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VETERANS ADMINISTRATION
DEPARTMENT OF MEDICINE AND SURGERY
WASHINGTON, D.C. 20420

July 14, 1978

IN REPLY
REFER TO: Dr Schepers (11

MEMBERS OF ADVISORY COMMITTEE ON HERBICIDES

Please review the attached draft of the minutes of the meeting which we held on July 7. Please return your copy with suggested changes marked on it.

We did not have a column for your degrees and your title on our sign in sheet. Please accept our apologies if we have accorded you the wrong degree or title and supply the correct information.

After the comments have been received from you we shall prepare a formal version incorporating your suggestions and corrections. I may have missed some points while performing my dual role of chairman and scriba.

Please also indicate your preference for the date of the next meeting by circling the appropriate day in September on page 7.

The appendices are not included at this time. They will be attached to the final version of the minutes.

G M Schepers

Gerrit Schepers, M.D.

Draft

Veterans Administration Central Office

MINUTES OF MEETING OF THE VACO ADVISOURY COMMITTEE ON HERBICIDES
July 7, 1978
810 Vermont Ave, NW
WASHINGTON, DC

1. Attendance:
Members:
Gerrit W.H. Schepers, MD, Sc.D. , Medical Service,VACO, Chairman
Richard Levinson, MD, Deputy ACMD for Professional Services
William J Jacoby, MD, Director, Medical Service, VACO
John J. Castellot, MD, Deputy Director, Medical Service, VACO
Lawrence Hobson, M.D. Ph.D., Deputy Director for Research and Development, VACO
Charles Peckarsky, J.D., Director, Compensation and Pension Service, VACO
Abraham Dury, Ph.D, Consultant to Medical Service, VACO
Ben B. Holder, MD, Medical Director, DOW Chemical Company Midland, MI
Philip C Kearney, Ph.D, Office of the Secretary for US Department of Agriculture.
Walter W. Melvin, M.D. Sc.D., Professor of Environemental Health, Colorado State Univ
Carolyn Offutt , Dioxin Project Manager, Environmental Protection Agency
Donna Kuroda, Ph.D. , Environmental Protection Agency / -mental Health Sciences
Hans Falk, Ph.D., Director, Pesticides Division, National Institute of Environ- /
Cipriano Cueto, Ph.D., Director, Pesticides Program, National Cancer Institute.
Joseph A Thomasino, MD, Aberdeen Proving Grounds, US Army , Major, MC
Marjorie Williams, MD, Director, Pathology Service, VACO
Johan Bayer, United States Airforce, Office of Surgeon General, Colonel.

Visitors:

Hank Spring, Representing Congressman S.B. McKinney
Jim Michie , Representing Senator E. Kennedy

2. Dr Schepers introduced the members of the committee and explained the manner in which it came into being. In authorizing the committee the Chief Medical Director required it to explore the following:
a) The potential adverse effects of defoliants on the health of Vietnam Veterans, including the symptoms and signs associated with those effects.
b) Methods for diagnosing and treating the adverse health effects of defoliants.
c) Approaches through which the VA might attempt to discover the prevalence of the adverse effects of the defoliants on its patient population.
The CMD further expected the Committee to accomplish its task within one year , to prepare interim reports and a final report
Dr Schepers outlined the manner in which VACO became involved with the herbicide problem since March 1978 and the steps which have been taken. About 500 claims have been lodged with the regional offices of the department of veterans benefits. An almost equal number of Vietnam Veterans have also applied for medical examinations. Since only a minority of VA health care specialists is conversant with the discipline of toxicology a brief brochure (Appendix A) was prepared and sent to all health care

Interim
facilities/telephonic and written orientation also was provided for these HCFS concerning the administrative aspects of managing veterans who claim exposure to potentially toxic chemicals. A final version of this directive is currently being reviewed by VACO departmental chiefs. A copy will be mailed to the members of the committee. Because of the many inter-service problems which have arisen the CMD also created a VACO Steering Committee. The steering committee sent the questions listed in Appendix B.

3. Dr Levinson reviewed the perspectives of the Office of the ACMD for Professional Services concerning the herbicide issue. He pointed out that the VA has traditionally managed only diseases of biological origin and that it has only recently become involved with diseases of environmental etiology such as radiation effects, asbestos exposure and now herbicides. Since VA professionals are relatively poorly informed concerning these environmental health problems(although not necessarily more so than is the general health care system in the USA) the need for education of the staff is apparent. Education of patients is equally important, the more particularly because environmental diseases are to a large extent preventable. There may be specific areas which will require more research, and perhaps research which the VA should sponsor or accomplish. The deliberations of the committee should address these issues.

4. Dr Dury provided highlights of his reviews of the literature on herbicides and promised to provide a written summary. He referred to the work Captain A. Young of the USAF has done to summarize the numerous publications. This report still is being evaluated by the USAF prior to its release. Dr Dury reported that in both experiments with animals and experience with human subjects accidentally exposed to herbicides short term toxicity effects are on record. There is considerable disagreement concerning long term or delayed adverse health effects. Both the dosage and the duration of exposure influence the severity and type of health effects elicited in animal experiments. Little is known about the adjuvant or neutralizing action of mixtures of herbicides. Health effects have been recorded for animals and man with respect to symptoms, gross pathology , biochemical responses, histological changes. The best information about human subjects derive from the DOW experiences with inadvertent exposures. Other information is suggested by the St Louis horse farm accident and the Globe Arizona event. There is slight evidence that dioxin and perhaps 2,4,5-T may induce teratogenesis and carcinogenesis in experimental subjects of a limited variety. There may be receptor site inhibition sothat delayed indirect effects may become possible. There is no recorded evidence of this for man.

5. Dr Holder pointed out that it is important to distinguish between the health effects of individual herbicides. Chemicals with closely similar names are not necessarily capable of the same biological action. This is selectively true for the dioxins, of which there are many variants. The higher chlorinated dioxins appear to be more toxic than the lesser chlorinated moieties. Some of the misunderstanding about the toxicity of dioxin stem from failure to differentiate one dioxin type from another. For the Vietnam

War herbicide issue only TCDD proper (2,5,7,8 tetrachlorodibenzo-para -dioxin) is of relevance. It also is important to realize that not all herbicides contain dioxins and when presentthe dioxin is not always in the same amount. For 2,4,5-T supplied by DOW to the military during the Vietnam War the concentration of TCDD varied from zero to about 50 parts per million. No 2,4,5 - T was made specially for the war effort. The herbicide was standard grade agricultural production. Since the war, chemical maufacturing techniques have improved sothat current batches of herbicides tend to have very much less dioxin than was originally likely. Most of DOW's/experience with human subjects and much of the toxicology work on animals(adverse) goes back many years. DOW has been studying these herbicides for the past 36 years since the chemicals have been produced for agriculture since the early 1940's. The main human experience involving serious exposure leading to symptom production commenced during 1965 when about 60 employees received excessive exposure at one point in their factory. These all developed chloracne. There was no lost time. All recovered completely, except that two individuals statistically developed some depression, not necessarily attributable to the chemical excessive/exposure. No/carcinogenesis has been observed, but the company is still adopting a guarded position on this issue since the embryonating period for chemically induced cancers may be longer than ten years. The acne may have resulted as much from oils and inadequate hygiene as from direct chemical action of dioxin. The embryonating period for chloracne ranged from 6 to 8 weeks after exposure. Not all employees developed this symptom. Other symptoms were not observed unless there was concurrent chloracne. For this reason it seems doubtful whether Vietnam War veterans who never developed chloracne at the time of exposure in Vietnam will now develop symptoms. Dr Holder also expressed doubt about whether there was any TCDD exposure in the Globe AZ, St Louis MO or the Seveso , Italy episodes, which are so often quoted as examples of the baleful consequences of dioxin exposure. In response to a question by Dr Cueto, Dr Holder affirmed that DOW is looking into the possibility of delayed effects on fertility and teratogenesis, Karyotyping studies and reproductivity studies are being conducted.

6. Dr Falk has had considerable experience with animal experimentation , but no direct involvement with human subjects. The chemical formulation of types of herbicides determines to a large extent whether they are more or less toxic. The position of the chlorine atom affects toxicity and so does whether one deals with the acid or the ester formulation of the herbicide. Some of the experiments with animals which yielded teratogenic and carcinogenic results were conducted with esters. Similar results have not been produced by means of the acid formulations. In the Agent Orange the 2,4-D and 2,4,5 -T were acids. The rate of biodegradation of the herbicides is also affected by whether the herbicide is an acid or ester. Dr Falk attributed some of this information to Dr Dianne Courtney. He will summarize his observations and send these as a supplement to the minutes.

7.Dr Melvin said that mention frequently is made of the Globe and St Louis episodes, about which there is some doubt with respect to the role of dioxin, whereas a much better documented event occurred in West Virginia during 1940 in which 228 persons were relatively grossly exposed to herbicidal chemicals. This included factory workers and their families. Much of the

material was carried home on the clothes of the workers sothat their wives and children also were exposed. Most bec_ame seriously ill, with significant neurological symptoms and chloracne. There were no deaths. All recovered symptomatically except for the chloracne scars. Although this group has survived for more than thirty years, epidemiological data have never been derived from their individual health experiences. Since the population of West Virginia is relatively stable, it may be possible to trace many if not most of these individuals They would constitute a valuable source of guidance concerning the remote effects of herbicides on human health. Dr Melvin also dscribed some aspects of an industrial accident in Rotterdam, Netherlands, during 1963 involving the exposure of a t least 10 individuals. Since the Dutch government maintains relatively good public health records it may be possible to trace the health histories of these individuals. Dr Melvin also worked with the USAF during 1970 in connection with the disposal of millions of gallons of Agent Orange. About 200 AF employees were involved with the dedrumming process. Some if not all probably made significant contact with the chemicals. It may be worthwhile following up the health histories of these individuals. Dr Melvin further stated that it is his impression that the acute biological observations reported after exposure to Agent Orange (animal and human) are due to the 2,4-D and the 2,4.5-T themselves and not to the dioxin. The occurence of symptoms shortly after exposure to Agent Orange therefore does not signify that dioxin exposure necessarily had occurred, but only that there had been exposure to 2,4-D and or 2,4,5-T. The cutaneous reaction (chloracne) also does not correlate precisely with the intensity or duration of exposure to the herbicides. Often individuals who have had minimal exposure will show more chloracne than others known to have had significantly more exposure. Individual susceptibility, personal hygiene and other factors may be significant determinants of health effects.

8. Dr Kearney described the involvement of the department of agriculture with the same herbicides which were used in Agent Orange. They of course have regulatory responsibility for other herbicides too. Recently the department has had a flood of letters of inquiry, protest and complaint. Much concerns the fear of residents in forrested area of the US that the use of herbicides and pesticides spryed from low flying aircraft may exert health effects of an undesirable kind either through direct exposure or through the herbicides entering the ecosystem. Although the present assessment of the USDA is that these fears are groundless, based on the known information concerning the biological actions of herbicides and pesticides, the department has never-the-less created a medical team which will systematically examin persons who claim that they may have been significantly exposed to these chemicals. Dr Sheldon Wagner, a dermatologist is heading this investigation. Dr Kearney has had an opportunity to remain in touch with the authorites who are monitoring the outcome of the Seveso industrial chemical accident in Italy. One death has been reported. This was an elderly woman who died from cancer shortly after the incident. It is generally held that this cancer developed too soon after the chemical trauma to have been caused by the chemicals.

9. DR Kuroda outlined the rebuttable presumption document which the EPA has filed against 2,4,5-T which is published in the Friday 21, 1978, Part II issue of the Federal Register. (Appendix C). The principal concerns of EPA is that there are literature citations suggesting that dioxins may have

mutagenic and carcinogenic properties. Dr Kuroda desired to know what evidence there is that mutagenicity may not be an effect which may be mediated independently from chloracne. She also discussed the influence of individual species used as test animals on the type of biological action which chemicals my elicit. Thus animals which do not possess sebaceous glands may not be able to produce a chloracne symptom, yet be able to produce other lesions. This of course does not change the fact that human subjects do have sebaceous glands and may therefore be expected to register the chloracne response.

10. Dr Cueto discussed the effects of mixtures of herbicides versus the effects of the individual ingredients. He could not recall any research which has specifically been done with the actual Agent Orange used in Vietnam. He is aware of only one paper incriminating 2,4,5-T is being capable of producing excess tumors in experimental animals. There was however no specific tumor type produced- only total tumor counts were slightly increased as compared with the natural incidence of tumors in the control animals. Until more research has been done he believes that carcinogenicity can be neither ruled out nor accepted as a valid effect. He knows of no literature showing that 2,4 -D can produce a similar effect. The NCI has sponsored several investigations. The results of these are still unreported and thus not yet analysed by the institute staff. His institute may be willing to sponsor additional needed research. However he cannot make a firm commitment at this time since the institute is currently undergoing reorganization sothat command lines and action centers may change.

11. Col. Bayer stated, in response to various questions, that the DOD never contracted with chemical companies to have the components of Agent Orange specially made for DOD. a The available production of chemical industry in the USA (approximately 18 companies) was used. Agent Orange therefore possibly varied by lot according to the sources of the component. DOD has kept records of individual lot numbers sothat the composition of each lot can perhaps be traced if the chemical companies kept similar records. b DOD destroyed all its stock of Agent Orange during 1970. However, it should be possible to reconstitute the formulations of individual lots if the action of precise mixtures is deemed relevant to the inquiry concerning Agent Orange. To the present nothing has been published to show that the combination of 2,4-D and 2,4,5-T in itself produces effects different from the biological action ascribable to the individual components separately.

12. Dr Williams described the current plan of the VA to test about 100 fat biopsy specimens for dioxin. a This may cost about $80,000. The biopsies will include specimens derived from Vietnam War Veterans with undoubted exposure to Agent Orange, some with dubious exposure, veterans with symptoms, others without symptoms. Possibly also control specimens will be obtained from veterans who have not had any exposure to Agent Orange. The tests will be done by a contracting laboratory, with known expertise and suitable equipment and staff. Wright Patterson Airforce Base has such a laboratory. b.

13. Dr Thomasino queried the value of this proposed biopsy endeavor by the VA. His main concern is that there is no known body of knowledge linking tissue ~~concentrations~~ of dioxin to any specific syndrome of biological effects. He compared the work done at the Kettering Laboratory in Cincinnati on

tissue lead levels versus clinical evidence of lead poisoning. It took many years of experimentation and clinical investigation before the threshold for toxic tissue burdens of lead could be arrived at. In the case of lead one has a specific atomic moiety to measure. Matters are much more vague for dioxins. If dioxin is found in any of the fat samples obtained from veterans, it would be impossible to ascribe any meaning to such findings since there is no defined disease syndrome with which the dioxin tissue burden can be correlated. Likewise, if no dioxin is found in any of the specimens, it would still be impossible to say what this signifies, since the dioxin could have been in the tissues or in some other vital organ formerly, may or may not have induced biological responses, and subsequently may have leached out of the tissue. Until there are biomonitor data with which to correlate tissue dioxin levels, it may not be worth the enormous expense to start this biopsy program.

13. Dr Hobson outlined the political overtones which have relevance to this biopsy issue. In the CBS presentation of Agent Orange, there was a scenario showing a physician extracting a fat sample from a patient and the physician stated emphatically that he has been obtaining confirmation of dioxin poisoning through finding dioxin levels in such biopsy specimens. Veterans, and action groups speaking for the veterans are firmly convinced that the VA must test them for dioxin. A populist scientific spokesman also said in the CBS program that dioxin accumulates in fat and may later be released to re-exert toxic actions on vital organs during periods of stress when the metabolism may be deranged. Many veterans therefore believe firmly that they may be walking around with such a chemical 'time bomb' in their tissues. The VA essentially has no option but to check whether there is any proof that dioxin even is stored in fat eight years after the last exposure in Vietnam. If no dioxin is found in the men who are known to have had significant exposure to Agent Orange or who may even have had specific symptoms, this will be meaningful information. If as much dioxin is found in persons who have never been in Vietnam as is determined for veterans who were decisively exposed to Agent Orange, this also would be meaningful information. If the determination for dioxin proves exceedingly difficult or erratic , as suggested by Dr Holden, confirmation of this through the VA endeavor, would again be meaningful, since , if no reliable data can be obtained in even the best laboratory, the validity of the CBS statement can be challenged. Dr Gueto supported this approach.

14. Dr Schepers mentioned the current review of cancer incidence statistics which can be derived from the VA's enormous data file which is compiled from the diagnoses reported for each hospitalized veteran (Patient Treatment File-PTF) The annual incidence of liver cancer has recently been reviewed. Records are available for the period 1963 thru 1977. There is no indication that liver cancer has increased in the age categories representative of veterans who served in the Vietnam War. On the contrary, the incidence of liver cancer in the cohort of veterans aged less than 25 years, the cohort aged 25 to 34 years, and the chort aged 35 thru 44 years has actually declined over the past fifteen years. For example, in 1969 the incidences for these three cohorts were respectively 0.37%,0.74 % and 3.50 %, counting all cases and all types of neoplasm. No liver cancer of any kind occurred in the less than 25 year cohort since 1970. No liver cancer has been recorded in this cohort and in the next (25 -34 years)since 1974. Since 1977 no cancers have been reported in any of the three cohorts(ie below 25 years through age 44 years). This contrasts

sharply with increases in liver cancer in veterans of the 55-64 and 65 and over age group cohorts over the same fifteen year period. These older veterans perhaps obviously were not in Vietnam during the time when Agent Orange was being used. More detailed statistical data are to be found in Appendix D. Dr Schepers also inquired whether it would be possible for the VA to obtain biopsy specimens from the West Virginia
15. group described by Dr Melvin. Ms Offutt stated that the EPA can probably assist with the identification of these individuals. She described the serious concerns of her agency with the question of pollution of the ecosystem by herbicides and pesticides. The rebuttable presumption injunction to which Dr Kuroda had referred is an illustration of the posture the EPA may adopt on these matters. She clarified that if as a result of the evidence which may be offered during hearings concerning this rebuttable presumtion, the hypotheses on which it is based are destroyed, the EPA will withdraw the presumtion. Until such retraction occurs, the presumption reflects the persuasions of the EPA concerning herbicide 2,4,5-T. The EPA has a voluminous collection of literature on herbicides, and Ms Offutt invited members of the committee to consult their library rather than attempting to start all over again.

16. The meeting was adjourned at 4 pm. Themembers all expressed preference for a morning meeting. The next session of the committee will be called for September 8, 11, 22 or 25.

↓ 2nd ↓ 1st choice

Gerrit W.H.Schepers,MD,Sc.D.
Chairman

Appendix A : VA brochure on Herbicides
B: Steering Committee request to advisorory committee
C: Rebuttable presumption of EPA regarding 2,4,5-T
D: Liver cancer in Veterans
E: Toxity data on herbicides prepared by US Army Environmental Hygiene Agency
F: VA administrative instructions to Field Health Care Facilities

file in RH II

ECE,

Al, I agree that D. Melson did an excellent job critiquing the draft minutes. I note in para. 11. that Col Bazer suggested that HD could be reconstituted if "... the action of precise mixtures is deemed relevant ..." We may want to rethink our decision to destroy all HD archived.

V
22

Bill,

These are the VA meeting minutes with Dr. Melvins "Corrections". He asked that we not let them get out of house.

Jack

DEPARTMENT OF THE AIR FOI
USAF OCCUPATIONAL AND ENVIRONMENTAL HEALTH LABORATORY (AFSC)
BROOKS AIR FORCE BASE, TEXAS 78235

Memorandum from the Commander

22 Aug 78

Dr Calcagni

Capt Young (F.U)

These are to be closeheld!

VA Minutes - Meeting 17 July '78
Dr Melvin's Comments to Minutes

College of Veterinary Medicine
and Biomedical Sciences
Institute of Rural Environmental Health
Microbiology Building

Colorado State University
Fort Collins, Colorado
80523

Gerrit W. H. Schepers, M.D., Sc.D. Ref. (111)
Chairman
VACO Advisory Committee on Herbicides
Department of Medicine and Surgery
Veterans Administration
Washington, D. C. 20420

Dear Doctor Schepers:

I have carefully reviewed the draft minutes of the July 7, 1978, meeting of the ad hoc advisory committee on herbicides and have a number of comments which I feel obligated to make.

It is not my intent to be hypercritical but considering the nature and alleged magnitude of the problem as envisioned by the Veterans Administration, all statements made and opinions expressed must be as carefully, accurately and objectively presented as is possible. There are a number of errors and misrepresentations to which I must call attention.

My comments are attached. I have indicated the paragraph by number, e.g., 4, and the phrase, clause sentence or section to which the comment is directed has been underlined in red. Where two or more comments have been made, these are indicated by the paragraph number followed by a small letter, e.g., 7b, etc.

I trust that the attached comments will be of some assistance in the preparation of the final minutes.

Sincerely,

Walter W. Melvin, Jr., M.D., Sc.D.
Professor
Environmental Health Sciences

WWM:jbw

Enclosures

2a. The only known, documented adverse effects in man have followed industrial accidents or incidents in the production of 2,4,5-trichlorophenoxyacetic acid derived herbicides from 2,4,5-trichlorophenol which contained 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as a contaminant. Another source of possible TCDD exposure in industry is to pentachlorophenol which may contain TCDD as a contaminant introduced during primary production. The adverse effects are the residual scars of chloracne in some persons who were exposed to and absorbed TCDD. The experiences at the Monsanto Chemical Company 2,4,5,-trichlorophenol (2,4,5-TCP) plant accident at Nitro, WV in 1949, at BASF Ludwigshafen-am-Rhein (Fed. Repub. of Germany) in 1953, Phillips Duphars Ltd. plant, near Amsterdam, The Netherlands, in 1963, and more recently, on July 10, 1976 at the ICMESA (Industrie Chimice Meda Societa Anonyma) plant in Meda, near Seveso, Italy, clearly point to this conclusion. Similar accidents have occurred in a plant operated by Coalite and Chemical Products Ltd., Bolsover, Derbyshire, England, in 1968, in Czechoslovakia in somewhat different types of accidents from 1965-1969 and in France on at least three occasions. Any other long term, adverse effects are unknown and are, currently, undetectable.

2b. To the best of my knowledge there are no known diagnostic laboratory methods which are specific, either singly or in combination, for the detection of tissue or organ damage due to TCDD exposure and absorption. For example, none of the following laboratory determinations, some of which are rather sophisticated and difficult to interpret, specifically indicate cellular or subcellular damage from the action of dioxins, including TCDD, at cellular levels: fructose-1,6-diphosphate aldolase (ALD), d-hydroxybutyrate dehydrogenase (d-HBD), alkaline phosphatase

(ALP), creatine phosphokinase (CPK), gamma-glutamyl transpeptidase (GGTP), glutamate dehydrogenase (GLDH), glutamate oxal acetate transaminase (SGOT), glutamate pyruvate transaminase (SGPT), leucine aminopeptidase (LAP) and lactate dehydrogenase (LDH). However, an enzyme of particular interest would be aryl hydrocarbon hydroxylase (AHH) with associated cytochrome P_1-450. Another enzyme which might also be of interest is δ-aminolevulinic acid synthetase. It would be possible to expand this list but one would come to the same conclusion. These are valuable tools which can be and have been used in experimental animal studies of TCDD but they are of no value in the evaluation of cellular damage in man when the last exposure—in the case defined by the Veterans Administration—occurred in Vietnam over eight years ago.

2c. Retrospective epidemiological studies offer a faint and difficult hope. Prospective epidemiological studies may be of value if a true and reasonable population at risk is defined. For this purpose, I would suggest concentration on former members of the "Ranch Hands." These were personnel who were assigned to the aerial application flights who serviced and flew the aircraft from which the Herbicide Orange was applied to limited areas in South Vietnam. But first, adverse effects must be medically and scientifically—not emotionally and politically—defined. Secondly, a population at risk of reasonable size and composed of persons who can be identified must be established. The following information may be of value in estimating the population at risk in Vietnam. About 3.58 million acres or only about 8.6% of the total area of South Vietnam were sprayed with herbicides one or more times. Only 10.3% (2.67 million acres) of inland forest were sprayed while 36.1% (0.26 million acres) of mangrove forest were sprayed and 3.2% (0.26 million acres) of cultivated

land were sprayed. For this purpose, Herbicide Blue (hydroxymethylarsine oxide) was used. Herbicide Orange was not intentionally used on cultivated land. The total area of South Vietnam was approximately 41.6 million acres. Many acres were sprayed only once. For example, one treatment with either Herbicide Orange or Herbicide White killed essentially all of the mangrove species. Thus, it is apparent that not all members of the U.S. military forces who served in Vietnam were exposed to 2,4,5-T and to TCDD. The population actually exposed is far less than the 3-4 million persons estimated by the Veterans Administration. I have talked with many Air Force veterans and others who were in South Vietnam, were not exposed to Herbicide Orange and were completely unaware of the defoliation program. The source of the above data is: National Academy of Sciences, 1974, "The effects of herbicides in South Vietnam. Part A, Summary and Conclusions." NAS. Wash. D.C.

4a. Again accuracy and careful, truthful statements are vitally necessary. Until reading these draft minutes, I had never hear of a "...St. Louis horse farm accident" because there was no St. Louis horse farm accident. The incident referred to occurred at the Shenandoah Horse Farm, near Moscow Mills, MO which is approximately 59 miles northwest of St. Louis, MO. The farm was operated by Judy Piatt and Frank Hampel. The child who was most severely involved was Andrea Piatt, who was six years old on May 21, 1971, when approximately 2000 gallons of waste oil were applied as a dust control measure. I should also like to point out that the causative compound was not identified until 1974 at the Center for Disease Control (CDC) by Dr. Renaté Kimbrough. In 1977, six years after the exposure, the Piatt family was examined by physicians at the Washington University School of Medicine in St. Louis. Andrea Piatt had grown normally and

both her height and weight were abouve the 75th percentile. Detailed physical, chemical and neurological examinations were also conducted and found to be normal. The examining physicians concluded: "Our experience demonstrates that people exposed to dioxin can recover completely with no apparent sequelae from the toxin. It remains to be determined whether the exposure to dioxin in these children will result in abnormal pregnancies or affect their offspring." [Beale, M. G., W. T. Shearer, M. M. Karl, and A. M. Robson. 1977. Long Term Effects of Dioxin Exposure. Lancet *1* (8014):748] (see Atch. 1). The Nitro, WV and the more recent ICMESA accidents confirm the abouve conclusion.

4b. I agree that the events occuring during several years, i.e., 1965, 1966, 1968 and 1969 of aerial application of herbicide in the Pinal Mountains in Arizona are commonly referred to as the "Globe event" or the "Globe cases." Herbicide Orange formulation was <u>not</u> used in this area. The formulations used, the manufacturers names, USDA Registration numbers, pounds acid equivalent per gal. applied and application rates as pounds acid equivalent per acre are available. This event is still under study.

5. I am in general agreement with the comments made by Dr. Holder. I do believe, however, that even more emphasis should be placed on the importance of chloracne. The presence of chloracne is central to making the diagnosis of TCDD intoxication in man. The latent period for the development of clinically apparent chloracne in man is, at a minimum, about two weeks, and usually four to eight weeks. To the best of my knowledge no cases of chloracne were diagnosed among United States personnel stationed in Vietnam during the period of 19621970. While TCDD has been shown to be the causative agent of chloracne, its role in the development of porphyria cutanea tarda is less clear. However, again to the best of

my knowledge, no cases of this condition were diagnosed in Vietnam. There are residual scars following chloracne but porphyria cutanea tarda appears to be reversible. There is another point to be made. Very few physicians in the United States and, of course, those serving in Vietnam, have seen cases of chloracne and fewer still would be aware of the acquired condition of porphyria cutanea tarda. (After all, you cannot make a diagnosis unless you have knowledge of the disease and think of it at the time!) Again, as I did at the meeting on July 7, 1978, I strongly recommend that Raymond R. Suskind, M.D., Director, Institute of Environmental Health, College of Medicine, University of Cincinnati (telephone: 513-872-5701) be asked to join the ad hoc committee. He examined and followed for some period of time patients from the Nitro, WV plant accident in 1949 (see paragraph 7).

6. Generally, I aggree with the comments of Dr. Falk. However, the sentence (underlined in red) is completely incorrect. The 2,4-D and 2,4,5-T used in Herbicide (Agent) Orange were <u>not</u> acids but were esters and in all but a few thousands of gallons of herbicide, they were the normal butyl esters of both 2,4-D and 2,4,5-T referred to as Orange I. Some formulations contained the isooctyl esters and were known as Orange II. Procurement Specifications are listed in Atch. 2. Data on the physical properties of 2,4-D, 2,4,5-T, TCDD, Orange I and Orange II are provided in Atch. 3.

7a. See Comment 4 relative to the Globe and St Louis episodes.

7b. This industrial accident occurred in 1949 <u>not</u> 1940. It occurred in a 2,4,5-trichlorophenol (2,4,5-TCP) reaction vessel in a plant operated by Monsanto in Nitro, WV (see Comment 5, relative to Dr. Raymond R. Suskind).

7c. The words "...many if not most..." should read "...an unknown number of these people."

7d. I was the scientific director for the United States Air Force in its efforts to dispose of Herbicide Orange from April 1970 to December 1977.

7e. The sentence beginning "Some if not all..." is completely incorrect as are the following sentences. First, the contact with the herbicide was not significant; it was minimal. The personnel were selected after reasonable medical evaluation and worked under very complete industrial hygiene surveillance. Air and water samples were collected based on a carefully determined sampling protocol. Analyses were performed for the herbicides and TCDD. Biological monitors, e.g. rapidly growing 4"-6" high, tomato plants were also used. The concentrations of TCDD in air and water were determined in and adjacent to dedrum facilities at NCBC, Gulfport, MS and on Johnston Island. These environmental data should be available from Air Force sources. Within the limitations of the Privacy Act, copies of physical examinations might also be available.

7f. The sentence beginning "Dr. Melvin further stated..." must be completely rewritten. I stated that the immediate effects on man, animals, birds, reptiles, insects and vegetations were due to process products from reaction vessels which had undergone process malfunction, i.e., temperature buildup and pressure overload with discharge of the reaction products into the plant and, in the case of the ICMESA accident ("Seveso incident"), drift of the cloud into adjacent environmental (neighborhood) areas. The reaction products include 2,4,5-trichlorophenol, other chlorinated phenols, chlorphenates, NaOH or KOH and, in some accidents, ethylene glycol and, of course, TCDD. The production of 2,4,5-T requires additional chemical reactions and 2,4,5-T was not present in the reaction

products in these accidents. 2,4-D is not present for the simple reason that it is produced by an entirely different direct chlorination process. 2,4-D does not contain TCDD as a contaminant. In the case of man and other animals, the immediate effects (24-48 hours) are the result of the direct caustic (burn) action of the polychlorinated phenols and resemble, at certain stages, burns resulting from other phenols or cresols. Chloracne, caused by TCDD, does not appear for a minimum of two weeks and, most commonly, four to eight weeks following exposure. In this sense, TCDD does not have an immediate or acute toxic action. This is verified by animal experimentation. I might further add that direct skin contact with TCDD is not necessary for the development of chloracne. It has occurred after exposure by the inhalation route alone.

8. At the request of Italian medical and paramedical authorities, Captain Alvin L. Young and I visited Meda-Seveso and adjacent areas in Italy and Zurich-Dubendorf, Switzerland in November 1977. We have remained in contact with many of these authorities since that time. The death mentioned by Dr. Kearney was that of an elderly woman who died of carcinoma of the head of the pancreas with widespread metastases. While in Italy and since then, I have received official documents from Italian and Swiss authorities. Some of these documents have been translated and are attached (see Atch's 4 and 5). Note that the report form the Mario Negri Institute of Pharmacological Research, signed by Dr. Roberto Fanelli and dated November 7, 1977 contains data on the concentrations of TCDD in the liver and mesenteric fat from the necropsy on Mrs. Colombo. The sensitivity of the analytic method used was 0.25 nanograms per gram of tissue (see Atch. 4 and 5).

9. There are probably just as many literature citations which provide evidence that TCDD is not mutagenic.

10. No comment.

11a. There were 8 not 18 manufacturers of Herbicide Orange. The herbicide did not possibly vary by the source and lot number, it varied significantly and the extent of these variations has been documented and the data are available (see Atch. 6).

11b. Destruction of Herbicide Orange occurred in a 10,000 sq. mi. EPA designated "burn" area approximately 120 nautical miles west of Johnston Island, Central Pacific Ocean during July-September, 1977.

12a. I must seriously question the value of this costly program. The detection of TCDD in a biopsy specimen from a veteran who served in Vietnam as long as eight years ago does not *a priori* estalish that exposure, absorption and storage occurred while the person was in Vietnam, especially with a study population of only 100 subjects. One of the most difficult problems that we face in the Institute of Rural Environmental Health, Epidemiologic Pesticide Studies Center at Colorado State University in studies of chemicals in the environment, including an on-going study of TCDD in human milk, is the identification of suitable control groups. Again (see comment number 2c), I strongly recommend that if a study of this general type is to be conducted that the "Ranch Hands" be considered as the exposed cohort with a control group consisting of crews assigned to the same type of aircraft but not engaged in the aerial application of chemicals, at least not Herbicide Orange, and not assigned to Vietnam. Having been involved for seven years in studies of TCDD concentrations in the tissues of mammals, birds, reptiles and fish with known—sometimes semiquantified—exposure data to 2,4,5-T and TCDD, I can only state that

this will be an extremely costly program and may well be completely non-productive.

13. (Dr. Thomasino) In general I agree with the comments.

13. (Dr. Hobson) Based upon my seven year involvement with Herbicide Orange while in the Air Force and my many encounters with political officials including members of the Congress, governors, the media, environmentalists, etc., I can well apprecite the position in which the Veterans Administration finds itself. It is indeed an appalling position to be in.

15. No comment relative to Herbicide Orange or TCDD. However, I must wonder if these data may possibly reflect an aging population, nitrosamines in man, his food chain and the long latent period of these and other carcinogens prior to the development of malignant tumors.

16. My opinion is that there is a reasonable possibility that much useful data could be derived from a study of those persons who were involved in the Monsanto plant accident at Nitro, WV in 1949 and are still living and can be identified and located. The causes of death of those now deceased might also be of interest though probably difficult to evaluate.