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MINUTES OF THE ADHOC VACO ADVISORY COMMITTEE ON HERBICIDES
MEETING OF JULY 7, 1978
810 VERMONT AVE. N.W.
WASHINGTON, D.C.

1. Attendance

Members:

Gerrit W.H. Schepers, M.D., Sc.D., Medical Service, VACO, Chairman
Richard Levinson, M.D., Deputy ACMD for Professional Services
William J. Jacoby, Jr., M.D., Director, Medical Service VACO
John J. Castellot, M.D., Deputy Director, Medical Service, VACO
Lawrence Hobson, M.D., Ph.D, Deputy Director for Research and Development, VACO
Abraham Dury, Ph.D, Consultant to Medical Service, VACO
Philip C. Kearney, Ph.D, Office of the Secretary for U.S. Dept. of Agriculture.
Carolyn Offutt, M.S., Dioxin Project Manager, Environmental Protection Agency
Donna Kuroda, Ph.D., Ecological Effects Division, Environmental Protection Agency
Hans Falk, Ph.D., Associate Director, Health Hazarad Assessment, National Institute of Environmental Health Sciences
Cipriano Cueto, Ph.D., Director, Pesticides Program, National Cancer Institute.
Joseph A. Thomasino, M.D., Aberdeen Proving Grounds, Major, Mc, U.S. Army
Charles Peckarsky, L.L.B., Director, Compensation and Pension Service, VACO
Marjorie Williams, M.D., Director, Pathology Service, VACO
Johan Bayer, Office of Surgeon General, Colonel, MC U.S. Airforce.

Consultants:

Ben B. Holder, M.D., Medical Director, DOW Chemical Company, Midland, MI
Walter W. Melvin, M.D., Sc. D., Professor of Environmental Health Sciences, Colorado State University

Visitors:

Hank Spring, Representig Congresman 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. Inauthorizing th committee the Chief Medical Director required it to explore the following:

a.) The potential adverse effects on veterans of defoliants used in Vietnam and to assess the symptoms and signs associated with those effects.

b.) Methods for diagnosing and treating adverse health effects of defoliants.

c.) Approaches through which the VA might discover the prevalence of adverse effects of defoliants used in Vietnam on its patient population. The CMD further expected the Committee to accomplish its task within one year, to preare 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 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 skillful in the discipline of toxicology a brief brochure (Appendix A) was prepared and sent to all health care facilities. Interim telephonic and written orientation also was provided for these HCFs concerning 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 members of the committee. The CMD also created a VACO Steering Committee to deal with inter-service issues on this problem. The steering committee submitted 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 disease 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. The need for education of the HCF staff is apparent. Education of patients is equally important,

particularly because environmentally caused diseases are potentially 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 of Captain A. Young of the USAF who has summarized 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 any 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, and histological changes. The best information about human subjects derives from the DOW experiences with inadvertent exposures. Other information is suggested by the Missouri horse farm accident and the Globe Arizona event. There is evidence that dioxin at the 10 ng/kg level and 2,4,5-T at 500 ppt may induce fetotoxicity, teratogenesis and carcinogenesis in experimental rodents. There may be receptor site inhibition so that 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 and their contaminants. These chemicals are not necessarily capable of the same biological action. This is especially true for the dioxins, of which there are many variants. The 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) appears to be the most toxic. Some of the misunderstanding about the toxicity of dioxin stems from failure to differentiate one dioxin type from another. For the Vietnam War herbicide issue, the proper dioxin (TCDD) is of relevance. It also is important to realize that not all herbicides contain dioxins and, when present, the dioxin is not always in the same amount. The 2,4,5-T supplied to the military during the Vietnam War had concentrations of TCDD varying from one part-per-million (ppm) to about 50 ppm. The phenoxy herbicide was a standard grade agricultural product. Since the war, chemical manufacturing techniques have improved so that current batches of phenoxy herbicides tend to have much less dioxin contamination. Most

of Dow's experience with human subjects and much of their toxicology work on animals goes back many years. Dow has been studying these phenoxy herbicides for the past 36 years. Their main human experience involving over-exposure to TCDD leading to symptoms commenced during 1965 when about 60 employees received excessive exposure to TCDD in a trichlorophenol plant. No 2,4,5-T was involved. These 60 employees developed chloracne. Two individuals developed some depression, but all recovered. There was no lost time. It is the concensus of world experts that symptoms from TCDD toxicity does not occur in the absence of chloracne. For this reason, it seems doubtful whether Vietnam War veterans, who never developed chloracne at the time of exposure in Vietnam, did or will show signs of other disease. Little TCDD in Globe and no 2,4,5-T in Missouri or Seveso again remind that one must not group chemicals, but must relate to specific materials. In a response to a question by Dr. Queto, Dr. Holder affirmed that Dow is studying possible human reproductive effects from TCDD and has completed some karyotyping on a 2,4,5-T population.

6. Dr. Falk has had considerable experience with animal experimentation, but no direct involvement with human subjects. The chemical structure of herbidides may determine the toxicity depending, in case of the esters of 2,4,5-T, on the ease with which they can be metabolized. The position of the chlorine atoms also may alter toxicity. This applies similarly to the impurities in 2,4,5-T and its esters which have different potencies depending on whether the chlorine atoms on the dibenzo-p-dioxins are located in critical positions.

Early experiments were carried out with the acid which was contaminated with nearly 30 ppm of the tetrachlorodibenzodioxin, giving rise to teratogenicity in mice and rats. When purified 2,4,5-T was used, the teratogenicity with regard to the kidney disappeared, which was largely due to the dioxins but remained noticeable regarding cleft palates in mice. With regard to rats, teratogenic potency declined considerably. This susceptibility of the mouse to 2,4,5-T (pure) in producing malformed offspring appears to be unique because subsequent studies in other species like the rabbit, the sheep, as well as, the rat produced little evidence of teratogenicity.

Agent Orange consists of the n-butyl esters of 2,4-D and 2,4,5-T in equal amounts and was also studied for teratogenicity in mice. It did not produce as much toxicity as its two components when tested separately although this finding is hard to interpret. It suggests that the two agents together are not showing enhanced toxicity.

The teratogenic activity of 2,4,5-T was first observed by Dr. Courtney, who had obtained a sample of 2,4,5-T which was contaminated with 2,3,7,8-tetrachloro-p-dioxin. When it was pointed out that the impurity was not present in most of the samples of 2,4,5-T and was itself highly toxic, additional studies were carried out to evaluate 2,4,5-T as distinct from its impurities for teratogenicity. It turned out that the "dioxin" impurity was teratogenic and that the purified 2,4,5-T was without effect in the rat but was still producing malformations in the mouse. The dioxin, however, produced kidney anomalies in the rat and the mouse. Because of the difference in response of mice and rats to 2,4,5-T in the absence of dioxins, it is of importance to learn that in other laboratories 2,4,5-T produces no malformations in the rabbit and in sheep. In a study by Collins and Williams impure 2,4,5-T was teratogenic in the Syrian hamster which seemed to be a function of the impurity present in the sample. King, et al. confirmed that purified 2,4,5-T and 2,4-D did not produce malformations in the rat and studies in the chick embryo did not produce evidence of teratogenicity that was clear cut. The teratogenic effect of 2,4,5-T in mice when the content of the dioxin was less than 0.1 ppm was reported by Roll confirming that in the mouse indeed the pure 2,4,5-T was active. Khera and McKinley studied 2,4,5-T and 2,4-D as well as certain esters of these herbicides in rats and observed malformations at comparatively high dose levels. Similar studies on esters were also carried out by Courtney in CD-1 mice and fetotoxicity as well as teratogenicity was observed for each one of the compounds. The solvent seemed to make a contribution in altering the toxicity. Courtney also carried out several studies to dermine the distribution of 2,4,5-T between the pregnant animal and its fetuses in the mouse as well as the rat to clarify the difference in toxicity.

7. Dr. Melvin said that mention frequently is made of the Globe and Missouri episodes, about which there is some doubt with respect to the role of dioxin. A much better documented event occurred at Natro, West Virginia, during 1949 in which 282 persons were grossly exposed to 2,4,5-TCP. This included factory workers and their families. Much of the material was carried home on the clothes of the workers so that their wives and children also were exposed. Most became seriously ill, with significant neurological symptoms and chloracne. There were no deaths. All recovered symptomatically except for 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 some of these individuals. They would constitute a valuable source of guidance concerning the long term or delayed effects of herbicides on human health. Dr. Melvin also described some aspects of an industrial accident in Rotterdam, Netherlands, during 1963, involving exposure of at 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 was the Scientific Director of the USAF from 1970 thru 1977 and thus is familiar with the disposal of millions of gallons of Agent Orange. About 200 AF employees were involved with the dedrumming process. Some probably made contact with the chemicals. However, there was strict, biological, medical and industrial hygienic monitoring of the operation so that contact was minimized. Agent Orange was fully studied for its chemical characteristics at this time (Appendix G). 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. By contrast, Dioxin has not manifested an immediate toxic symptomatic response. It does evoke chloracne about 4 to 8 weeks later both after cutaneous and after inhalation exposure. This cutaneous reaction (chloracne) does not correlate precisely with the intensity or duration of exposure to the dioxin. 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. Although the EPA has the principal regulatory responsibility for perticides, USDA has some additonal control over herbicides in general. Recently, the Department has had a flood of letters of inquiry, protest and complaint. Much concerns the fear of residents in forested areas of the US that the use of herbicides and pesticides sprayed 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 nevertheless created a medical team which will systematically examine persons who claim that they may have been significantly esposed to these chemicals. Dr. Sheldon Wagner, a dermatologist is heading this investigation. Drs. Kearney and Melvin have remained in touch with the Italian and Swiss authorities 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 metastasising pancreatic cancer shortly after the incident. It is generally held that this cancer developed too soon after the chemical trauma to have been caused by chemicals released in that incident. No TCDD was found in liver or mesenteric fat samples analysed to a tolerance of 0.25 nanograms per gram.

9. "Dr. Kuroda outlined the Rebuttable Presumption Against Registration with EPA filed against 2,4,5-T and its contaminant 2,3,7,8-tetracholordibenzo-p-dioxin. This document was published in the Federal REgister for Friday, April 21, 1978. The Agency is concerned about the carcinogenic and teratogenic effects found in laboratory animals when exposed to either 2,4,5-T or the dioxin. TCDD is a potent teratogen in almost every laboratory animal tested and 2,4,5-T containing low levels of TCDD (.05 ppm) is teratogenic in several strains of laboratory rodents. Even Down studies have determined that levels of TCDD as low as 10ng/day cause adverse reproductive effects in laboratory rats. Laboratory studies have shown statistically significant increases in the number of tumors in rats fed levels of TCDD as low as 5 ppt. One laboratory study has shown 2,4,5-T containing 0.05 0.05 ppm TCDD to be carcinogenic in mice. Although the evidence for mutagenic effects of TCDD did not meet the multi-test criteria for issuing the RPAR, the Agency is continually reviewing all new data especially any forthcoming from the Seveso incident. Dr. Kuroda raised the question of whether TCDD can cause effects, especially chronic effects, without causing chloracne in exposed individuals. Although there are animal species that do exhibit adverse effects without chloracne when administered TCDD, these species may not have sebaceous glands. Dr. Kuroda suggested that we look at individuals living around forested areas such as Oregon that may have been sprayed by 2,4,5-T for possible adverse effects. This population may exhibit some of the same effects supposedly seen by the Vietnam veterans since the type of exposure is similiar, although the levels may be lower. She believed the Agency has received some data on people exposed (sprayed) to 2,4,5,-T that would be of interest and would try to make it available to the committee. She commented that the "Zero" content for dioxin in some military tests are not absolute zeros but reflect the limited analytical sensitivity of chemical tests available ten years ago. Dr. Melvin commented that there

is an equal number of publications which provide evidence that TCDD is not mutagenic.

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 as 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 of which the results 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 so that 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. The available production of the chemcial industry in the USA (eight (8) companies) was used. Agent Orange therefore varied quantitatively by lot according to the source of manufacture. DOD has kept records of individual lot numbers so that the composition of each lot can perhaps be traced if the chemical companies kept similar records. DOD destroyed all its stock of Agent Orange during 1977 by burning it at sea in an EPA designated area. 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 steps that had been taken to ascertain availability of sources for analysis of dioxin levels in body fat. Dr. Williams noted that they have identified two individuals at academic institutions who have experience with the analysis and are willing to accept specimens from the VA. The costs per analysis are in the range of $600-800 but are volume dependent. Both individuals need some reasonably firm estimates of likely number of specimens requiring analysis over a given

time period such as one year. Dr. Williams noted that in-house experience in VA Laboratory Services with dioxin analysis does not exist. However, it could be developed if there were to develop a continued demand over years for a 100 or more analyses per year.

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. He pointed out that it took many years of experimentation and clinical investigation before that 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 diseases yndrome 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 hve 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. Dr. Melvin concurred with this critique.

14. 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 could obtain confirmation of dioxin poisoning through 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 weight loss. 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 remains in fat eight years after the last exposure in Vietnam. If no dioxin is found in the men 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 in those 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. Holder, 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. Cueto supported this approach.

15. 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 hosptialization 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 conclusive indication that liver cancer has increased in the age categories representative of veterans who served in the Vietnam War. For veterans below the age 25 years, there have been 32 cases over the period 1967 thru 1977. This represents an average of about 3.0 cases per year. However, during 1974 there were 7 cases and in 1976 5 cases occurred. In between these two years there were none. (Appendix D-1) When these cancers are averaged out over three year periods (Appendix D-2) there does appear to be a slight increase of cases between 1969 and 1974. For the age group 25 years thru 34 years there were 63 cases with an average of about 5.6 per year. However, spurts of cancer increase also occurred in 1973 and 1976. These spurts yielded higher values for the final six years of this review period. There is no explanation yet for this. The records have been called for to determine whether any of these cases represented Vietnam War veterans. The tables do however show that liver cancer has all along been relatively prevalent in the older age group veterans, none of whom may be expected to include Vietnam War veterans.

16. 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 presumption, the hypotheses on which it is based are destroyed, the EPA will withdraw the presumption. 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.

17. The meeting was adjourned at 4 PM. The members all expressed preference for a morning meeting. The next session of the committee will be called for September 8, 11, 22 or 25, 1978.

GERRIT W.H. SCHEPERS, M.D.
Chairman

Appendix A: VA brochure on Herbicides
B: Steering Committee request to Advisory Committee
C: Rebuttable Presumption of EPA Regarding 2,4,5-T
D. Liver Cancer in Veterans 1963 thru 1977
E. Toxicity Data on Herbicides Prepared by US Army Environmental Hygiene Agency
F. VA Administrative Instructions to Field Health Care Facilities
G. Chemical Characterization of Agent Orange