certain matrix cells, additional cell members would be physically examined to validate the initial findings. Mortality analysis of the full cohort would be undertaken.

2. Personnel to be studied

While the greatest involvement of personnel did occur in the time period 1965-1972, the greatest concentration of TCDD in 2,4,5-T containing herbicides occurred prior to 1965. Any exposure criteria uniformly applied across the years of involvement would indicate that early year personnel would have been exposed to greater levels of TCDD. Also, it would seem advantageous to include people who had multiple year exposure.

Personnel who volunteered to go to Vietnam should be included in the study. If desired the differentiation of volunteer/draftee and enlisted/officer personnel could be entered into the independent variable matrix. The illicit drug and alcohol habits of the four possible groups may have been different.

Note: The Marines had a policy of no hard liquor while in Vietnam. It is unclear if this was for all Marines.

3. Cost of Study

At the present time cost is not a consideration of study design. Only after the best possible scientific design has been established must a judgement be made to accept the anticipated cost. In this case it could seem cost acceptance becomes the ultimate burden of the Congress after the Veteran's Administration describes what can or cannot be done scientifically.

4. Assessing Herbicide Orange Exposure by Questionnaire

This technique frequently used in an occupational setting is extremely risky in this case. Since the same aircraft sprayed White and Blue, the recollection of a study participant that a plane or helicopter "flew near or over him spraying something" will not establish exposure to Herbicide Orange. The additional observation that a camouflaged aircraft was used doesn't narrow the possibilities.

The first Ranch Hand planes sent to Vietnam for defoliation had bright silvery skins.

5. Active Duty Deaths

One should not assume that an active duty death occurring within one year was due to traumatic battle injury. Additionally, the fact of contributory cause may be important if the immune system were compromised. Lastly some deaths may have occurred as a result of disease only.

67346

FSA

Available Formulations Containing 2,4,5-T
as of February 1, 1973

Amchem Products, Ambler, Pennsylvania 19002

2,4,5-T

Emulsamine 2,4,5-T Alkylamine salt	58.9% act. ing.	33.7% a.e.	3 lb/gal
Envert-T Butoxyethanol ester	33.9% act. ing.	24.3% a.e.	2 lb/gal
Trinoxol Butoxyethanol ester	59.7% act. ing.	42.9% a.e.	4 lb/gal
Trinoxol Super 6 Butoxyethanol ester	81.5% act. ing.	58.5% a.e.	6 lb/gal
Weedar 2,4,5-T Triethylamine salt	57.2% act. ing.	41.0% a.e.	4 lb/gal
Weedone 2,4,5-T Butoxyethanol ester	58.3% act. ing.	41.9% a.e.	4 lb/gal
Weedone 2,4,5-T Special Air Spray Formula Butoxyethanol ester	58.7% act. ing.	42.2% a.e.	4 lb/gal

2,4-D and 2,4,5-T mixtures

Dinoxol Butoxyethanol ester	2,4-D	31.5% a.i.	21.7% a.e.	2 lb/gal
	2,4,5-T	30.2% a.i.	21.7% a.e.	2 lb/gal
Emulsamine BK Alkylamine salts	2,4-D	31.4% a.i.	16.9% a.e.	1.5 lb/gal
	2,4,5-T	29.5% a.i.	16.9% a.e.	1.5 lb/gal
Dinoxol Super 6 Butoxyethanol esters	2,4-D	43.5% a.i.	29.8% a.e.	3 lb/gal
	2,4,5-T	41.7% a.i.	29.8% a.e.	3 lb/gal
Emulsavert 100 acid & amine salt	2,4-D	21.2% a.i.	11.9% a.e.	1 lb/gal
	2,4,5-T	21.2% a.i.	11.9% a.e.	1 lb/gal
Emulsavert 248 acid & amine salt	2,4-D	13.2% a.i.	6.1% a.e.	1/2 lb/gal
	2,4,5-T	19.3% a.i.	12.2% a.e.	1 lb/gal

Envert - DT				
Butoxyethanol ester	2,4-D	17.7% a.i.	12.2% a.e.	1 lb/gal
	2,4,5-T	17.0% a.i.	12.2% ae.	1 lb/gal
Weedar Amine BK				
Dimethylamine salt	2,4-D	24.5% a.i.	20.4% a.e.	2 lb/gal
Trimethylamine salt	2,4,5-T	28.5% a.i.	20.4% a.e.	2 lb/gal
Weedone BK 6h				
Butoxyethanol ester	2,4-D	19.7% a.i.	14.2% a.e.	1.33 lb/gal
	2,4,5-T	41.5% a.i.	28.6% a.e.	2.67 lb/gal
Weedone IBK				
Butoxyethanolester	2,4-D	31.1% a.i.	21.4% a.e.	2 lb/gal
	2,4,5-T	29.7% a.i.	21.4% a.e.	2 lb/gal

Dow Chemical Co., Midland, Michigan 48640

2,4,5-T

Esteron 245 Concentrate				
Propylene glycol butyl ether ester		92.5% a.i.	60.2% a.e.	6 lb/gal
Esteron 245				
Propylene glycol butyl ether ester		69.2% a.i.	45.0% a.e.	4 lb/gal
Reddon				
Propylene glycol butyl ether ester		20.4% a.i.	13.3% a.e.	1 lb/gal
Veon 245				
Trimethylamine salt		56.1% a.i.	40.2% a.e.	4 lb/gal
Verton 2T				
Propylene glycol butyl ether ester		37.2% a.i.	24.2% a.e.	2 lb/gal

2,4-D and 2,4,5-T mixtures

Brush Killer LV 2-2				
Isooctyl esters	2,4-D	34.7% a.i.	23.0% a.e.	2 lb/gal
	2,4,5-T	33.1% a.i.	23.0% a.e.	2 lb/gal
Brush Killer LV hT				
Isooctyl ester	2,4,5-T	65.0% a.i.	45.3% a.e.	4 lb/gal
Esteron Brush Killer				
Propylene glycol butyl ether esters (PGBE)				
	2,4-D	36.0% a.i.	22.2% a.e.	2 lb/gal
	2,4,5-T	34.1% a.i.	22.2% a.e.	2 lb/gal
Tippon 2-2				
PGBE esters	2,4-D	36.3% a.i.	22.4% a.e.	2 lb/gal
	2,4,5-T	34.4% a.i.	22.4% a.e.	2 lb/gal

Veon Brush Killer				
Dimethylamine	2,4-D	24.3% a.i.	20.2% a.e.	2 lb/gal
Trimethylamine	2,4,5-T	28.2% a.i.	20.2% a.e.	2 lb/gal
Verton CE	2,4-D	36.0% a.i.	22.2% a.e.	2 lb/gal
(PGBE)	2,4,5-T	34.1% a.i.	22.2% a.e.	2 lb/gal

TORDON and 2,4,5-T Mixtures

Tordon 155				
Isooctylester Picloram		15.1% a.i.	10.3% a.e.	1 lb/gal
PGBE	2,4,5-T	63.4% a.i.	41.3% a.e.	4 lb/gal

Thompson-Hayward

2,4,5-T

DED-WEED LV-6				
Isoocetyl ester	2,4,5-T	64.0% a.i.	44.4% a.e.	4 lb/gal
DED-WEED LV-9				
Isoocetyl ester	2,4,5-T	83.5% a.i.	58.8% a.e.	6 lb/gal

2,4-D and 2,4,5-T mixture

DED WEED LV-33				
Isooctylester	2,4-D	33.5% a.i.	22.2% a.e.	2 lb/gal
Isooctylester	2,4,5-T	31.9% a.i.	22.2% a.e.	2 lb/gal

Transvaal Inc., Jacksonville, Arkansas 72076

2,4,5-T

Brush-Rhap A-4T	2,4,5-T	57.0% a.i.	40.8% a.e.	4 lb/gal
Triethylamine salt				
Brush-Rhap LV-4T	2,4,5-T	65.3% a.i.	45.4% a.e.	4 lb/gal
Ethyl hexyl ester				
Brush-Rhap LV-6T	2,4,5-T	87.0% a.i.	60.4% a.e.	6 lb/gal
Ethyl hexyl ester				
Brush-Rhap A-2D-2T				
Dimethyl amine salt	2,4-D	24.7% a.i.	20.5% a.e.	2 lb/gal
Triethylamine salt	2,4,5-T	28.6% a.i.	20.5% a.e.	2 lb/gal
Brush-Rhap LV-2D-2T				
Ethylhexyl ester	2,4-D	34.7% a.i.	23.0% a.e.	2 lb/gal
Ethylhexyl ester	2,4,5-T	33.1% a.i.	23.0% a.e.	2 lb/gal

E

This document entitled "Draft Protocol for Epidemiological Studies of Agent Orange" was prepared under the direction of Dr. Gary H. Spivey, University of California, Los Angeles, California, Veterans Administration Contract V-101(98)3P-842. It consists of three parts. The first 19 pages are primarily an introduction. The second 65 pages which are entitled "Research Methods and Proposed Protocol" primarily represent a discussion of the difficulties normally faced in epidemiology studies, and the rest of the document is a literature review covering about 141 pages. In addition, an outline of a proposed cursory physical examination is also attached.

From the information provided in this draft, it is not possible to constructively criticize any proposed study since insufficient information is provided to determine how this study is to be conducted. Apparently the authors of this proposed protocol had a number of difficulties; among them, the inability to obtain exposure data partly because they did not have any security clearance. Basically, the authors of this draft document recommend that cohorts be established for follow up, that they receive a basic physical examination, and that a questionnaire be administered.

The proposal in the document on how to determine exposure appears rather cumbersome and will probably not be very rewarding. I, therefore, suggest that battalions be identified and that the basic exposure of these battalions be determined. The individual soldiers should then be assigned to their respective battalions. In addition, the amount of time each veteran spent in Viet Nam should be determined. It could then be established on a subsample how great the variation is for the amount of time that the different veterans actually spent within the battalion versus the amount of time spent in Viet Nam. If it turns out that the amount of time per soldier spent away from his battalion in Viet Nam does not differ a great deal, it is unnecessary to check for the presence or absence of all soldiers in the morning report since the exposure for all of them will be roughly the same. It is recommended that this be determined by the Department of Defense under the supervision of the IHS working group and be reviewed by an outside advisory group.

Since the sprayed Agent Orange is persistent in the environment, it is assumed that, in addition to the exposure to spraying missions, the soldiers had additional exposure while in sprayed areas. It is recommended that it be determined whether battalions who were sprayed on were also usually battalions that were in sprayed areas. In addition, all battalions that were exposed to aborted missions should be identified and their special additional exposure determined.

While the Department of Defense is determining exposure levels of Viet Nam veterans and identifying veterans who could be grouped into cohorts, it is recommended that the Veterans Administration review the morbidity data which have been collected in different Veterans Administration Hospitals from Viet Nam veterans to determine whether any obvious clustering of certain symptoms and signs can be identified, or any disease patterns which are out of the ordinary. Concurrently with these efforts, a prospective and retrospective mortality study should be conducted. Approximately twenty people should be trained to locate death certificates of Viet Nam era veterans. Information about deaths of Viet Nam era veterans will have to be obtained from different sources since particularly in the early part of the Viet Nam War, social security numbers were not used as serial numbers. However, by using a multifaceted approach, it should be possible to locate better than 95% of the death certificates within an eight-month's period. Once death certificates have been located, the Viet Nam veterans have to be separated from veterans who served in other areas during the same time period. In addition, all casualties can be separated before a retrospective mortality study is done. In addition to this retrospective mortality study, a prospective mortality study can also be initiated at the same time. A more detailed outline of this study will be provided later.

Since the Veterans Administration and the Department of Defense are most familiar with their own records and since this is merely a search for records, no obvious bias could be introduced into this part of the study or into the interpretation of the analysis of death certificates, particularly if the raw data are made available to a review group. There is, therefore, no reason why this should be done by a group outside of the military, particularly if outside help is solicited in areas where no internal expertise is available.

It is stated on pages 64 and 65 of the present draft document that from the Viet Nam era veterans during the period from 1965 to 1972, there are now 130,000 deaths and that approximately one-third (i.e., 43,000) of the soldiers are expected to be Viet Nam veterans. These numbers should be rechecked since there have been statements in the press that a total of about 50,000 veterans were killed in action in Viet Nam. One would have to assume that there should be many more death certificates than 43,000.

In summary, prior to any further attempts to design a study on Viet Nam veterans, it is recommended that the Veterans Administration review the morbidity data they have collected thus far, that the Department of Defense establish detailed exposure data and determine what the sizes of prospective cohorts might be, and that the Veterans Administration embark on a mortality study. Since any outside group is unfamiliar with the record keeping system of the military, it would be redundant, wasteful, and time consuming to have outside groups do this preliminary work for the military.

As requested at our last Advisory Committee meeting on Health Related Effects of Herbicides, I have reviewed the Draft Protocol submitted by Dr. Gary H. Spivey and Dr. Roger Detels of the Division of Epidemiology, School of Public Health, University of California, Los Angeles, California. I have read the report, but I am not professionally qualified to comment on many of the medical and epidemiological aspects of the Draft Protocol. It is my understanding that the Department of Health and Human Services (HHS) will provide sufficient epidemiological expertise to comment on those segments of the report. Dr. Spivey does make a good case, however, for the historical cohort design in his proposed epidemiological protocol.

I am qualified to comment on two issues in the report, i.e., (1) Review of Environmental Behavior of Agent Orange, and (2) Exposure.

Experimental Studies

The section dealing with environmental studies is understandably brief and should be so for a report of this nature. The authors have done an acceptable job of reviewing the major environmental issues. However, since the magnitude of the literature is substantial, they have only treated it in a superficial manner. Its major problem is that it presents a non-critical evaluation of the literature. Consequently, it presents selected references without really commenting on the relevance of such data to the proposed epidemiological study. There are numerous typos in this section that should be corrected in the next typing.

Exposure

I am deeply troubled by this aspect of the report. On page 43, the authors correctly surmise, "We have not identified a mechanism which would document actual exposure." Over the past year in our Committee, as well as the Agent Orange Working Group in the White House, we have wrestled, frankly unsuccessfully, with trying to establish some mechanism for documenting exposure. I recall clearly our meeting with the members of the National Academy of Sciences and their comments regarding any proposed epidemiological study on Agent Orange exposure in Vietnam. The take-home message was, "If we can not scientifically validate and document exposure, we can not do a scientific epidemiological study." Although Spivey's approach suggests a mechanism by which we might overcome this problem, I suspect we are justifiably due some criticism for the grouping approach. I am now persuaded that we will never be able to do an epidemiology study on individual veterans per se, but must examine military units serving in specific spray areas. There is now some hope from recent DOD activities that we might be able to document some segments of the military population in Vietnam exposed to Agent Orange. Every effort then must be made to work closely with Mr. Christian and his associates in DOD in meticulously reviewing records and films to establish some case for exposure.

I believe Dr. Spivey and his associates have made a start on identifying the kind of epidemiology study needed and the information necessary to begin the project. I am not impressed, however, that we have a working program that could be used for the basis of funding a large epidemiological study mandated by Congress. We have a long way to go, and a major problem is the quality of the record of documented exposures that can be elicited from the DOD Record Center. I recommend we do not fund any additional feasibility studies until a thorough and comprehensive search and cataloging of available DOD records, films, and reports is completed.

G

INITIAL MESSAGE

In accordance with your request for comments on the subject document, I reviewed the document. However, I found that the document was too general and non-specific for preparing definitive criticisms. Comments to be prepared would have to start at designing the program from the foundation up.

H

As a concise detailed protocol this document is clearly only a preliminary outline, primarily, as the authors stress repeatedly, because they have yet to be able to assess the data sources on which the studies will depend. As a result, the document consists mostly of extensive reviews of various aspects of the Agent Orange/dioxin issue, its history, and public reaction. It also presents much material describing epidemiologic principles and techniques. The latter is well written, clear and concise, a good statement of principles and issues underlying the choice of cohort study approach.

Considering the lack of access as yet to data sources, the proposal as presented seems quite reasonable: a retrospective cohort study, preceded by some feasibility work and several preliminary studies using existing overall veteran mortality/morbidity data. The cohort study itself would be a massive effort, the details of which cannot be fleshed out until the investigators examine first-hand the materials they will need to use. Until they get to that point, however, one cannot expect them to produce a protocol document of the sort we were able to construct for our birth defects/veterans study (given the fact that data sources and methodology were all at hand and familiar to us). Unfortunately, from our experiences with the "Smoky" cohort followup, I would be pessimistic that the investigators will have easy and prompt access to data or that tracing cohort members will go smoothly.