Item ID Number	05650	☐ **Not Scanned**
Author	Arnett, Dixon	
Corporate Author	Agent Orange Working Group (AOWG)	
Report/Article Title	The Domestic Policy Council, Agent Orange Working Group (AOWG), Status Report	
Journal/Book Title		
Year	1985	
Month/Day	October	
Color	☐	
Number of Images	268	
Description Notes		

THE DOMESTIC POLICY COUNCIL

Agent Orange Working Group

STATUS REPORT

OCTOBER 1985

The Honorable Dixon Arnett
Chair Pro Tempore
Agent Orange Working Group

Peter E.M. Beach, Ph.D.
Executive Secretary/
Staff Director
Agent Orange Working Group

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Washington, D.C. 20201

October 4, 1985

The Honorable Frank H. Murkowski
Chairman
Committee on Veterans Affairs
United States Senate
Washington, D.C. 20510

Dear Senator Murkowski:

I take pleasure in sending you a copy of the status report of the Cabinet Council Agent Orange Working Group, which I am forwarding today to the Honorable Edwin Meese as Chair Pro Tempore of the Cabinet Domestic Council.

Of particular note in the Progress Report is Section X complied by the Science Panel, on the "State of the Art" in all Federal Government Agent Orange related research. Through Fiscal Year 1987 this research totals $152.5 million and is estimated to reach $184 million by 1990.

The commitment of the President and the Executive Branch as made to Vietnam veterans in July 1981, is evident in the time and energy and research devoted to this controversial issue.

I would be pleased to hear from you should you have questions. Copies of the Executive Summary, the Science Panel report, the Fact Sheet or the entire report will be made available if requested from Dr. Peter E.M. Beach, Executive Secretary, Telephone 245-6156.

With best wishes,

Dixon Arnett
Chairman (Acting)
Cabinet Council Agent Orange
Working Group

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Washington, D.C. 20201

October 4, 1985

The Honorable G.V. "Sonny" Montgomery
Chairman
Committee on Veterans Affairs
U. S. House of Representatives
Washington, D.C. 20515

Dear Mr. Montgomery:

I take pleasure in sending you a copy of the status report of the Cabinet Council Agent Orange Working Group, which I am forwarding today to the Honorable Edwin Meese as Chair Pro Tempore of the Cabinet Domestic Council.

Of particular note in the Progress Report is Section X complied by the Science Panel, on the "State of the Art" in all Federal Government Agent Orange related research. Through Fiscal Year 1987 this research totals $152.5 million and is estimated to reach $184 million by 1990.

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With best wishes,

Dixon Arnett
Chairman (Acting)
Cabinet Council Agent Orange
Working Group

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EXECUTIVE SUMMARY

The Agent Orange Issue

A legacy of the Vietnam conflict is the concern of many Vietnam veterans that they may be at risk of a spectrum of adverse health effects as a result of their service in Vietnam. These concerns focus largely on Agent Orange, a herbicide used for defoliating areas of enemy troop concentration and staging.

History

In late 1979, the White House established an Interagency Work Group to bring together knowledgeable government scientists to oversee the research, develop areas where scientific study is needed, and report the results as soon as they become available to the Congress and the public. On August 21, 1981, President Reagan established an Agent Orange Working Group (AOWG) as part of the Cabinet Council on Human Resources, elevating and enlarging the scope of the prior group. Secretary Margaret Heckler, as Chair pro tempore of this Cabinet Council, named John (Jack) Svahn, at that time Under Secretary, to chair the AOWG and in a Press Release dated June 6, 1983 stated her well known concern for veterans and her particular concern in the Agent Orange question "By designating the second highest official of my department as Chairman, I am reaffirming this administration's commitment to the prompt and scientifically responsible resolution of the health concerns of Vietnam veterans who were exposed to Agent Orange and other environmental factors during their service to their country in that conflict. His leadership of this vital working group will help us get the answers we need " the Secretary said.

Subsequent chairpersons have been Assistant Secretary for Health, Dr. Edward Brandt September 1983 - December 1984, Under Secretary Charles N. Baker, December 1984 - August 1985.

On April 11, 1985 the eight Cabinet Councils, including Human Resources were combined into two, the Council on Economic Policy Council and the Council on Domestic Policy to which the AOWG now reports.

Organization

The Agent Orange Working Group is under the leadership of the Department of Health and Human Services and includes scientific, legal and policy representatives from that Department, the Departments of Defense and State, the Veterans Administration, the Environmental Protection Agency, the Department of Agriculture, the Occupational Safety and Health Administration of the Labor Department, the White House Offices of Policy Development and of

the Science and Technology Policy, Office of Management and Budget, Council of Economic Advisors, ACTION, and Congress' Office of Technology Assessment (observor status).

The Science

The issue of possible adverse health effects in humans as a consequence of exposure to Agent Orange in Vietnam has attracted and maintained the attention of the nation for nearly a decade.

For the past four years, the AOWG has been evaluating the direction and extent of the government's scientific research in Agent Orange and related issues. When the AOWG was formed in 1981, it was clear from animal studies and the limited human studies that the toxic contaminant of Agent Orange (TCDD) has the potential to cause a broad range of deleterious effects. The extent to which these effects were likely to appear in humans exposed to Agent Orange in Vietnam, however, was unknown.

Between 1981 and 1987, AOWG member agencies will have expended $150 million in Agent Orange-related research with over one hundred and fifty (150) studies. The majority of these funds has been directed at closing the largest gap in our knowledge on Agent Orange: the effects of Agent Orange on humans. Ten major epidemiological studies scheduled for completion by 1990, and five ongoing health surveillance projects should provide information on whether exposure to Agent Orange has affected the health of Vietnam veterans and for framing hypotheses which can be tested in follow-up studies if necessary. Additional resources have been expended to better characterize known toxic properties of 2,3,7,8-TCDD and Agent Orange.

The Public

The Agent Orange Working Group has received support from veterans organizations and members of Congress and its recommendations have been accorded significant weight.

The President

In a July 17, 1981 meeting with veterans leaders, President Reagan indicated that the Administration took seriously the concerns of Vietnam veterans and their families about their health status as a result of their actual or presumed exposure to Agent Orange in Vietnam and was firmly committed to con- tinuing and according the highest priority to the current scientific research studies now being conducted and planned by Federal agencies.

The President cautioned that the scientific research may never yield definitive answers to the question of whether Agent Orange -- or any other single factor -- has adversely affected the health of an individual veteran but that we can learn whether Vietnam veterans as a group are suffering any chronic health effects not present in a comparable population that did not serve in Vietnam.

The Results

The results of the scientific research will prove useful in helping to formulate sound public policy regarding health care and compensation for Vietnam veterans. Some studies are completed and are inconclusive; the major Epidemiologic studies underway by the Centers for Disease Control, mandated by Congress is the most comprehensive but will not be completed until late 1989.

Based on the growing body of information in hand, the worst case scenarios envisioned by some as a consequence of exposure to Agent Orange are not being realized. Populations known or possibly exposed to Agent Orange which are being studied have not so far exhibited increased incidences of cancer, or death from other causes, or abnormally high rates of birth defects in their offspring. This optimism is tempered by the knowledge that other, less-well characterized effects of concern may by associated with 2,3,7.8-TCDD (e.g., immunotoxicity). Some effects (e.g., cancer) may not become manifest for several more years, due to a longer latency period.

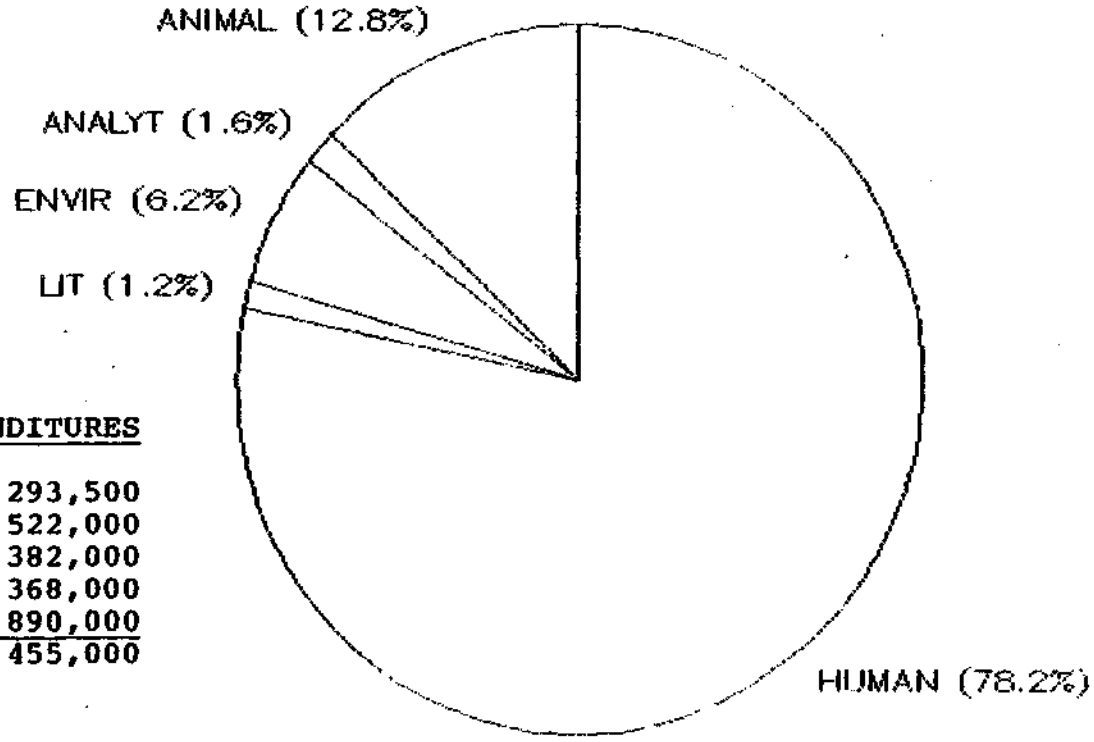
The consensus of the Science Panel is that initiation of any new, major epidemiological study should await and be built upon the results of studies already underway.

A large number of ongoing research projects designed to characterize the toxicity and mechanisms of action of 2,3,7,8-TCDD in laboratory animals will also help to identify possible adverse human health effects and will assist in the interpretation of epidemiologic study results.

AGENT ORANGE/DIOXIN EXPENDITURES

AGENCY EXPENDITURES BY STUDY TYPE

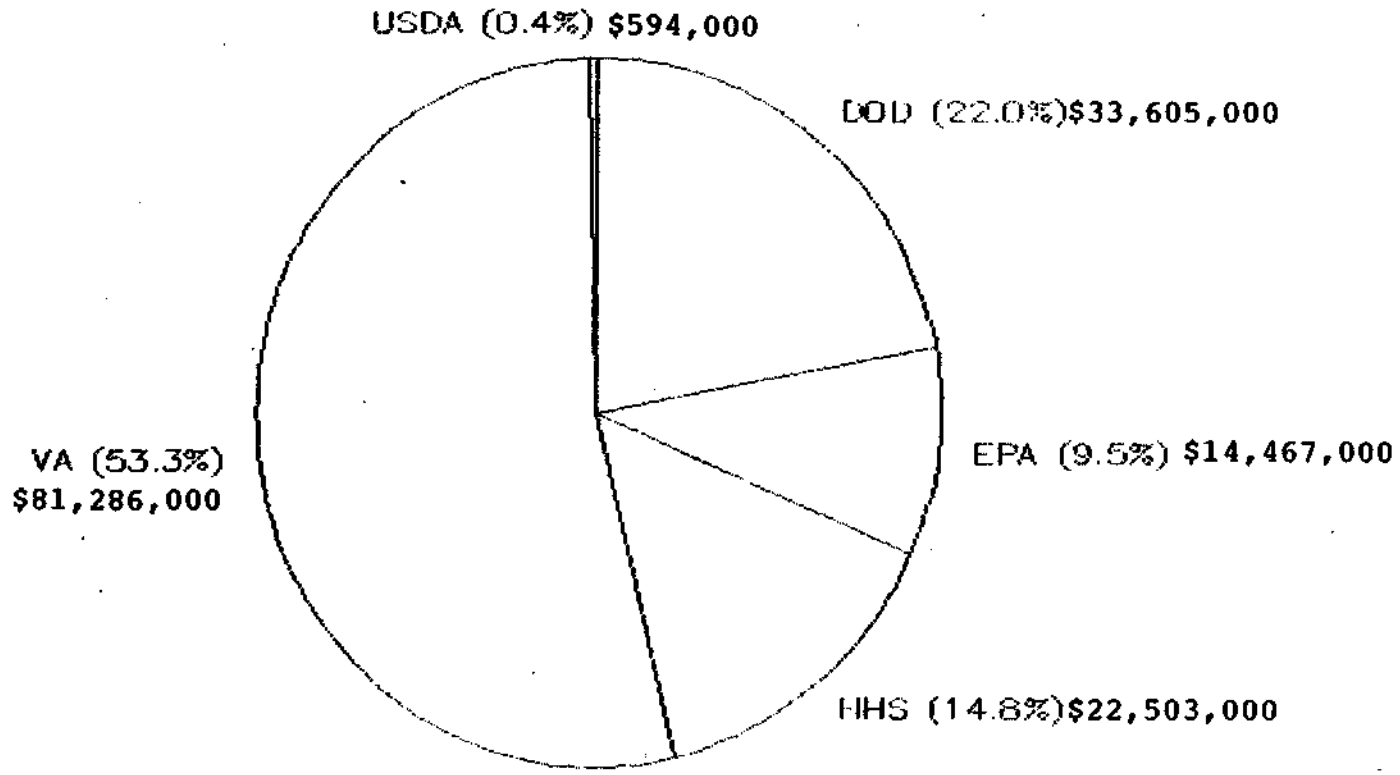
$152,455,000 TOTAL EXPENDITURES



STUDY TYPE	EXPENDITURES
HUMAN	$119,293,500
ANIMAL	19,522,000
ENVIRONMENT	9,382,000
ANALYTICAL	2,368,000
LITERATURE	1,890,000
TOTAL	$152,455,000

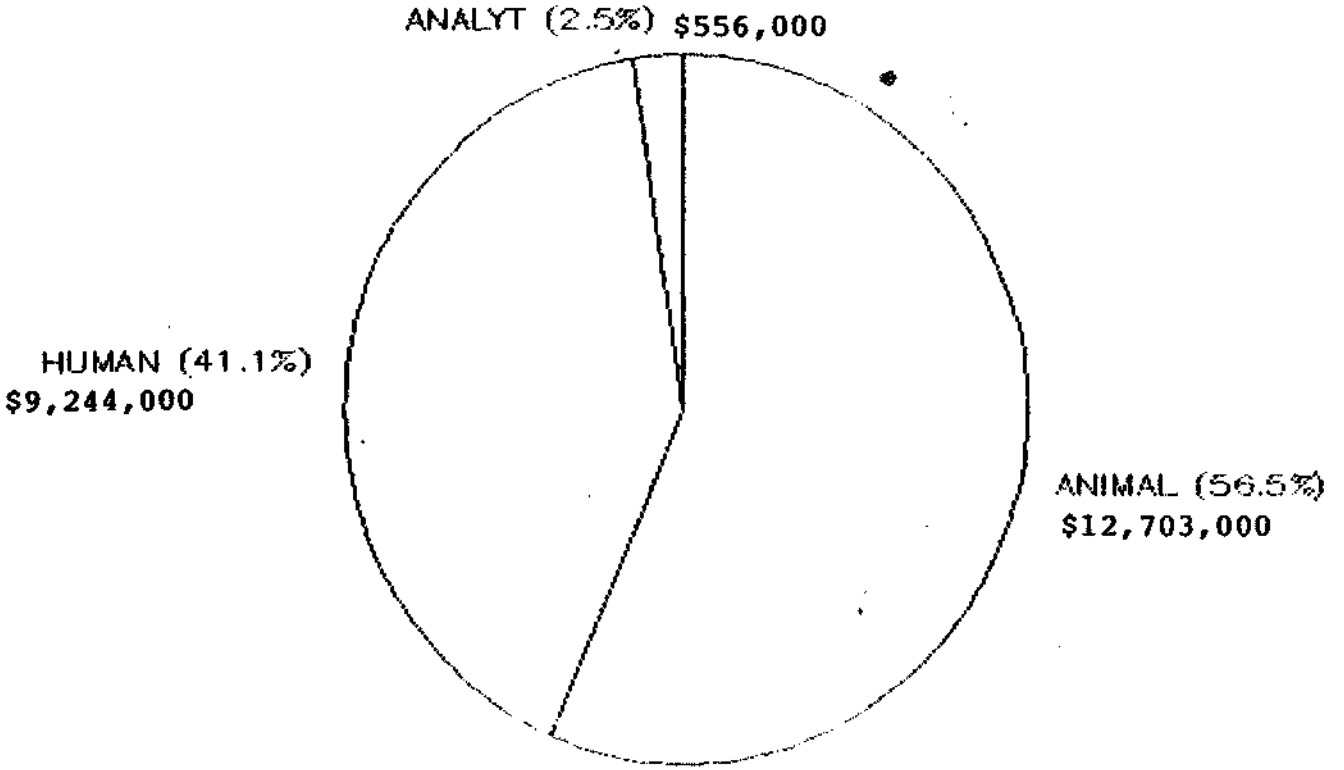
AGENT ORANGE/DIOXIN EXPENDITURES

$152,455,000 TOTAL COST



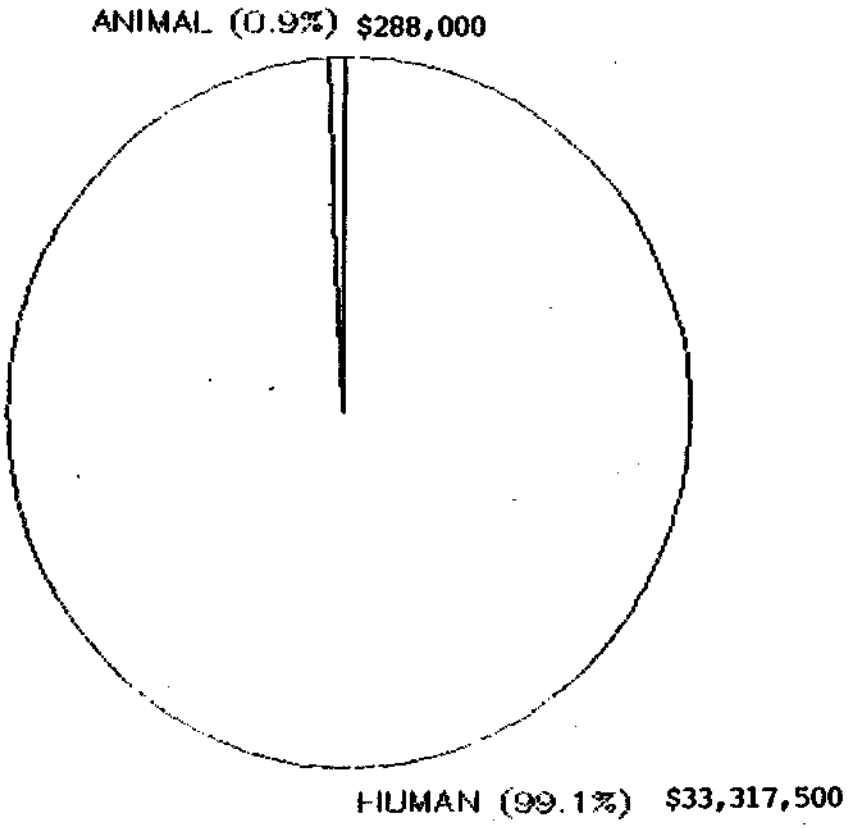
HHS A.O./DIOXIN EXPENDITURES

$22,503,000 TOTAL EXPENDITURES



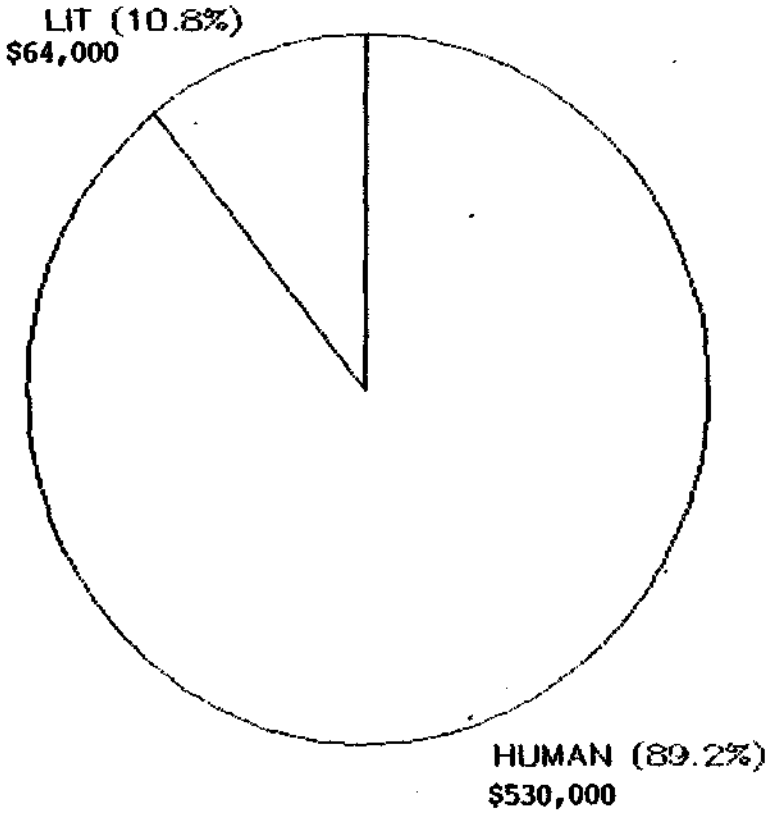
DOD A.O./DIOXIN EXPENDITURES

$33,605,500 TOTAL EXPENDITURES



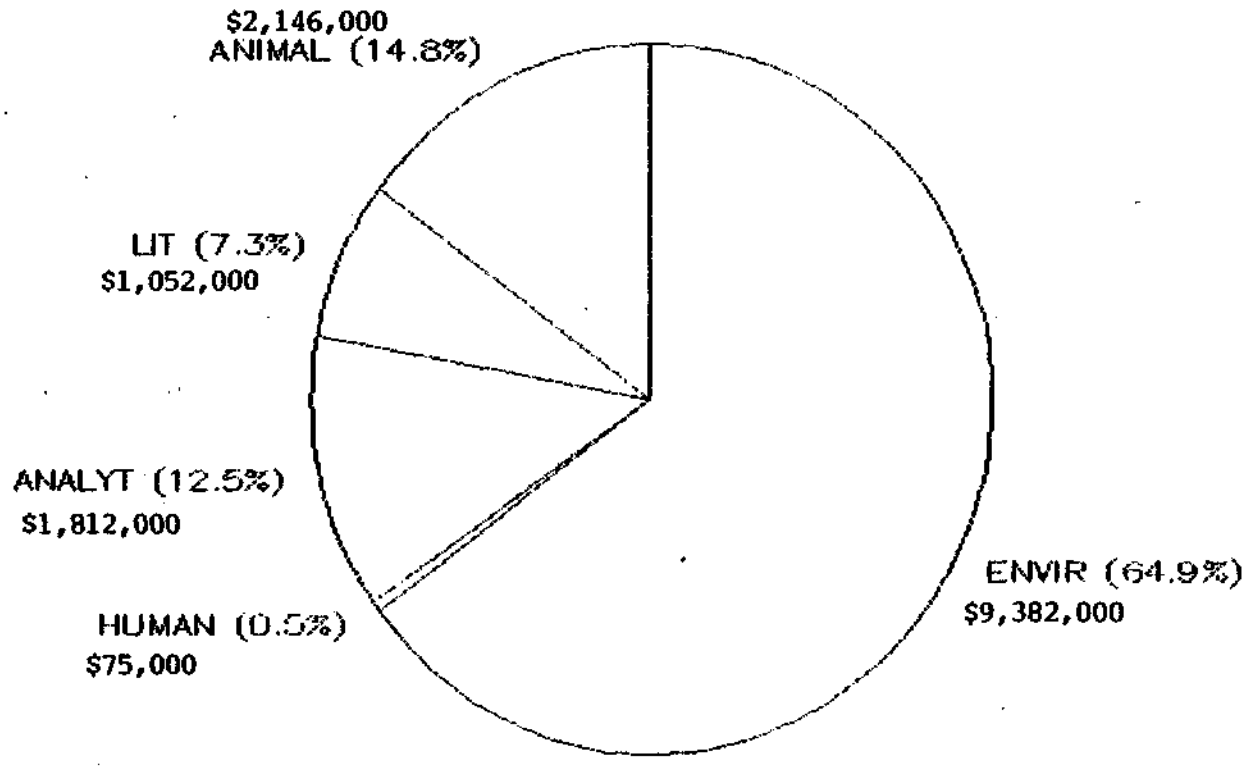
USDA A.O./DIOXIN EXPENDITURES

$594,000 TOTAL EXPENDITURES



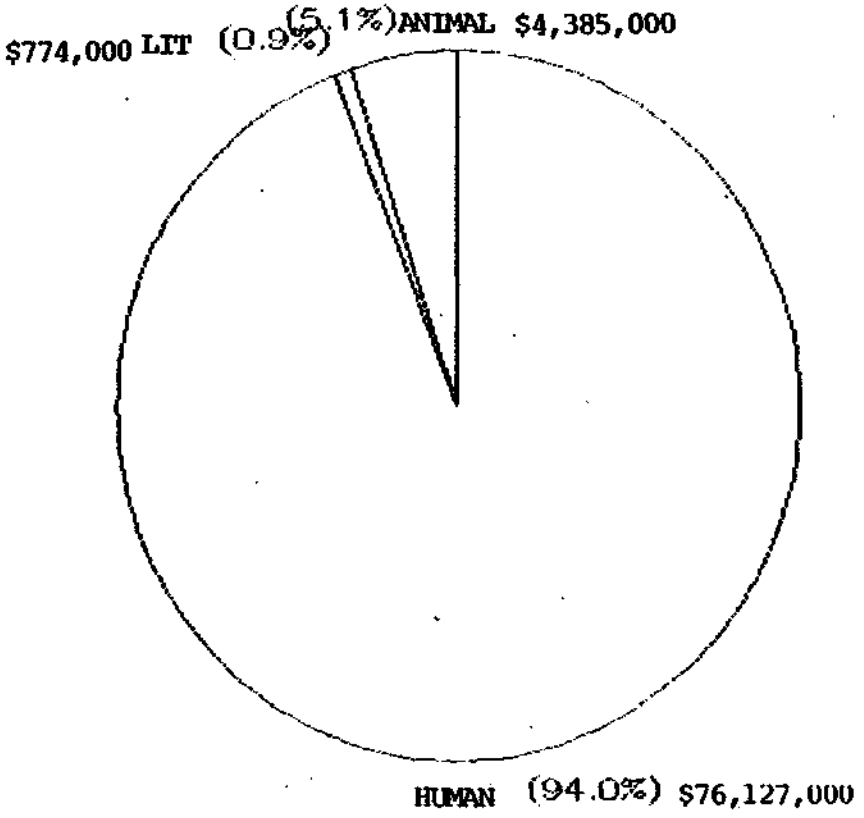
EPA A.O./DIOXIN EXPENDITURES

$14,467,000 TOTAL EXPENDITURES



V.A. A.O./DIOXIN EXPENDITURES

$81,286,000 TOTAL EXPENDITURES



STATEMENT OF PRESIDENT REAGAN
JULY 17, 1981

"One of the most unfortunate legacies of the Vietnam conflict is the continuing concern of many Vietnam veterans that they are, or may be, at increased risk of a broad spectrum of adverse health effects as a result of their service in Vietnam. These concerns have largely focused on Agent Orange, a herbicide used for defoliating areas of enemy ground troop concentrations and staging. Agent Orange was made by combining two herbicides that were in widespread use in forestry and agriculture.

Unfortunately, despite much discussion in the media and among scientists, there are still few definitive answers to the difficult scientific issues involved. Indeed, we may never be able to determine with certainty whether Agent Orange -- or any other single factor -- has adversely affected the health of an individual veteran. The scientists working on this problem are hopeful, however, that we can learn whether Vietnam veterans as a group are suffering any chronic health effects not present in a comparable population that did not serve in Vietnam. In addition, several studies -- including an epidemiological study of the Air Force Personnel who sprayed Agent Orange -- are directly examining the Agent Orange issue. The results of these and other studies, including a congressionally mandated VA epidemiological study of the health status of Vietnam veterans, should be extremely useful in helping to formulate sound public policy regarding health care and compensation for Vietnam veterans.

I believe that the Federal Government has made significant progress in the past year in organizing and beginning a serious scientific inquiry into the Agent Orange issue. Much, however, remains to be done and I share the deep and abiding concern of Vietnam veterans about their health and that of their children. I am committed to assuring that the important scientific research now under way and being planned under the overall guidance and coordination of the White House Interagency Work Group continue to completion in an efficient, expeditious manner, consistent with sound scientific principles. Accordingly, I am hereby reaffirming the mandate of the Work Group and making its work a major priority of my Administration."

Agent Orange

The term "Agent Orange" is derived from the orange color code painted on the barrels of herbicide shipped to Vietnam. Other herbicides used in Vietnam carried various other color codes depending on the nature of the herbicide.

Agent Orange was a 50/50 mixture of the herbicide 2,4,-D and 2,4,5-T. The product was provided on contract with the Department of Defense by a number of chemical companies.

A by-product created in extremely small amounts during the manufacture of 2,4,5-T was the chemical, dioxin. The average contamination amount of dioxin was, according to the Veterans Administration, two parts per million.

Dioxin has caused lethal and toxicological effects in some laboratory animals at lower levels than any other man-made chemical. However, both the lethal dose levels and the toxicological effects vary considerably among different animal species. The toxicological effect upon humans remains under study and additional work must be done before an authorized view of the risks can be made.

THE HUMAN STUDY

CABINET COUNCIL ON DOMESTIC POLICY
AGENT ORANGE WORKING GROUP

FEDERALLY SPONSORED HUMAN STUDIES RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY					STATUS		
STUDY TITLE	Mortality	Morbidity	Cancer	Reproduction	Analytical	Completed	Ongoing	Estimated Completion Date
DEPARTMENT OF HEALTH AND HUMAN SERVICES								
NIOSH Investigation of Leukemia Cluster in Madison County, Kentucky Allegedly Associated with Pentachlorophenol Treated Ammunition Boxes			X			X		Published NTIS 1984
NIOSH Dioxin Registry	X		X				X	Late 1985
NIOSH Soft Tissue Sarcome Investigation			X					Published Scan. J. Work Environ Health 1984
NIOSH NJ/Missouri plant worker and worker's spouse reproductive outcome study	X	X	X	X			X (begins 1985)	
Reproductive outcomes in persons possibly exposed to 2,3,7,8 RDP				X			X	
Measurement of TCDD levels in adipose tissue from potentially exposed persons in Missouri.			X	X	X	X	X	

FEDERALLY SPONSORED HUMAN STUDIES RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY					STATUS		
STUDY TITLE	Mortality	Morbidity	Cancer	Reproduction	Analytical	Completed	Ongoing	Estimated Completion Date
DEPARTMENT OF HEALTH AND HUMAN SERVICES cont'd								
NIEHS Establishment and Maintenance of an International Register of Persons Exposed to Phenoxy Acid Herbicides and Contaminants	X		X				X	Indefinite
NIEHS Effects on Intestinal Cells UNC-CU Grad student	X					X 1984		
Lipid Assimilation NRSA						X 1984		
Membrane/LP Receptor NRSA	X						X	1986
NIEHS Pesticides and transport across bilayer Lipid membranes (toxicology)	X						X	1987
NIEHS Occupational and Environmental Health Center Grant (toxicology)	X						X	1987
NIEHS - Dioxin Environmental Health Sciences Center Grant Clinical Studies	X						X	1987
NIEHS Dioxin Mechanism(s) for toxicity of chlorinated dibenzodioxins (toxicology)	X						X	1987

FEDERALLY SPONSORED HUMAN STUDIES RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY					STATUS		
STUDY TITLE	Mortality	Morbidity	Cancer	Reproduction	Analytical	Completed	Ongoing	Estimated Completion Date
NIEHS Dioxin Environmental pollutants and toxicology of the liver	X						X	1986
NIEHS Dioxin Xenobiotic induction of pleiotropic responses in liver	X						X	1986
NIEHS Dioxin molecular toxicology of TCDD	X						X	1986
NIEHS Dioxin chlorinated dibenzo-p-dioxins; mechanisms of toxicity	X						X	1987
NIEHS Dioxin - Toxic halogenated wastes: In vitro bioassay development	X						X	1986
NIEHS Dioxin - Atomic emission spectrometry for dioxin trace anlaysis (detection)	X						X	1986
NCI Study of Mortality Among Pesticide Applicators from Florida						X		Publications in Press
NCI Case Control Study of Lymphoma and Soft Tissue Sarcoma			X				X	Indefinite

FEDERALLY SPONSORED HUMAN STUDIES RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY					STATUS		
STUDY TITLE	Mortality	Morbidity	Cancer	Repro-duction	Analytical	Completed	Ongoing	Estimated Completion Date
CDC Birth Defects and Military Service in Vietnam Study				X			X	Published Aug. 1984
*CDC Epidemiologic Study of Ground Troops Exposed to Agent Orange during the Vietnam Conflict	X	X	X	X	X		X	Sept 1989
CDC Study for Body Burden for Dioxin in the General Population					X		X	Late 1988
VETERANS ADMINISTRATION								
Vietnam Veteran Mortality Studies	X						X	December 1985
Vietnam Veteran Identical Twin Studies		X		X				Under Review by OTA and AOWG
VA/AFIP Case Control Study of Soft Tissue Sarcoma			X				X	July 1986

*Mandated to the VA by P.L. 96-151 Sec. 307. Transferred from VA to CDC under Interagency Agreement January 14, 1983.

FEDERALLY SPONSORED HUMAN STUDIES RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY						STATUS	
STUDY TITLE	Mortality	Morbidity	Cancer	Reproduction	Analytical	Completed	Ongoing	Estimated Completion Date
VETERANS ADMINISTRATION cont'd								
Survey of Patient Treatment File for Vietnam Veteran In-Patient Care		X	X				X	Initial 1983 Survey
Review of Soft Tissue			X				X	December 1985
Sarcoma Study in Patient Treatment File								
Agent Orange Registry Examinations		X	X				X	Indefinite
TCDD in Body Fat of Vietnam Veterans and Other Men		X		X	X			Published
Retrospective Study of Dioxins and Furans in Adipose Tissue of Vietnam-Era Veterans					X		X	1986
DEPARTMENT OF DEFENSE								
Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicide Orange (Air Force Health Study)	X	X	X	X			X	Baseline 1983 Complete 1999
Armed Forces Institute of Pathology Agent Orange Registry of Vietnam Veteran Biopsy Tissues			X				X	Indefinite

FEDERALLY SPONSORED HUMAN STUDIES RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY					STATUS		
STUDY TITLE	Mortality	Morbidity	Cancer	Reproduction	Analytical	Completed	Ongoing	Estimated Completion Date
ENVIRONMENTAL PROTECTION AGENCY								
Report of Assessment of a Field Investigation of Six-Year Spontaneous Abortion Rates in Three Oregon Areas of Relation to Forest 2,4,5-T Spray Practices				X		X (Published)		
National Pesticide Monitoring Project of Human Adipose Tissue					X		X	Indefinite (Annual Reports)
DEPARTMENT OF AGRICULTURE								
A Case Control Study of the Relationship Between Exposure to 2,4-D and Spontaneous Abortions in Humans				X		X		
Exposure Measurements of Mixers, Loaders and Applicators of 2,4-D on Wheat					X	1982		
Exposure of Forest Workers to Ground Applications of 2,4-D					X	1983		

THE ANIMAL STUDY

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion Date
DEPARTMENT OF HEALTH AND HUMAN SERVICES							
NIEHS							
Bioassay of Octachlorodibenzo-p-dioxin	X					X	Indefinite
Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in Swiss Webster Mice	X					X	Indefinite
Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in Osborne-Mendel Rats and B6C3F1 Mice	X				X		
Bioassay of a Mixture of 1,2,3,6,7,8- and a Mixture of 1,2,3,6,7,8-Hexachlorodibenzo-p-dioxins for Possible Carcinogenicity	X					X	Indefinite
Comparative species Evaluation of Chemical Disposition and Metabolism of 2,3,7,8-Tetrachlorodibenzofuran (TCDF) in Rat, Monkey, Guinea Pig and Two Strains of Mice	X				X		
Neurotoxicity of 2,4,-D in Rodents	X				X		

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion Date
DEPARTMENT OF HEALTH AND HUMAN SERVICES cont'd							
Studies of the Chemical Disposition and Metabolism of Octachlorodibenzodioxin (OCDD)	X					X	Indefinite
Effects of Agent Orange Components on Male Fertility and Reproduction		X			X		
Mutagenicity Studies of TCDD, 2,4-D; 2,4,5-T and Esters of 2,4-D and 2,4,5-T		X				X	Indefinite
Implications of Low Level Exposure of Dioxins		X				X	Indefinite
Mechanisms of Toxicity of the Chlorinated-p-dioxins		X				X	Indefinite
Research Toward Understanding the Molecular Level Mechanisms of Toxicity of TCDD and Related Compounds	X					X	Indefinite
Synthesis of Selected Chlorinated dibenzo-p-dioxins and Related compounds as Analytical Standards			X			X	Indefinite

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion Date
DEPARTMENT OF HEALTH AND HUMAN SERVICES cont'd							
Methods for the measurement of dioxins and furans in human adipose tissue			X			X	Indefinite
Matrix Effect and Sub Parts-per-billion Quantitative Analysis of TCDD by Mass Spectrometry - With Special Reference to Milk	X		X			X	Indefinite
Toxic Actions of Tetrachloroazobenzene Dioxins	X					X	Indefinite
Xenobiotic Induction of Pleiotropic Responses in Liver	X					X	Indefinite
Molecular, Biochemical Actions of Chlorinated-p-dioxins	X					X	Indefinite
Mechanism(s) for Toxicity of Chlorinated Dibenzo-dioxins	X					X	Indefinite

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion Date
NIEHS							
Teratogenicity of TCDD - Cleft palata Induction (mice)	X					X	1986
Disposition of TCDD Fetal Distribution in mice	X					X	1986
2,3,7,8-Tetrachlorodibenzofuran-Disposition in Rats, Mice, Guinea Pigs	X				disposition 1983	metabolism	1986
1,2,4,6,8,9 Hexachlorodibenzofuran-Disposition	X				disposition	X	1986
DIOXIN							
Structure-Toxicity Relationships	X				1984		
Theoretical Modeling of Dioxin Receptor					1984		
Molecular Modeling of Dioxin Binding Proteins						X	1986
Molecular Basis of Dioxin Toxicity	X Theoretical Biochemical					X	July 1986
Lipid Assimilation NRSA	X				X		
Membrane /LP Receptor NRSA	X					X	Nov. 1986

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion Date
ENVIRONMENTAL PROTECTION AGENCY							
Evaluation of Large Scale Combustion Sources		X	X			X	
Evaluation of Municipal Waste Combustors		X				X	
Bacterial Decomposition of TCDD		X				X	
Investigation of Bioavailability to Fresh Water Fish of TCDDs in Fly Ash	X	X				X	
Analysis of Environmental Samples for PCDDs and PCDFs		X	X			X	
DEPARTMENT OF AGRICULTURE							
Survey of Phenoxy Herbicide Use by Agricultural Commodity				X		X	
Survey of Phenoxy Herbicide Literature				X		X	Annaul Bibliographies Published

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion Date
DEPARTMENT OF AGRICULTURE cont'd							
Photolysis of 2,4,5-T			X			X	
Biological and Economic Assessment of 2,4,5-T and Silvex				X		X	
TCDD Residue Monitoring in Deer	X	X			X		Report in Preparation
DEPARTMENT OF DEFENSE							
Environmental Chemistry of Herbicide orange and TCDD		X	X			X	Indefinite
VETERANS ADMINISTRATION							
Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins				X	Published 1981		Annual Update Approved
Urinary 6-Hydroxy Cortisol: Physiological and Pharmacologic Studies (Including Agent Orange)	X					1982	
Effect of TCDD on Lipid Metabolism	X					1983	

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion Date
VETERANS ADMINISTRATION cont'd							
Mechanisms of Dioxin Induced Toxicity Using the Chloracne Model - Phase I	X				X		Publication in Press
Behavioral Toxicity of An Agent Orange Component 2,4-D	X					1984	
Effects of 2,3,7,8-Tetrachlorodibenzodioxin on Hepatobiliary Function in Animals	X					X	1986
Mechanism of TCDD Absorption and Toxicity on Lipid and Lipoprotein Metabolism	X					X	1986
Metabolism of the Herbicides Present in Agent Orange and Agent White	X					X	1986
TCDD Exposed Rhesus Monkeys: Effects on Behavior and Stress Hormones	X					X	1986

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion Date
VETERANS ADMINISTRATION cont'd							
Neuromuscular Toxicity of Agent Orange	X					X	1986
Mechanisms of Dioxin Induced Toxicity Using the Chloracne Model - Phase II	X					X	1986
Effects of Low Dose TCDD on Mammalian Chromosomes and Liver Cells	X					X	1986
Mechanism of Porphyria Caused by TCDD and Related Chemicals	X					X	1986
Effects of Agent Orange on Sleep	X					X	1986

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion Date
ENVIRONMENTAL PROTECTION AGENCY							
Evaluation of TCDD destruction technologies		X				X	December 1985
Assessment of exposure to TDCC from contaminated media			X(Thought-wise)			X	December 1985
Assessment of methods used for analysis of human adipose tissue			X(Lab-wise)		Oct. 1984		
Behavior of TCDD in blood	X		X			X	December 1985
Clearance of TCDD from dose organisms	X	X	X				December 1985
Analytical methods development of monoclonal antibodies			X				December 1985
Workshop report on bioavailability				X		X	December 1985
Movement of TCDD in the environment		X				X	December 1985
Evaluation of combustion sources		X	X	X		X	December 1985

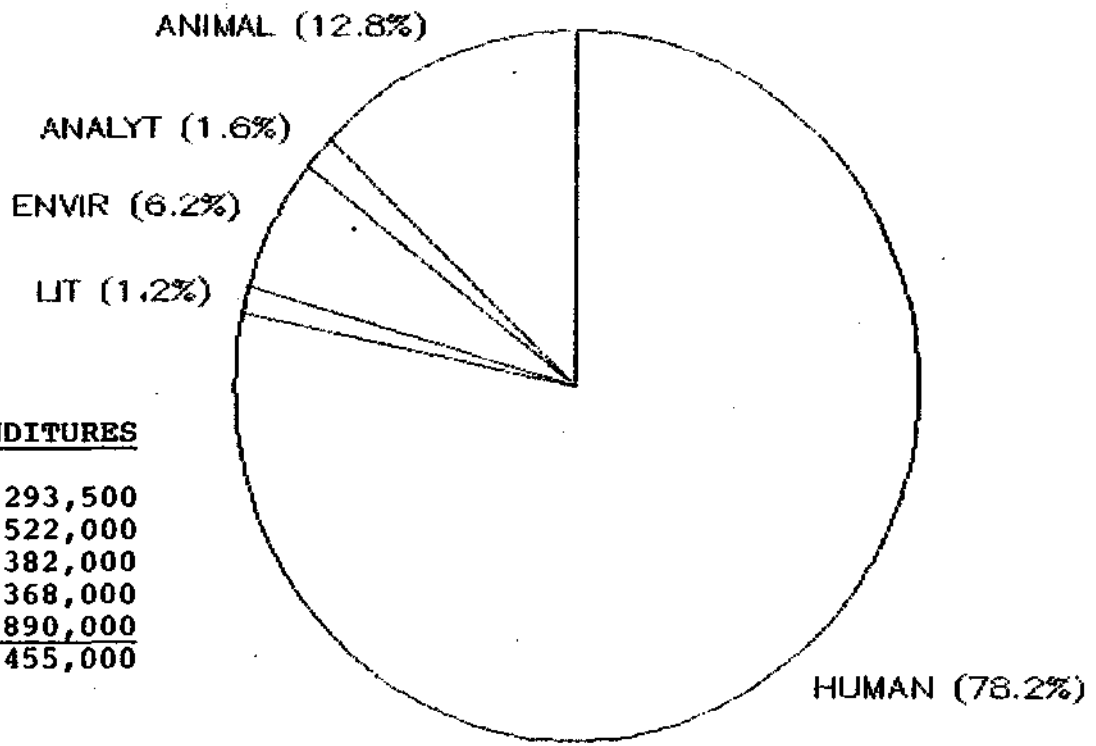
FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion Date
Analysis of background levels of TCDD in the US environment		X	X	X		X	December 1985
Health assessment of PCDDs		X	X			X	December 1985
Health assessment of PCDFs				X		X	December 1985

AGENT ORANGE/DIOXIN EXPENDITURES

AGENCY EXPENDITURES BY STUDY TYPE

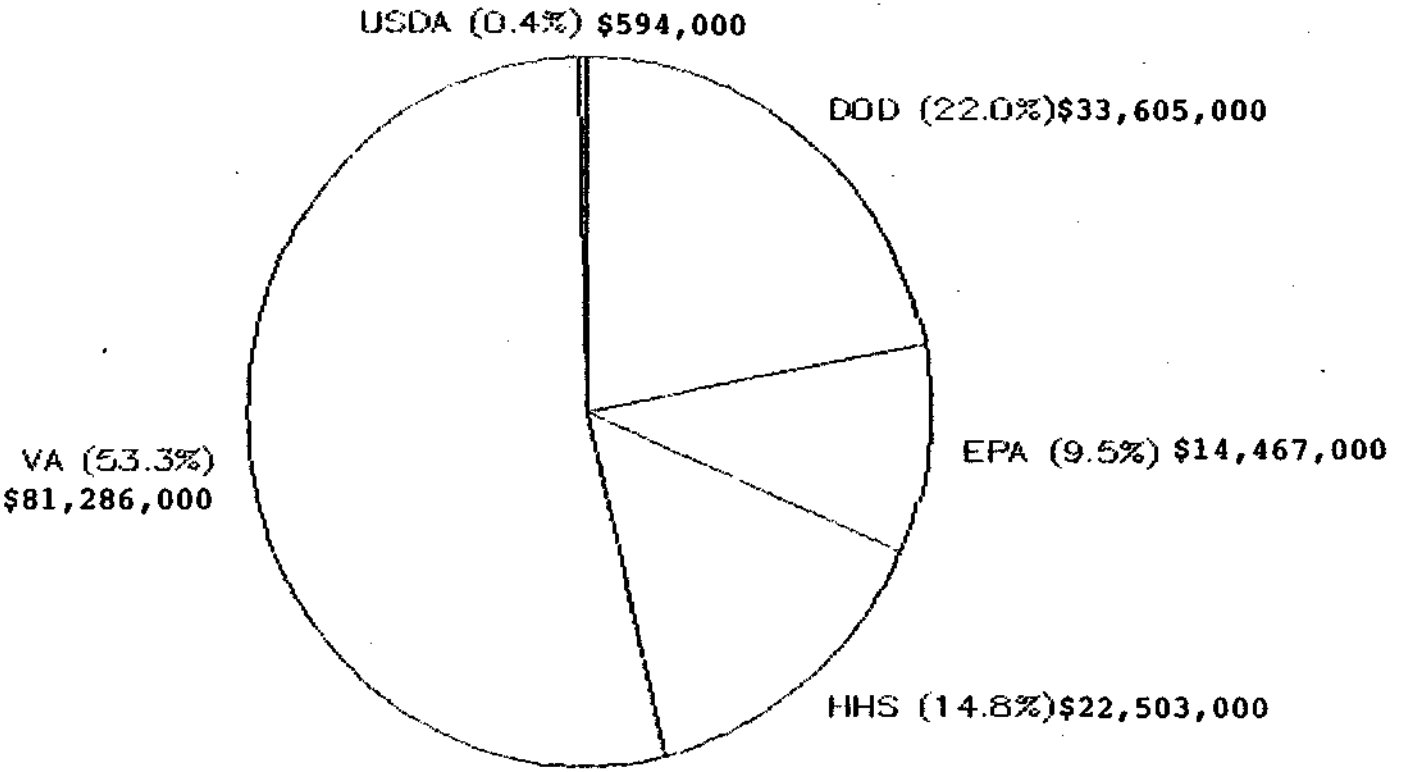
$152,455,000 TOTAL EXPENDITURES



STUDY TYPE	EXPENDITURES
HUMAN	$119,293,500
ANIMAL	19,522,000
ENVIRONMENT	9,382,000
ANALYTICAL	2,368,000
LITERATURE	1,890,000
TOTAL	$152,455,000

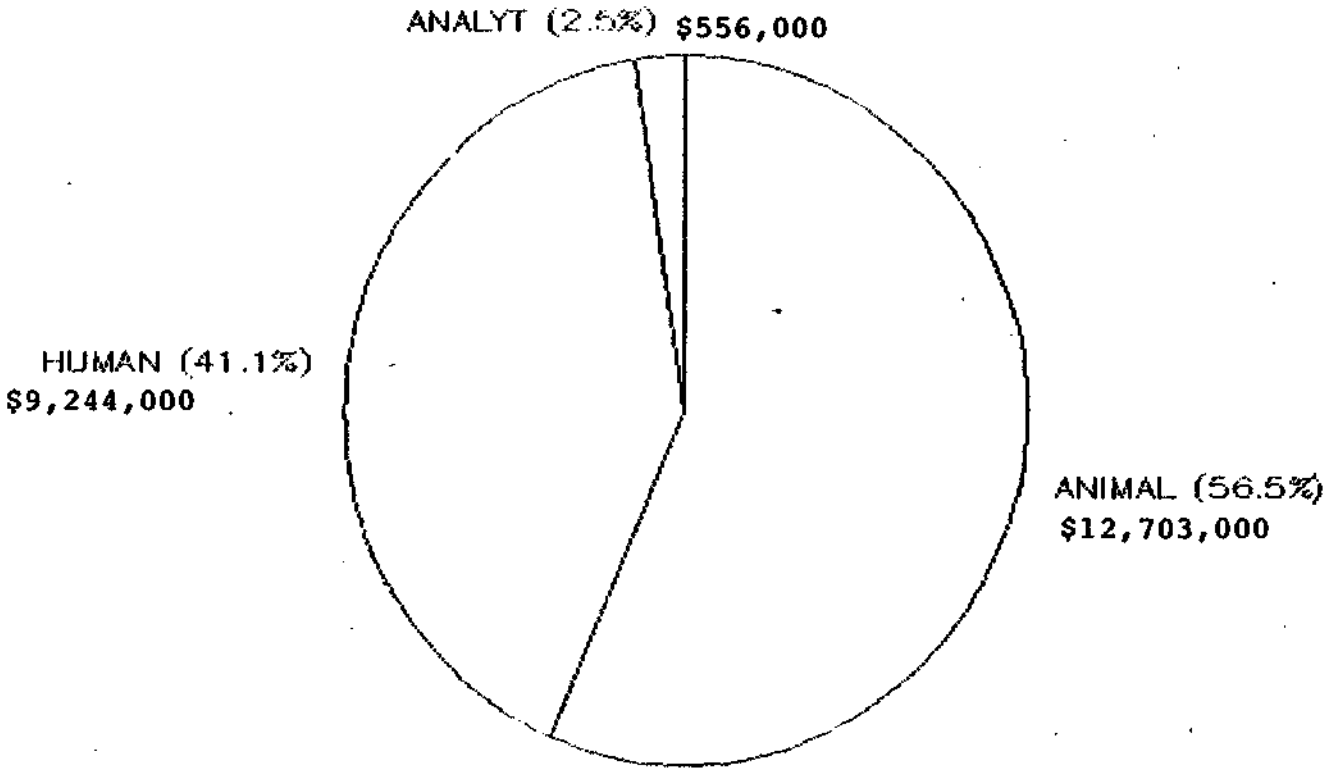
AGENT ORANGE/DIOXIN EXPENDITURES

$152,455,000 TOTAL COST



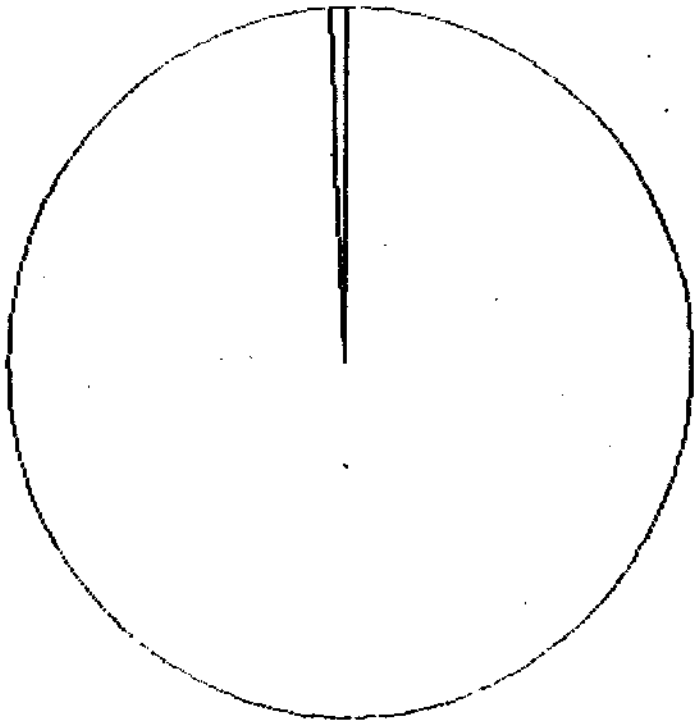
HHS A.O./DIOXIN EXPENDITURES

$22,503,000 TOTAL EXPENDITURES



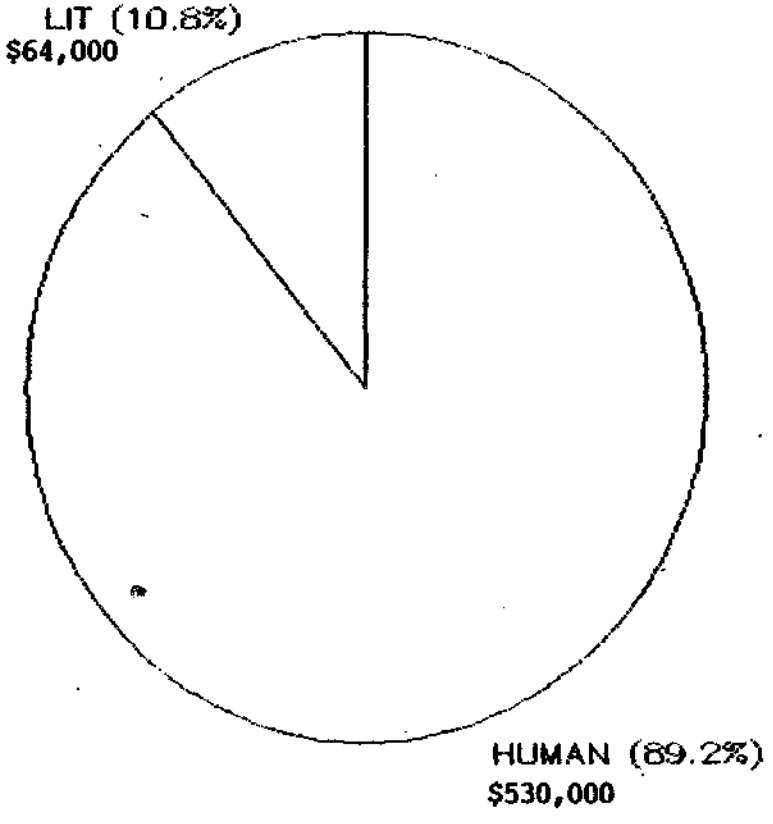
DOD A.O./DIOXIN EXPENDITURES

$33,605,500 TOTAL EXPENDITURES



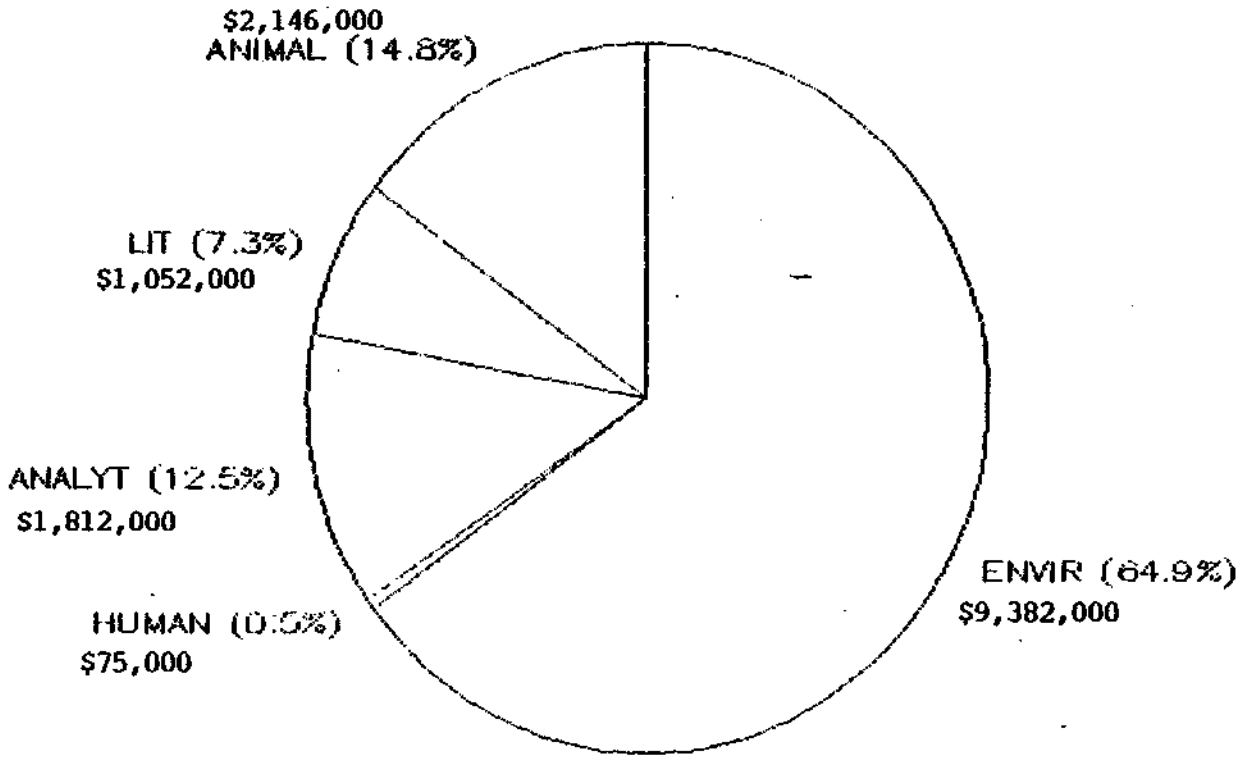
USDA A.O./DIOXIN EXPENDITURES

$594,000 TOTAL EXPENDITURES



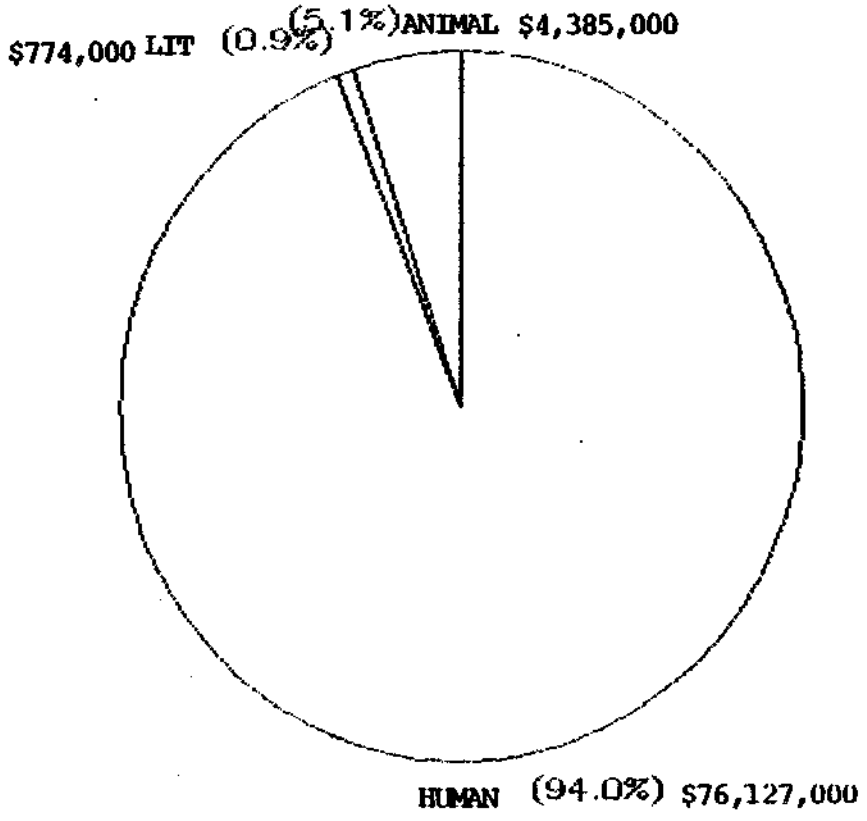
EPA A.O./DIOXIN EXPENDITURES

$14,467,000 TOTAL EXPENDITURES



V.A. A.O./DIOXIN EXPENDITURES

$81,286,000 TOTAL EXPENDITURES



SUMMARY

- Short-term health effects do occur
- Long-term health effects may occur
  - No conclusive evidence to date
- Massive research program underway on long-term effects

SCIENTIFIC CONSENSUS EXPECTED

• Birth Defects	1984
• Mortality	1984
• Soft Tissue Sarcoma	1985
• Other Health Problems	1986-87

ON-GOING VA PROGRAMS WHILE RESEARCH IN PROGRESS

- Health Surveillance
  - Agent Orange Registry
  - Patient Treatment File
- Health Care
  - Public Law 97-72

Background of Agent Orange Working Group

On December 11, 1979, Stuart Eizenstat, Assistant to President Carter, requested HHS to take the lead in convening an Interagency Work Group (IWG) to study possible long-term health effects of phenoxy herbicides and contaminants (Tab A). The IWG was to oversee, coordinate and set priorities among Federal government research activities in this area. In designing a research agenda, the IWG was to take into consideration the possible health effects of exposure to Agent Orange by Vietnam veterans.

President Reagan announced on July 17, 1981, that he was reaffirming the mandate of the Interagency Work Group and his intention to "make its work a major priority of my Administration". The Interagency Working Group was renamed the Agent Orange Working Group (AOWG) and raised in status to Cabinet Council level (Tab B). In his implementing memorandum of August 21, 1981, Secretary Schweiker stated that the President had been motivated because he shared the widespread public and Congressional concern over possible adverse health effects among Vietnam veterans exposed to Agent Orange and other substances (Tab C). In the same memorandum the Secretary reaffirmed the charter language of December 11, 1979, and added the responsibility for guiding the epidemiologic study of the health of Vietnam veterans authorized by P.L. 96-151 as amended by P.L. 97-72.

In appointing her Under Secretary as chair of the AOWG in a Press Release dated June 6, 1983, Secretary Heckler added her personal long time interest and concern for Vietnam veterans. "I am reaffirming this administration's commitment to the prompt and scientifically responsible resolution of the health concerns of Vietnam veterans who were exposed to Agent Orange and other environmental factors during their service to their country in that conflict" she said. (Tab D)

The charter of IWG, and now of AOWG, is a broad mandate which provides in explicit terms the authority to design and direct all research activities on the health effects of exposure to phenoxy herbicides and contaminants, with exposure to Agent Orange by Vietnam veterans as one part of the total research design (Tab E). The contaminants mentioned include that class of chemicals known as the dioxins produced during the manufacture of these herbicides The renaming of the IWG by President Reagan focused the Work Group's primary responsibility on Agent Orange, but without a change in the language of the charter, a lack of clarity regarding the AOWG's purpose and scope resulted.

Agent Orange Use In Vietnam

Agent Orange was the most widely used of the various herbicides. During the period 1964-1970, approximately 12 million gallons were sprayed in Vietnam. In addition, approximately five million gallons of Agent White, composed of the chemical Picloram and 2, 4-D, and approximately three million gallons of Agent Blue composed of cacodylic acid were sprayed. Neither Agent White nor Agent Blue contained the contaminant dioxin.

The herbicides were used to defoliate jungle areas to expose enemy troop movements and staging areas and to eliminate ambush opportunities. Base perimeters, river banks and enemy crop resources were also defoliated. The principal means of distribution was by C-123 fixed wing aircraft (Operation Ranch Hand). Helicopters, back-packs, truck-equipped equipment and Navy river boats were also used. In all, it is estimated that 10% of the land area of South Vietnam was sprayed at least once.

Its use was discontinued in late 1970 because of allegations of a link between 2, 4, 5-T and birth defects of children born in South Vietnam. These allegations have never been substantiated.

All remaining stocks of Agent Orange were incinerated at sea near Johnston Island (a remote island in the South Pacific) in 1977.

I-3

THE WHITE HOUSE

WASHINGTON

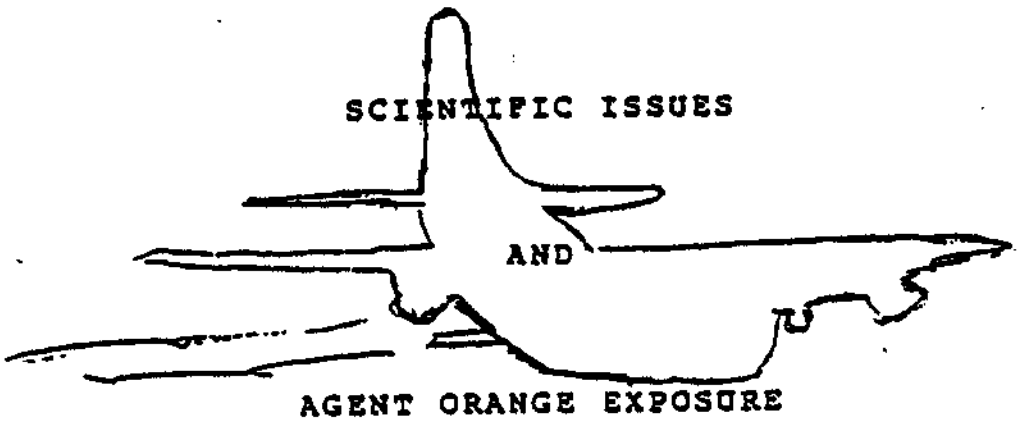
SCIENTIFIC ISSUES AND AGENT ORANGE EXPOSURE

October 27, 1983

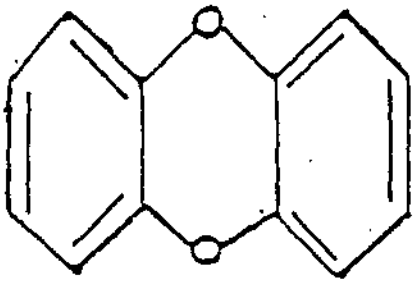
Introduction: Dr. G. A. Keyworth
Science Advisor to the President

Briefing: Dr. Alvin Young
Scientific Advisor, Veterans Administration

Discussion

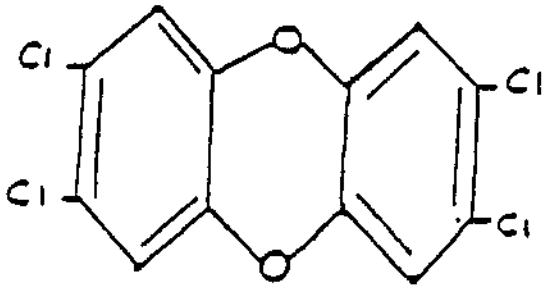

SCIENTIFIC ISSUES
AND
AGENT ORANGE EXPOSURE

"DIOXIN" IS A FAMILY OF 75 COMPOUNDS



DIBENZO-PARA-DIOXINS

DIOXIN OF CONCERN



2,3,7,8-TCDD

TOXICITY OF 2,3,7,8-TCDD

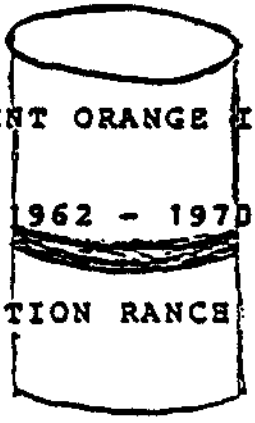
Acute Toxicity:	Single Dose LD_{50} (µg/kg)
Guinea Pig	0.6
Rat	40
Monkey	70
Rabbit	115
Dog	150
Mouse	200
Hamster	3,500
Bullfrog	Over 1,000
Man	No deaths reported

IN LABORATORY ANIMALS, DIOXIN CAUSES

- BIRTH DEFECTS
- FETAL DEATH
- CANCER
- MUTATION?

SOURCES OF HUMAN EXPOSURE

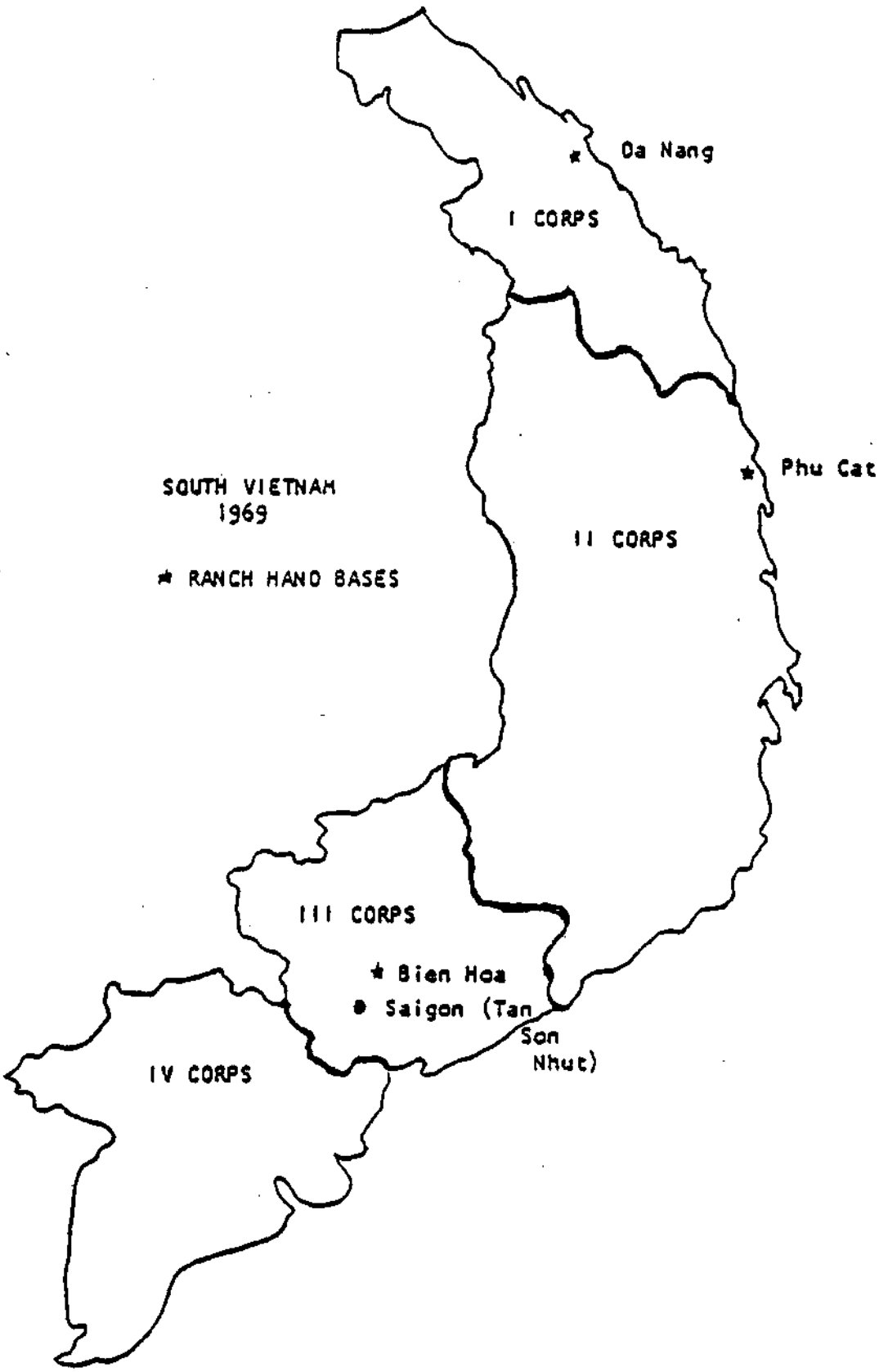
- Industrial Accidents
- Occupational Exposure
- Contaminated Industrial Wastes
- → Herbicide Applications
- Contaminated Food
- Low Temperature Combustion



USE OF AGENT ORANGE IN VIETNAM

1962 - 1970

"OPERATION RANCH HAND"


SOUTH VIETNAM
1969
* RANCH HAND BASES
Da Nang
I CORPS
Phu Cat
II CORPS
III CORPS
* Bien Hoa
● Saigon (Tan Son Nhut)
IV CORPS

ESTIMATED QUANTITES OF HERBICIDES AND
TCDD SPRAYED IN VIETNAM,
JANUARY 1962 - FEBRUARY 1971*

Chemical	Pounds
2,4-D	55,940,150
2,4,5-T	44,232,600
TCDD	368

ESTIMATED QUANTITES OF HERBICIDES AND
TCDD SPRAYED IN UNITED STATES,
JANUARY 1962 - JANUARY 1971

Chemical	Pounds
2,4-D	327,627,000
2,4,5-T	78,100,000
TCDD	650

VIETNAM VETERANS ARE WORRIED ABOUT

- Birth Defects and Miscarriages
- Cancers
  - Soft Tissue Sarcoma
  - Other
- Early Death
- Skin Disorders
  - Chloracne
  - PCT
- Disease Due to Dioxin in Tissue

HOW DO SCIENTISTS ADDRESS THESE CONCERNS?

EPIDEMIOLOGY: STUDY OF FREQUENCY AND CAUSE OF DISEASE IN HUMAN POPULATIONS

CASE-CONTROL STUDY -

- Experiences compared between subjects selected for Disease and Subjects without the disease.

COHORT STUDY -

- Exposed and non-exposed populations examined for disease.

SCIENTIFIC CONSENSUS ACHIEVED WHEN:

- Statistically significant data
- Withstand peer review, and
- Results duplicated by others

MEDICAL CONSENSUS NOW RELATES DIOXIN EXPOSURE TO:

- Chloracne
- Porphyria Cutanea Tarda (PCT)
- Temporary Health Effects

DIOXIN EXPOSURE - TEMPORARY EFFECTS

- Headache
- Fatigue
- Muscle and Joint Pain
- Tingling in extremities
- Sexual dysfunction
- Loss of appetite and weight
- Sleep disturbances
- Impaired memory and learning ability
- Abnormal liver function

FEDERAL GOVERNMENT ADDRESSES VETERAN CONCERNS:

WHITE HOUSE

CAPITOL

AGENT ORANGE WORKING GROUP

CONCERN - BIRTH DEFECTS AND MISCARRIAGES

COMPLETED: EPA ARKANSAS STUDY-1979

NIOSH NEW YORK STATE STUDY 1979

NEW ZEALAND APPLICATOR STUDY-1982

AUSTRALIAN BIRTH DEFECTS STUDY-1983

CONCLUSION: MEN AND WOMEN ARE AT NO INCREASED RISK

ON-GOING: CDC/DOD/VA BIRTH DEFECTS STUDY- 1984

AIR FORCE HEALTH STUDY- 1984

CONCERN - MORTALITY: NUMBER/AGE/CAUSE

COMPLETED: FOUR INDUSTRIAL HEALTH STUDIES-1980-1983

FINLAND MORTALITY STUDY OF HERBICIDE APPLICATORS-1982

AIR FORCE HEALTH STUDY-BASELINE MORTALITY-1983

CONCLUSION: NO EVIDENCE OF INCREASED DEATH RATE

ON-GOING: NEW YORK STATE MORTALITY STUDY - 1984

VA MORTALITY STUDY - 1984

CONCERN - CONNECTIVE TISSUE CANCER
(SOFT TISSUE SARCOMA, STS)

COMPLETED: SWEDISH STS STUDIES - 1978-1983
NEW ZEALAND STS STUDY-1982
FINLAND CANCER STUDY-1982
INDUSTRIAL STUDIES-1980-1983

CONCLUSION: NO CONSENSUS

ON-GOING: NEW YORK STATE STUDY - 1984
NCI STUDIES - 1984-85
VA/AFIP STUDY - 1985
NIOSH REGISTRY STUDY - 1985
CDC STUDY - 1986

CONCERN - OTHER FORMS OF CANCER

COMPLETED: FINLAND CANCER STUDY-1982

SWEDISH RISK EVALUATION OF PESTICIDES-1982

NCI FLORIDA PESTICIDE APPLICATOR STUDY-1983

INDUSTRIAL STUDIES-1980-1983

CONCLUSION: NO CONSENSUS

ON-GOING: AIR FORCE HEALTH STUDY-1984

NIOSH DIOXIN REGISTRY-1985

CDC AGENT ORANGE STUDY-1987

CONCERN - CHLORACNE

CURRENT EVIDENCE: RARE

ON-GOING STUDIES: AIR FORCE HEALTH STUDY

CONCERN - OTHER HEALTH PROBLEMS

ON-GOING STUDIES: AIR FORCE HEALTH STUDY-1984
VA TWIN STUDY-1986
CDC STUDIES-1987

OTHER EFFORTS: VA AGENT ORANGE REGISTRY
VA PATIENT TREATMENT FILE

CONCERN - DIOXIN IN BODY TISSUE

COMPLETED: VA FEASIBILITY STUDY-1982
CANADIAN STUDY-1983

CONCLUSIONS: SMALL AMOUNTS DETECTED
NO CORRELATION WITH EXPOSURE OR HEALTH

ON-GOING: VA/EPA DIOXIN STUDY

SUMMARY

- Short-term health effects do occur
- Long-term health effects may occur
  - No conclusive evidence to date
- Massive research program underway on long-term effects

SCIENTIFIC CONSENSUS EXPECTED

• Birth Defects	1984
• Mortality	1984
• Soft Tissue Sarcoma	1985
• Other Health Problems	1986-87

ON-GOING VA PROGRAMS WHILE RESEARCH IN PROGRESS

- Health Surveillance
  - Agent Orange Registry
  - Patient Treatment File
- Health Care
  - Public Law 97-72

CONCERN - OTHER FORMS OF CANCER

COMPLETED: FINLAND CANCER STUDY-1982

SWEDISH RISK EVALUATION OF PESTICIDES-1982

NCI FLORIDA PESTICIDE APPLICATOR STUDY-1983

INDUSTRIAL STUDIES-1980-1983

CONCLUSION: NO CONSENSUS

ON-GOING: AIR FORCE HEALTH STUDY-1984

NIOSH DIOXIN REGISTRY-1985

CDC AGENT ORANGE STUDY-1987

CONCERN - CHLORACNE

CURRENT EVIDENCE: RARE

ON-GOING STUDIES: AIR FORCE HEALTH STUDY

CONCERN - OTHER HEALTH PROBLEMS

ON-GOING STUDIES: AIR FORCE HEALTH STUDY-1984
VA TWIN STUDY-1986
CDC STUDIES-1987

OTHER EFFORTS: VA AGENT ORANGE REGISTRY
VA PATIENT TREATMENT FILE

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CANADIAN STUDY-1983

CONCLUSIONS: SMALL AMOUNTS DETECTED
NO CORRELATION WITH EXPOSURE OR HEALTH

ON-GOING: VA/EPA DIOXIN STUDY

DEPARTMENT OF AGRICULTURE HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS			
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING	STUDY PERIOD	TOTAL $ 1981-87
A CASE CONTROL STUDY OF THE RELATIONSHIP BETWEEN EXPOSURE TO 2,4-D AND SPONTANEOUS ABORTIONS IN HUMANS				X			X	1980-1981	365,000
EXPOSURE OF FOREST WORKERS TO GROUND APPLICATIONS OF 2,4-D					X		X	1981-1984	165,000

DEPARTMENT OF AGRICULTURE OFFICE OF SCIENTIFIC RESEARCH LAB/LITERATURE STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
BIOLOGICAL AND ECONOMIC ASSESSMENT OF 2,4,5-T AND SILVEX				X	X		1977-1983	64,300

DEPARTMENT OF DEFENSE/AFIP HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS		STUDY PERIOD	TOTAL $ 1981-87
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING		
ARMED FORCES INSTITUTE OF PATHOLOGY MORPHOLOGIC STUDIES/VIET VETS			X				X	1980-1986	350,000

DEPARTMENT OF DEFENSE/AIR FORCE HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS			
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING	STUDY PERIOD	TOTAL $ 1981-87
PROJECT RANCH HAND EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDE ORANGE (AIR FORCE HEALTH STUDY)	X	X	X	X			X	1981-1999	28,600,000

DEPARTMENT OF DEFENSE/AIR FORCE OFFICE OF SCIENTIFIC RESEARCH LAB/LITERATURE STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
2,3,7,8-TCDD INDUCED IMMUNOSUPPRESSION	X					X	1985-1987	62,600
MECH OF CELLULAR MEMBRANE EFFECTS OF TCDD	X					X	1984-1987	225,000

DEPARTMENT OF DEFENSE/ARMY ENVIRONMENTAL SUPPORT GROUP HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS		STUDY PERIOD	TOTAL $ 1981-87
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING		
VA SOFT TISSUE SARCOMA			X			X		1985	12,000
VA MORTALITY STUDY	X						X	1984-1987	561,000
CDC BIRTH DEFECTS STUDY				X		X		1983-1984	225,000
CDC EPIDEMIOLOG. STUDY	X	X	X	X	X	X		1984-1988	768,000
VA TWIN STUDY		X		X				1985-1987	75,000
VA ADIPOSE TISS. STUDY					X			PENDING	-
AFI SARCOMA STUDY			X					1984-1989	86,000
CDC SELECTED CANCERS			X				X	1984-1989	72,000
VA CHLORACNE		X						1984-1989	55,000
DIOXIN WORKERS		X				X		1984	12,000
VA PATIENT TREATMENT FILES		X						1984-1989	47,000
SERVICES HERBS TAPES					X			1982-1989	172,000
MISCELLANEOUS SUPPORT CDC VIETNAM EXPERIENCE STUDY	X	X	X	X	X	X		1980-1989	1,377,500
CDC VIETNAM EXPERIENCE STUDY							X	1984-1985	194,000

ENVIRONMENTAL PROTECTION AGENCY HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS			
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING	STUDY PERIOD	TOTAL $ 1981-87
REPORT OF ASSESSMENT OF A FIELD INVESTIGATION OF SIX-YEAR SPONTANEOUS ABORTION RATES IN THREE OREGON AREAS OF RELATION TO FOREST 2,4,5-T SPRAY PRACTICES				X		X		1979	0
NORTHWEST HUMAN MILK STUDY					X	X		1980	0
NATIONAL MONITORING OF HUMAN ADIPOSE					X		X	1983-1985	75,000
NEBRASKA ADIPOSE TISSUE STUDY					X	X		1980	0
RETROSPECTIVE STUDY OF DIOXINS AND FURANS IN ADIPOSE TISSUE OF VIETNAM-ERA VETERANS (VA/EPA)					X		X	1982-1989	VA FUNDING

ENVIRONMENTAL PROTECTION AGENCY LAB/LITERATURE STUDIES

EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
ASSESS OF PCB TRANSFORMER/ CAP FIRES			X		X		1984-1985	140,000
UPTAKE OF DIOXINS BY FISH	X					X	1984-1987	909,000
MICROB. DISSIM. OF 2,3,7,8-TCDD		X			X		1980	0
POTENTL FOR 2,3,7,8-TCDD TRANSPORT IN SOILS		X				X	1984-1987	812,000
BACTER DECOMP OF TCDD		X				X	1982-1987	486,000
MISSISSIPPI CATFISH STUDY	X				X		1980	0
EXPOS ASSESS MTHDS FOR TCDD AND OTHER DIOXINS				X		X	1984-1987	667,000
OF ENV. SAMPLES .DS AND CDFS		X			X		1982-1984	290,000
BIOAVAIL. OF FR. WATER FISH FOR TCDDS	X				X		1982-1984	250,000
OREGON MONKEY STUDY	X				X		1980	0
EVAL OF MUNIC. WASTE COMBUSTORS		X			X		1982-1984	300,000
QUALITY ASSUR. SUPPORT			X			X	1984-1985	1,162,000
REGION X DEER & ELK STUDY	X				X		1980	0
UPTAKE OF DIOXINS BY PLANTS AND LARGE ANIMALS		X				X	1984-1987	435,000
LA. CRAYFISH/CATFISH STUDY	X				X		1980	0
EVAL OF LARGE SCALE COMBUSTION SOURCE		X			X		1982-1983	400,000
RISK ASSESS APPROACH TCDD AND OTHER DIOXINS				X		X	1984-1987	335,000
.AL DIOXIN STUDY		X				X	1984-1985	4,600,000
BEEF FAT PHASE II	X				X		1980	0

ENVIRONMENTAL PROTECTION AGENCY LAB/LITERATURE STUDIES

EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
EVAL UV PHOTOLYSIS/ APEG CHEM DETOX		X				X	1984-1987	607,000
HEALTH ASSESS OF PCDDS & PCDFS				X		X	1985	50,000
BIODEG AND CARBON ADSORPTION OF TCDD		X			X		1980	0
INVEST OF IN SITU STABIL. TECHNOLOGY		X				X	1984-1987	397,000
SORPTION/DESORPTION OF TCDD		X				X	1984-1987	670,000
METHODS ANALYS. ENVIR. OF TCDD BY MASS. SPECT.			X			X	1984-1985	300,000
PHARMACO. OF TCDD IN MONK. & [illegible]TH ASSES. OTHER DIOXINS	X					X	1984-1987	837,000
MO[illegible]ON. ANTIBOD. METHOD OF DIOXIN ANALYSIS			X			X	1984-1985	200,000
INACTIVE MINES FOR REPOS. OF DIOXIN SOIL		X				X	1984-1985	185,000
ROUND ROBIN SURVEY-METHODS DIOXIN ANALYSIS IN ADIPOSE			X			X	1985	10,000
WISCONSIN MONKEY STUDY	X				X		1980	0
PHOTOCHEMISTRY		X				X	1986-1987	200,000
BIOAVAILABILITY TO ANIMALS	X					X	1985-1986	150,000

HEALTH AND HUMAN SERVICES/CDC HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS		STUDY PERIOD	TOTAL $ 1981-87
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING		
CDC BIRTH DEFECTS AND MILITARY SERVICE IN VIETNAM STUDY				X			X	PUBLISHED AUG. 1984	1,604,000
CDC EPIDEMIOLOGIC STUDY OF GROUND TROOPS EXPOSED TO AGENT ORANGE DURING THE VIETNAM CONFLICT	X	X	X	X	X		X	SEPT 1989	VA FUNDING
DEVELOPMENT OF TCDD REFERENCE STANDARDS FOR LAB ANALYSIS OF HUMAN TISSUES					X	X		1984-1985	EPA FUNDING
DEVELOPMENT OF LAB METHODS FOR TCDD ANALYSIS OF HUMAN A[illegible] TISSUES AND [illegible] ULTRALOW (PP[illegible]) LEVELS					X	[illegible]		1984-1985	EPA FUNDING
EXPOSURE STUDIES OF MO RESIDENTS OF TCDD-CONTAMINATED AREAS									
PILOT STUDY		X					X	1984-1985	EPA FUNDING
PILOT STUDY FOLLOWUP		X			X		X	1985-1986	EPA FUNDING
ADIPOSE TISSUE TESTING					X		X	1985-1986	EPA FUNDING
REPRODUCTIVE OUTCOMES				X			X	1985-1986	EPA FUNDING
ASSESSMENT OF HEALTH RISK OF EXPOSURE TO 2,3,7,8-TCDD IN SOIL IN A RESIDENTIAL COMMUNITY (TIMES BEACH, MO)					X	X		1984	EPA FUNDING
DETAILED CURRENT LITERATURE REVIEWS WITH PUBLISHED REPORTS ON THE STATE OF SCIENTIFIC KNOWLEDGE OF THE HEALTH EFFECTS OF TCDD					X		X	1975-1985	140,000

HEALTH AND HUMAN SERVICES/NCI HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS			
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING	STUDY PERIOD	TOTAL $ 1981-87
LUNG CANCER - STRUCTURAL PEST CONTROL WORKERS	X						X	1984-1986	100,000
CONTROL STUDY OF LYMPHOMA AND SOFT TISSUE SARCOMA			X			X		1981-1982	487,000
NCI PESTICIDE WORKERS			X				X	1983-1985	870,000

HEALTH AND HUMAN SERVICES/NIEHS LAB/LITERATURE STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
DED-WEED.LV-69: SALMONELLA	X				X		1980	0
2,4-D: DROSOPHILIA	X				X		1981	7,400
2,4,5-T: DROSOPHILIA	X				X		1981	7,400
2,4,5-T: N-BUTYL ESTER: SALMONELLA	X				X		1981	1,200
2,4-D. N-BUTYL ESTER: SALMONELLA	X				X		1981	1,200
2,4,5-T: SALMONELLA	X				X		1980-1981	1,200
CYTOGENETICS	X				X		1982	4,200
2,4,5-T: CYTOGENETICS	X				X		1982	4,200
DIBENZOFURAN: CYTOGENETICS	X				X		1981	4,150
2,4-D: SALMONELLA	X				X		1980-1981	1,200
2,7-DICHLOPODIBENZO-P-DIOX: SALMONELLA	X				X		1982	1,200
DIBENZOFURAN: SALMONELLA	X				X		1980	0
2,4-D. DIMETHYLAMINE SALT: SALMONELLA	X				X		1980	0
PENTACHLOR. & DIOXIN CONTAM IN PCP			X		X		1984	200,000
NEUROTOXICITY OF 2,4-D IN RODENTS	X				X		1980-1981	27,000
PEST. & TRANS. ACROSS BIL. LIP. MEM.	X				X		1980-1987	982,000
DLL. & TOX. OF THE LIVER	X					X	1980-1986	741,000
OCCUPTL. & ENVMTL. HLTH. CTR. GRANT	X				X		1980-1984	95,000

HEALTH AND HUMAN SERVICES/NIEHS LAB/LITERATURE STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
ALTER. OF CELL-SURF. MEMBRANE FOR DI TOX	X					X	1985-1989	415,000
EFFECTS ON NUTRIENT ASSIMILATION	X					X	1982-1986	760,000
BIOAVAILABILITY OF TCDD (RAT) DERMAL AND ORAL	X				X		1983-1994	110,000
TOXICANT DERES ENDOCRINE HEME BIOSYNTH	X					X	1985-1987	316,000
DI-EPITH CELL INTERACT. MECH AND ASSAY	X					X	1985-1997	219,000
. ARE-TOXICITY RELAT.	X					X	1990-1994	35,000
MOLECULAR TOXICOLOGY OF TCDD	X					X	1981-1996	462,000
IMMUNOSUPPRESSION BY IN UTERO EXPOS	X				X		1990	0
ARACHIDONATE PRODTS IN DI AND PCB TOX	X					X	1985-1987	497,000
IMPLCTNS. OF LOW LVL. EXP. TO DIOXIN	X				X		1990-1992	258,000
TOC. MOT. OF TETRACHLOROBENZIENE AND DIOXIN	X				X		1990-1993	214,000
XENTC. IND. OF PLE. REP. IN LIVER TOX	X					X	1980-1986	1,144,000
CHL. DIB-P-DIOX. MECH. OF TOX.	X					X	1982-1987	546,000
MLCLR. MOLS. OF DIOX. BNDG. PROTEINS			X		X		1983-1985	90,000
. ...HEXACHLORO-DIBENZO-P-DIOXIN	X				X		1990	0
MCH. FOR TOX. OF CHL. DIBENZODIOX.	X				X		1981-1987	471,000

HEALTH AND HUMAN SERVICES/NIEHS LAB/LITERATURE STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
TER. OF TCDD CLFT. PAL. INDC. (MICE)	X					X	1983-1985	400,000
DISPOSIT OF TCDD FTL. DIST. IN MICE	X					X	1984-1985	50,000
PRE-DIOX. IN PCP DIOCH., EF., & TOX	X				X		1980-1982	172,000
ATMC. EN. SPCT. FOR DIOXIN TR. ANLYS.	X					X	1983-1986	344,000
SYNTH. OF 6 CHLOR DIBENZO-P-DIOX			X		X		1982	61,000
MOLECULAR BASIS OF DIOXIN TOXICITY			X			X	1983-1985	120,000
[illegible] OF TETRACHLORO-DIBENZO-P-DIOX	X				[illegible]		1980	0
ROLE OF TCDD RECEPTOR IN TUMOR PROMO	X					X	1985-1989	400,000
TOXIC AND ANORECTIC EFFECTS OF TCCDD	X					X	1985-1987	456,000
MECHANISMS OF TCDD TOXICITY	X					X	1985-1987	320,000
MECHANISMS OF IMMUNOSUPPRESSION	X					X	1984-1985	130,000
RIOASSAY OF TETRACHLORO-DIBENZO-P-DIOXIN	X				[illegible]		1980	0
QUAN. ANAL. OF TCDD BY MASS SPECT.			X		X		1981	35,000
TOXC HLS WST IN ITR. BIASY. DVLMT.	X				X		1982-1984	181,000
[illegible] MS OF [illegible]. [illegible]OXICITY	X					X	1985-1988	253,000
THEORETICAL MDLG OF & DIOXIN RECEPTOR			X		[illegible]		1983-1984	25,000
MECHANISMS OF TOXICITY OF DIOXIN	[illegible]					[illegible]	[illegible]	[illegible]

HEALTH AND HUMAN SERVICES/NIEHS LAB/LITERATURE STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
ENVIRMTL HLTH SCI CNTR GRANT	X					X	1980-1987	597,000
DIOXIN NMR STUDY			X		X		1984	35,000
EFFECTS ON INTESTINAL CELLS	X				X		1981-1992	4,000
HEXACHL BENZ DISPOSIT	X				X		1981-1984	75,000
INTL. RES/EXPOS TO PHENOXY ACID HERB	X				X		1981-1983	456,000
MEMBRANE/LP RECEPTOR NRSA	X					X	1984-1987	36,000
LIPID ASSIMILATION NRSA	X				X		1981-1984	36,000
[illegible] 3-TCDD DISP [illegible] MICE & G.P.	X				X		1980-1993	300,000
2,3,7,8-TCDF METABOLISM IN RATS, MICE & G.P.	X				X		1981-1985	100,000
CONTROL OF GENE EXPRESSION BY DIOXIN	X					X	1985-1990	343,000
TCDD EFFECTS ON STEROID HORMONE SYNTHESIS	X					X	1985-1988	204,000

HEALTH AND HUMAN SERVICES/NIOSH HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS		STUDY PERIOD	TOTAL $ 1981-87
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING		
NIOSH HEALTH HAZARD EVAL AND LEUKEMIA CLUSTER IN MADISON COUNTY, KENTUCKY ALLEGEDLY ASSOCIATED WITH PENTACHLOROPHENOL TREATED AMMUNITION BOXES			X			X		1981-1984	> 615,000
NIOSH HEALTH HAZARD EVAL AND TECHNICAL ASSISTANCE		X					X	1983-1989	
NIOSH DIOXIN REGISTRY AND MORTALITY	X		X				X	1980-1987	1,328,600
NIOSH DIOXIN REGISTRY MORBIDITY & REPRO OUTCOME STUDY		X	X	X			X	1985-1988	4,095,000
NIOSH SOFT TISSUE SARCOMA INVESTIGATION (TECH. ARTICLE)			X			X		1981-1983	4,000

VETERANS ADMINISTRATION HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS			
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING	STUDY PERIOD	TOTAL $ 1981-87
VIETNAM VETERANS MORTALITY STUDY	X						X	1982-1989	2,334,000
EPIDEMIOLOGY STUDY (CDC)	X	X	X	X	X		X	1983-1989	67,694,000
BIRTH DEFECTS (CDC)				X			X	1981-1983	488,000
TWIN STUDY: VIETNAM EXPERIENCE TWIN STUDY (VETS I)		X		X			X	1982-1987	
TWIN STUDY: VIETNAM EXPERIENCE TWIN STUDY (VETS II)		X						SUSPENDED	3,339,000
VA/AFIP SOFT TISSUE SARCOMA			X				X	1984-1989	302,000
VA/AFIP SOFT TISSUE SARCOMA T TREATMENT FILE		X	X				X	NO FUNDING	-
TCDD IN BODY FAT OF VIETNAM VETERANS AND OTHER MEN		X			X	X		1980	-
RETROSPECTIVE STUDY OF DIOXINS AND FURANS IN ADIPOSE TISSUE OF VIETNAM-ERA VETERANS (VA/EPA)					X		X	1982-1989	810,000
CASE CONTROL STUDY OF LYMPHOMA			X				X	1985-1989	150,000
FEMALE VETERAN SURVEY	X						X	1985-1988	480,000
COHORT MORTALITY STUDY OF VIET VETS	X						X	1985-1989	370,000
PTF/VIETNAM SERVICE INDICATOR						X		1982-1984	140,000

VETERANS ADMINISTRATION HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS		STUDY PERIOD	TOTAL $ 1981-87
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING		
INVESTIGATOR INITIATED RESEARCH: CHRONIC EFFECTS OF HERBICIDE EXPOSURE ON TESTICULAR FUNCTION IN VIETNAM VETERANS		X					X		
INVESTIGATOR INITIATED RESEARCH: FAT TISSUE ANALYSIS FOR 2,3,7,8-TCDD (DALLAS)					X		X	1980-1989	INCLUDED BELOW
INVESTIGATOR INITIATED RESEARCH: FAT TISSUE ANALYSIS FOR 2,3,7,8-TCDD (SAN ANTONIO)					X		X		

VETERANS ADMINISTRATION LAB/LITERATURE STUDIES

EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
REVIEW OF LITERATURE ON HERBICIDES, INCLUDING PHENOXY HERBICIDES AND ASSOCIATED DIOXINS				X		X	1981-1989	439,000
INVESTIGATOR INITIATED RESEARCH: URINARY 6-HYDROXY CORTISOL: PHYSIOLOGICAL AND PHARMACOLOGICAL STUDIES (INCLUDING AGENT ORANGE)	X					X		
INVESTIGATOR INITIATED RESEARCH: EFFECT OF TCDD ON LIPID METABOLISM	X					X		
INVESTIGATOR INITIATED RESEARCH: MECHANISMS OF DIOXIN INDUCED TOXICITY USING THE CHLORACNE M[illegible]	X					X		
INVESTIGATOR INITIATED RESEARCH: BEHAVIORAL TOXICITY OF AN AGENT ORANGE COMPONENT: 2,4-D	X					X	→ 1980-1989	4,385,000
INVESTIGATOR INITIATED RESEARCH: EFFECTS OF 2,3,7,8-TETRACHLORODIBENZODIOXIN ON HEPATOBILIARY FUNCTION IN ANIMALS	X					X		
INVESTIGATOR INITIATED RESEARCH: MECHANISM OF TCDD ABSORPTION AND TOXICITY ON LIPID AND LIPOPROTEIN METABOLISM	X					X		
INVESTIGATOR INITIATED RESEARCH: METABOLISM OF THE HERBICIDES PRESENT IN AGENT ORANGE AND AGENT WHITE	X					X		
INVESTIGATOR INITIATED RESEARCH: TCDD EXPOSED RHESUS MONKEYS: EFFECTS ON BEHAVIOUR AND STRESS HORMONES	X					X		
[illegible] GATOR INITIATED RESEARCH: NE[illegible]USCULAR TOXICITY OF AGENT ORANGE	X					X		

VETERANS ADMINISTRATION LAB/LITERATURE STUDIES

S.	_FFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
		ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
	INVESTIGATOR INITIATED RESEARCH: EFFECTS OF LOW DOSE TCDD ON MAMMALIAN CHROMOSOMES AND LIVER CELLS	X					X		
	INVESTIGATOR INITIATED RESEARCH: MECHANISM OF PORPHYRIA CAUSED BY TCDD AND RELATED CHEMICALS	X					X	1980-1989	INCLUDED ABOVE
	INVESTIGATOR INITIATED RESEARCH: EFFECTS OF AGENT ORANGE ON SLEEP	X					X		
	INVESTIGATOR INITIATED RESEARCH: UPTAKE AND METABOLISM STUDIES AND PHARMACOL & TOXICOL	X					X		
	MONOGRAPHS				X		X	1982-1987	136,000
L	NE TASK FORCE				X		X	1983-1987	199,000

APPENDIX C

AGENCY SUMMARY STATEMENT OF AO-RELATED RESEARCH EFFORTS

Telecopy: Sandy Lange 629-3300
7 of 4 pages

12/11 This is Original Copy to Secretary & Randy Tucker
Mail be controlled first thing in A.M.

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DEC 11 12 13 PM '79

THE WHITE HOUSE

WASHINGTON

December 11, 1979

MEMORANDUM FOR SECRETARY OF DEFENSE
SECRETARY OF HEALTH, EDUCATION, AND WELFARE
ADMINISTRATOR OF VETERANS AFFAIRS

SUBJECT: Interagency Work Group to Study the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants

In recent months the public and the Congress have become concerned about adverse health effects to veterans following their possible exposure to herbicides, particularly Agent Orange, while serving in Vietnam. Although there are suggestions of adverse health effects of human exposure to such herbicides and contaminants, there is currently an inadequate scientific basis for concluding that health problems experienced by Vietnam veterans were caused by previous exposure to herbicides. Moreover, there is inadequate information on the long-term health effects of phenoxy herbicides in general.

Individually, each of your agencies has a strong interest in resolving this issue. Several studies have been initiated to answer questions about the possible health effects of exposure to herbicides and more generally to the class of substances called the dioxins. Collectively, the Federal government needs to have reliable data and criteria on which to base decisions and policies which affect the entire country. Although I am aware that there has already been extensive interagency cooperation on these issues, I believe there is a need for formal interagency coordination.

Therefore, I request that you establish an interagency work group to coordinate agency efforts to determine if there are long-term health effects following exposure to phenoxy herbicides and contaminants, with special immediate focus on exposure of Vietnam veterans to Agent Orange. This interagency group should:

1. Oversee, coordinate, and set priorities among Federal government research activities designed

to relate exposure to phenoxy herbicides to long-term health effects.

2. Develop a research agenda to assure that the Federal government conducts comprehensive research on the long-term health effects of these compounds, in response to both scientific and policy needs. The type and duration of exposure to Agent Orange by Vietnam veterans must be considered in the research agenda design so that the Veterans Administration will be able to establish sound policies for determining compensation for veterans exposed to Agent [illegible] in Vietnam, should a relationship between herbicide exposure and long-term adverse health effects be established. The research agenda should build on current agency activities, including the Department of Defense's Ranch Hand study. The interagency work group should identify the appropriate agencies to conduct the recommended research, either individually or through joint efforts.

3. Provide technical support to individual agencies and independent researchers in the formulation, development, and implementation of research on the biomedical effects of phenoxy herbicides and contaminants.

4. Assure that the protocols and methodology of ongoing and proposed Federally funded research studies will produce valid, reliable, timely, and relevant data, and periodically review the status of such research.

5. Assure that all relevant research findings, whether publicly or privately financed, are promptly made available to the public and the Congress, in a comprehensible and comprehensive fashion. The work group should establish a working relationship with the Veterans Administration's Advisory Committee on Health-Related Effects of Herbicides and should promptly provide the Committee all relevant information as it becomes available.

I am asking Secretary Harris to take the lead in convening the interagency group and would like to have an initial report on the progress of the group submitted to me by

February 15. The initial report should indicate the status of current agency activities, a proposed schedule for public progress reports, and any recommendations for inclusion of other agencies on the work group.

I have asked the Office of Science and Technology Policy to be an ex-officio participant on the work group. In addition, the Department of Agriculture, the Environmental Protection Agency, and the Occupational Safety and Health Administration will initially participate on the work group in an observer status.

Stuart E. Eizenstat
Assistant to the President
for Domestic Affairs and Policy

cc: Secretary of Agriculture
Administrator, Environmental Protection Agency
Assistant Secretary of Labor for Occupational Safety and Health
Director, Office of Science and Technology Policy

THE WHITE HOUSE

WASHINGTON

July 17, 1981

MEMORANDUM FOR: SECRETARY RICHARD SCHWEIKER
CHAIRMAN PRO-TEM, CABINET COUNCIL
ON HUMAN RESOURCES

FROM: ROBERT CARLESON
EXECUTIVE SECRETARY OF HUMAN RESOURCES
CABINET COUNCIL

SUBJECT: Agent Orange Working Group

The Secretariat of the Human Resources Cabinet Council has established an Agent Orange Working Group. The lead agency will be HHS, and participating members drawn from:

Department of Defense
Department of Agriculture
Department of Health and Human Services
Department of Labor
Environmental Protection Agency
Veterans Administration
Action
Office of Management and Budget
Council of Economic Advisers
Office of Science and Technology
Office of Policy Development

cc: Martin Anderson
Edwin Gray

THE WHITE HOUSE

WASHINGTON

AUG 21 1981

MEMORANDUM FOR: SECRETARY OF DEFENSE
SECRETARY OF AGRICULTURE
SECRETARY OF LABOR
DIRECTOR, OFFICE OF MANAGEMENT AND BUDGET
ASSISTANT TO THE PRESIDENT FOR POLICY DEVELOPMENT
CHAIRMAN, COUNCIL OF ECONOMIC ADVISERS
DIRECTOR OF ACTION
ADMINISTRATOR, ENVIRONMENTAL PROTECTION AGENCY
ADMINISTRATOR OF VETERANS AFFAIRS
DIRECTOR, OFFICE OF SCIENCE AND TECHNOLOGY POLICY

FROM : SECRETARY RICHARD SCHWEIKER
CHAIRMAN PRO-TEM, CABINET COUNCIL ON HUMAN RESOURCES

SUBJECT : Agent Orange Working Group

The Administration has reviewed the excellent work of the Interagency Work Group to Study the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants and believes that it has made significant progress toward fulfilling its important mandate. By bringing together knowledgeable scientists from the various Federal departments and agencies the Work Group has identified ongoing research activities on phenoxy herbicides and contaminants and begun to develop and organize the means to carry out additional needed scientific research.

President Reagan shares the widespread public and congressional concern over possible adverse health effects among Vietnam veterans exposed to Agent Orange and other substances. The President stated, during his meeting with national veterans organization leaders at the White House on July 17, 1981, that the Administration is giving special consideration to those concerns of Vietnam veterans.

At the White House meeting, the President announced that the administration had re-established an expanded Working Group as the Agent Orange Working Group and raised its status to Cabinet Council level. The President is personally determined to assure that the full resources of the Federal government are

available to support the Working Group's continuing efforts. The decision to re-establish and expand the membership of the Working Group and to make it an integral part of the Cabinet Council on Human Resources reflects the President's commitment and accords the highest priority to its mission.

As Chairman Pro-Tem of the Cabinet Council on Human Resources, I am, accordingly, reaffirming by this memorandum the Agent Orange Working Group's mandate of December 11, 1979 and providing specific guidance as to how that mandate is to be carried out in accordance with the Cabinet Council's decisions.

The Department of Health and Human Services shall continue to have lead responsibility for overall direction and management of the Agent Orange Working Group. The Secretary of Defense and the Administrator of Veterans Affairs shall continue to assure that their respective agencies participate fully in all Working Group activities. The Departments of Agriculture and Labor and the Environmental Protection Agency, each of which have until now been observers, shall assume full membership and their respective agency heads shall assure that those agencies participate fully in all Work Group activities.

In addition, ACTION, the Office of Management and Budget, and the Council of Economic Advisers, as well as the White House Office of Science and Technology Policy and the Office of Policy Development, shall assume membership on the Working Group and the heads of those agencies and offices shall assure that the resources of their respective agency or office are fully available to support it.

Also, the congressional Office of Technology Assessment, which has been actively involved in all Working Group activities as an observer, will be invited to continue to participate in that capacity, and the General Accounting Office, which has been extremely helpful to the Working Group in the past, will continue to be kept abreast of developments and invited to advise and assist as appropriate.

The Working Group has initiated research efforts designed to find answers to many of the questions surrounding Agent Orange that have been raised. These efforts include the birth defects study being conducted by HHS' Centers for Disease Control, the Ranch Hand Study being conducted by the Air Force, the epidemiological study being planned by the Veterans Administration pursuant to P.L. 96-151, and the compilation by HHS' National Institute of Occupational Safety and Health of a national registry of workers exposed to dioxins. Each of these research activities, as well as the other important research

activities being conducted under the overall guidance of the Working Group, are to be continued without interruption or delay.

The Working Group has developed an impressive record of scientific objectivity, impartiality and integrity and it is imperative to the success of the Working Group effort that this record and the Group's credibility be maintained. In this regard, regular progress reports to the Cabinet Council, the Congress and the public will continue to be made by the Agent Orange Working Group.

To assure effective leadership of the Working Group, I am hereby appointing James Stockdale, HHS Deputy Under Secretary for Intergovernmental Affairs, as Chair. Also, I am appointing Dr. Vernon N. Houk of the Center for Environmental Health of the Centers for Disease Control as Chair of the Working Group's Science Panel. In addition, I am appointing HHS Legal Counsel Leslie A. Platt, who has served as legal adviser to and staff director of the Working Group since its inception, to continue in those capacities. I know and believe you will find that these individuals share my commitment to carrying out this important mission.

Please review your representation on the Working Group to assure that your agency or office is adequately represented by appropriate technical experts, scientists and policy-level officials. In order to facilitate the Group's effectiveness, it is of course important that each agency's total membership be limited.

The first meeting of the full Working Group has been scheduled for Friday, August 28, 1981 and a meeting of the Science Panel will be scheduled for shortly thereafter. Accordingly, please let Mr. Bart Kull, Special Assistant to the Deputy Under Secretary for Intergovernmental Affairs (245-6156), or Dr. Peter Beach, HHS Director of Veterans Affairs (245-2210), know as soon as possible the name(s) of your designated representative(s) so that briefing materials may be forwarded to them.

Attached for your information is a copy of the memorandum of the Executive Secretary to the Cabinet Council on Human Resources establishing the Working Group.

Attachment

cc: Comptroller General of the United States
Director, Congressional Office of Technology Assessment
Mr. Robert Carleson
Mr. Edwin Gray

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Russell Mack--(202) 245-6343

FOR IMMEDIATE RELEASE
Monday, June 6, 1983

Health and Human Services Secretary Margaret M. Heckler today named her department's under secretary, John A. Svahn, as chairman of the Agent Orange Workin Group of the Cabinet Council on Human Resources.

The working group coordinates and oversees federal research into the possibili of long term adverse health effects resulting from exposure to phenoxy acid herbicides used during the Vietnam War. The herbicides, principally Agent Orange, were used primarily to defoliate dense jungle cover to reveal enemy troop movements and staging areas.

"By designating the second highest official of my department as chairman, I am reaffirming this administration's commitment to the prompt and scientifically responsible resolution of the health concerns of Vietnam veterans who were exposed to Agent Orange and other environmental factors during their service to their countr in that conflict. Jack Svahn's leadership of this vital working group will help us get the answers we need," Secretary Heckler said.

In response to veterans' concerns about the possibility of illness as a result of their exposure, the working group was created in late 1979. It was reestablished and upgraded to Cabinet Council reporting level by President Reagan in July 1981.

Under the aegis of the working group, various federal agencies, including HHS' Public Health Service, the Veterans Administration and Department of Defense, are conducting 64 separate research studies relating to Agent Orange and other health effects of service in Vietnam, at a cost estimated in excess of $100 million.

As chairman of the working group, Svahn will report to the president through Secretary Heckler in her capacity as chairperson pro-tem of the Cabinet Council on Human Resources.

Svahn was appointed under secretary of the Department of Health and Human Services March 8. Prior to that appointment he served as commissioner of Social Security since May 6, 1981.

Following service in the U.S. Air Force in 1968, Svahn held administrative positions with the state of California, the federal government and the private sector.

# # #

CHARTER
Cabinet Council Agent Orange Working Group
December 11, 1979, as Reaffirmed
on August 21, 1981

The Agent Orange Working Group shall:

1. Oversee, coordinate, and set priorities among Federal government research activities designed to relate exposure to phenoxy herbicides to long-term health effects.

2. Design a research agenda to assure that the Federal government conducts comprehensive research on the long-term health effects of the compounds, in response to both scientific and policy needs. The type and duration of exposure to Agent Orange by Vietnam veterans must be considered in the research agenda design so that the Veterans Administration will be able to establish sound policies for determining compensation for veterans exposed to Agent Orange in Vietnam, should a relationship between herbicide exposure and long-term adverse health effects be established. The research agenda should build on current agency activities, including the Department of Defense's Ranch Hand study. The Working Group should identify the appropriate agencies to conduct the recommended research, either individually or through joint efforts.

3. Provide technical support to individual agencies and independent researchers in the formulation, development, and implementation of research on the biomedical effects of phenoxy herbicides and contaminants.

4. Assure that the protocols and methodology of ongoing and proposed federally funded research studies will produce valid, reliable, timely, and relevant data, and periodically review the status of such research.

5. Assure that all relevant research findings, whether publicly or privately financed, are promptly made available to the public and the Congress, in a comprehensible and comprehensive fashion. The work group should establish a working relationship with the Veterans Administration's Advisory Committee on Health-Related Effects of Herbicides and should promply provide the Committee all relevant information as it becomes available.

6. Provide guidance to the epidemologic study of the health of Vietnam Veterans authorized by P.L. 96-151 as amended by P.L. 97-72.

Agent Orange Working Group Organization

Following a review of the work of the Interagency Working Group, President Reagan in July 1981 re-established and expanded the Interagency Work Group, raised its status to Cabinet Council level and renamed it the Agent Orange Working Group (AOWG). The purpose was to reflect his commitment to the work of the group and to place high priority on its mission. The President asked the Secretary of HHS, as Chair Pro-Tem of the Cabinet Council on Human Resources, to oversee its work. The AOWG now reports to the Cabinet Domestic Council.

The AOWG membership includes representatives from the Veterans Administration (VA), Departments of State, Defense and Labor, the Office of Management and Budget, the Environmental Protection Agency, the ACTION Agency, the Council of Economic Advisors, the White House Office of Science and Technology Policy and the Assistant to the President for Policy Development. The Congressional Office of Technology Policy participates as an observer.

The AOWG organization is headed by a Chair appointed by the Secretary as a member of the Cabinet. The Chair, AOWG, in turn appoints:

1. Chair, Science Panel
2. Legal Counsel
3. Executive Secretary
4. Chair, Resources Panel
5. Chair, Public and Congressional Affairs Panel

The Science Panel, composed of expert medical and scientific personnel drawn from various government agencies concerned with issues of public health, advises the AOWG on the conduct of research related to Agent Orange. The Science Panel includes two subpanels: a Research Agenda Subpanel to recommend needed research and a Research Review Subpanel to review all planned research for adequacy of design and conformance with the AOWG mission.

The Resources Panel is concerned with the proper allocation of available resources among planned and on-going research and the avoidance of duplication of effort.

The Public and Congressional Affairs Panel defines policies to be used in information dissemination to insure that such dissemination is timely, accurate and complete.

In addition to these structures, the AOWG is advised by the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants. This Advisory Committee is composed of pre-eminent scientists from outside the Government.

The agency membership with the current designated represenatives from each and the staff of the AOWG are listed at Tab A.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Washington, D.C. 20201

AGENT ORANGE WORKING GROUP MEMBERSHIP

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*Denotes Science Panel Member

Revised: September 1985

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Advisory Committee on Special Studies

The Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants had its genesis in the directives of the White House for an independent review from scientists outside the Government of the Air Force Ranch Hand Study (Tab A). This study compared mortality and morbidity of the Air Force personnel involved in the spraying of Agent Orange in Vietnam with a group of Air Force personnel who were not exposed to the herbicide.

Because of the value of this kind of independent review, the Advisory Committee on Special Studies was chartered to permit it, at the discretion of the Chair, Agent Orange Working Group (AOWG), to undertake a review of any study, proposed or on-going, which falls within the purview of the AOWG.

The Advisory Committee on Special Studies is established under the provisions of the Advisory Committee Act and is governed by the regulations of 45 CFR Part 11. The Charter of the Committee is at Tab B, and its membership is listed at Tab C.

THE WHITE HOUSE

WASHINGTON

September 16, 1980

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MEMORANDUM FOR THE SECRETARY OF DEFENSE
THE SECRETARY OF HEALTH AND HUMAN SERVICES
THE SECRETARY OF AGRICULTURE
THE ADMINISTRATOR OF VETERANS AFFAIRS
THE ADMINISTRATOR OF THE ENVIRONMENTAL PROTECTION AGENCY
THE ASSISTANT SECRETARY OF THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION

SUBJECT: Epidemiological Study of Ranch Hand Personnel

Last December, I asked you to participate in an interagency work group to coordinate federal agency efforts to determine if there are long-term health effects following exposure to phenoxy herbicides and contaminants, with special immediate focus on exposure of veterans to Agent Orange in Vietnam.

I am gratified by the progress that the Work Group has made in a short period and by the respect that the Work Group has earned with the Congress and the public. The members of your agencies who have participated on the Work Group should be commended for their diligence and spirit of cooperation.

Today, I am informing Secretary Brown that I have concurred with the Interagency Work Group's recommendation that the Air Force proceed to conduct the Epidemiological Study of Ranch Hand Personnel. I strongly believe that an essential component of this effort must be independent review and monitoring over the next few years by the Interagency Work Group's Scientific Panel.

In addition, I look to the Work Group to provide substantial assistance to the Veterans Administration, who also will conduct a major epidemiological study of the possible long-term health effects in veterans of service in Vietnam. The Work Group's expertise and credibility will provide valuable assistance to the VA.

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because of the ability that the Work Group has shown, demonstrated as well as the continuing requirements for governmental studies on phenoxy herbicides, Frank Press and I wish now to reaffirm the mandate of the Interagency Work Group. I hope that your agencies continue to give participation on the Work Group as much importance in the future as they have in the past.

Stuart E. Eizenstat
Assistant to the President
for Domestic Affairs and Policy

THE WHITE HOUSE

WASHINGTON

September 16, 1980

MEMORANDUM FOR THE SECRETARY OF DEFENSE

The Air Force has sought guidance from the Interagency Work Group on the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants on whether it should proceed with the Epidemiological Study of Ranch Hand Personnel because the National Academy of Sciences review of the Air Force protocol had expressed concern about the credibility of the Air Force to conduct the study.

Ranch Hand personnel, who applied Agent Orange between 1962 and 1971 in Vietnam, are the only population whose frequency and duration of exposure to Agent Orange are known with any accuracy. The Interagency Work Group agrees with the Air Force that the results of the Ranch Hand study should provide valuable information about the long-term health effects of exposure by veterans to Agent Orange in Vietnam.

Over the past 20 months, the Air Force has made a conscientious effort to design a scientifically valid study responsive to the recommendations of five separate peer reviews, including that of the National Academy of Sciences. After a thorough review of the proposed final study protocol, which includes certain changes based on the separate peer reviews, and after consultation with the Air Force scientists responsible for the study, the Work Group recommended to me that the Air Force be instructed to carry out the Ranch Hand study. In light of the progress already made by the Air Force and the need to proceed expeditiously with this important study, Frank Press and I concur with the Work Group's recommendation.

There remains deeply felt concern among some Vietnam veterans and others about the objectivity of the Air Force to study the possible health effects of Agent Orange. While affirming the capability of the Air Force to assure the proper conduct of the study, the Interagency Work Group has suggested that this concern can be reasonably addressed by independent review and monitoring of the study. I believe that the Scientific Panel of the Interagency Work Group, which is already familiar

with the Ranch Hand protocol, is the appropriate body to oversee the study and to provide technical assistance, as needed, to the Air Force scientists responsible for the study. For the purpose of assuring the public that the study results are reliable and valid, the Work Group plans to augment the Scientific Panel with reputable scientists from outside the government, including those suggested by veterans organizations.

The Interagency Work Group noted that the evaluation of Ranch Hand personnel may have to continue for a lengthy period of time in order to have a better chance of detecting latent or subtle health effects, particularly related to cancer. The Air Force, in consultation with the Scientific Panel, has already designed the protocol to reflect this recommendation.

I am advised that the Ranch Hand study presents a number of difficult technical problems. While recognizing the need to obtain study results promptly, the Air Force's primary responsibility must be to assure that the results will be reliable and valid. I urge the Air Force to utilize fully the expertise of the Scientific Panel of the Interagency Work Group to advise them on the difficult decisions that will surely arise during the course of the study.

In closing, I would like to reaffirm the importance of the Ranch Hand study to Vietnam veterans and their families. The Interagency Work Group and the White House are prepared to offer any assistance that the Air Force may require in discharging its responsibility to conduct a high quality scientific investigation.

Stu Eizenstat

Stuart E. Eizenstat
Assistant to the President
for Domestic Affairs and Policy

CHARTER
(As Amended May 1984)

Advisory Committee on Special Studies
Relating to the Possible Long-Term Health
Effects of Phenoxy Herbicides and Contaminants

Purpose

By memorandum of December 11, 1979, the Assistant to the President for Domestic Affairs and Policy directed the establishment of an Interagency Work Group to Study the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants (Work Group) under the leadership of the Secretary of Health and Human Services. The Work Group was specifically directed to assure that the protocols and methodology of proposed federal research studies will provide reliable data, as well as to provide technical support to individual agencies in the implementation of research.

On August 1, 1980, the Work Group recommended that the United States Air Force conduct its proposed Epidemiologic Studies of Ranch Hand Personnel (Rand Hand Study) and that the conduct of the study be overseen by an independent monitoring committee. By memorandum of September 16, 1980, the Assistant to the President for Domestic Affairs and Policy directed the Air Force to conduct the Ranch Hand Study. In addition, the memorandum directed the Scientific Panel of the Work Group, augmented by scientists from outside the government and including those suggested by veterans organizations, to oversee the study and to provide technical assistance, as needed, to the Air Force.

On July 17, 1981, the President re-established the Interagency Work Group as the Agent Orange Working Group (AOWG) and elevated it to Cabinet Council status. On August 21, 1981, the Secretary, DHHS, Acting as Chairman Pro-Tem, Cabinet Counsel on Human Resources, reaffirmed the Work Group's mandate of December 11, 1979 and appointed the Deputy Undersecretary for Intergovernmental Affairs as Chair of the AOWG.

Authority

The Committee on Special Studies was established under the provisions of section 222 of the Public Health Service Act, as amended, 42 U.S.C. 217a. The Committee is governed by the provisions of 45 CFR Part 11 which sets forth standards for the creation and use of advisory committees.

Function

The Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants shall advise the Secretary and the Chair, Cabinet Council Agent Orange Working Group (AOWG), concerning:

1. Its oversight of the conduct of the Ranch Hand Study by the Air Force;

2. Its oversight and evaluation of the Agent Orange/Vietnam Experience Study mandated by Section 307 of P.L. 96-151 as amended by P.L. 97-72; and

3. Other studies in which the Secretary or the Chair, AOWG, believes involvement by the Advisory Committee is desirable.

The Advisory Committee may provide technical assistance to the study under its consideration.

On the basis of its oversight and evaluation, the Advisory Committee may, inter alia, recommend to the Secretary and the Chair, AOWG, (a) approval, (b) deferral because of a need for further evaluation, (c) disapproval in whole or in part, or (d) imposition of additional conditions which in its judgemnt are necessary to assure or protect advancement of the study under consideration.

Structure

The Committee shall consist of the Secretary, or designee, as Chair, and eight members selected by the Secretary from authorities knowledgeable in fields related to the studies under its oversight and evaluation. The Executive Secretary shall be selected by the Chair.

Management and support services shall be provided by the National Cancer Institute.

Meetings

Meetings shall usually be held quarterly at the call of the Chair, who shall also approve the agenda. A government official shall be present at all meetings.

Meetings shall be open to the public except as determined otherwise by the Secretary; notice of all meetings shall be given to the public.

Meetings shall be conducted, and records of the proceedings kept, as required by applicable laws and Departmental regulations.

Compensation

Members who are not full-time federal employees shall be paid at the rate of $100 per day, plus per diem and travel expenses in accordance with Standard Governmental Travel Regulations.

Annual Cost Estimate

Estimated annual cost for operating the Committee, including compensation and travel expenses for members but excluding staff support, is $19,736. Estimate of annual man years of staff support required is one-quarter, at an estimated annual cost of $8,380.

Reports

An annual report shall be submitted to the Secretary through the Chair, AOWG, not later than November 1 of each year, which shall contain as a minimum a list of members and their business addresses, the Committee's functions, dates and places of meetings, and a summary of Committee activities and recommendations made during the fiscal year. A copy of the report shall be provided to the Department Committee Management Office.

Termination Date

The duration of the Advisory Committee on Special Studies Relating to the Possible Long-Term Effects of Phenoxy Herbicides and Contaminants is five years. Unless renewed by appropriate action prior to its expiration, the Committee will terminate on January 19, 1985.

PROFESSIONAL AREA BREAKDOWN - ADVISORY COMMITTEE ON SPECIAL STUDIES RELATING TO THE POSSIBLE LONG-TERM HEALTH EFFECTS OF PHENOXY HERBICIDES AND CONTAMINANTS

Authorized Positions: 8

Name	Term Ending	Expertise	Prof./Lay/Res.	Geog. Dist.	Minority/Female
Comstock	Duration of Committee	Epidemiology	X	MA	
Friedman	Duration of Committee	Pediatrics, human genetics	X	TX	
Kreiss	Duration of Committee	Occupational Health, epidemiology	X X	CO	X
Kurland	Duration of Committee	Epidemiology, neurology	X	MN	
Monson	Duration of Committee	Epidemiology	X	MD	
Nelson	Duration of Committee	Toxicology	X	NY	
Ramey	Duration of Committee	Statistics, psychology	X	NC	

PROPOSED CANDIDATE FOR VACANCY

Pardes	Duration of Committee	Psychiatry	X	NY	

CONGRESSIONALLY AUTHORIZED EPIDEMIOLOGICAL STUDY

In January 1979, the Congress enacted P.L. 96-151 which directed the Veterans Administration (VA) to investigate health effects of Agent Orange. The authorization was expanded in November 1981 by P.L. 97-72 to include "other factors."

In January 1983, responsibility for design and execution of the study was formally transferred from VA to the Centers for Disease Control (CDC), with resources, both FTE's and funding, to be provided by VA.

The CDC protocol for conducting the study was completed and distributed for scientific review in May 1983. Principal review was conducted by the Office of Technology Assessment. Reviews were also conducted by the Agent Orange Working Group Science Panel, by the Advisory Committee on Special Studies Relating to the Possible Long Term Health Effects of Phenoxy Herbicides and Contaminants (which oversees the Air Force Ranch Hand Study), and by the CDC Ad Hoc Review Panel. National veterans' organizations were invited to comment. All reviews were completed by September 1983.

The CDC protocol contains three study components: (1) Vietnam Experience; (2) Agent Orange; and (3) Selected Cancers Study.

1. The Vietnam Experience Study is to determine whether veterans who served in Vietnam are at greater risk for poor health than are similar veterans who did not serve in Vietnam. The study will identify, from personnel records, 6,000 one-term Army veterans who have served in Vietnam and 6,000 similar veterans who have never been in Vietnam. All of these will be followed for mortality or given a telephone interview covering general health information and demographic data. 2,000 from each group will be given comprehensive physical and psychological examination and health outcomes for the two groups will be compared.

   The questionnaire for this study has been reviewed by the Science Panel and cleared by OMB. A pilot test to determine locatability and participation rates of prospective subjects has been completed and reviewed by the Science Panel. Participation rates were better than anticipated and the study is proceding to the main data collection phase. Concerns were raised by the Science Panel that self-reported health data, including information on reproduction outcomes, should be verified from medical and/or vital records or not collected at all. Some

plans for utilization of these data are currently being developed at CDC and will be discussed at a Science Panel meeting in the near future.

2. The Agent Orange Study is to determine whether Vietnam veterans who were highly likely to have been exposed to Agent Orange while in Vietnam are at greater risk for poor health than are Vietnam veterans with similar experiences while in Vietnam but very unlikely to have been exposed to Agent Orange while there. The study will identify, from Battalion Daily Reports, 6,000 one-term Army Vietnam veterans who were likely to have been exposed to Agent Orange on several occasions, 6,000 similar Vietnam veterans who were not likely to have been exposed to Agent Orange, and 6,000 Vietnam veterans known to have served in areas where Agent Orange was never used. All of these will be followed for mortality or given a telephone interview and 2,000 from each group will be examined as in the Vietnam Experience Study.

   The questionnaire for this study is similar to the one being used in the Vietnam Experience Study. The pilot has not been completed but should yield similar results to the one which has been used for the Vietnam Experience Study. Since the identification of Agent Orange exposed and unexposed subjects who are similar in other ways is crucial to the successful completion of the Agent Orange Study, the selection of the three study cohorts will be reviewed by the Science Panel when this stage has been completed and before the main study begins.

3. The Selected Cancers Study is to determine whether Vietnam veterans are at greater risk for certain cancers than the rest of the population. The study will select post 1985 diagnoses of soft tissue sarcoma, Non-Hodgkins Lymphoma and other cancers from newly identified entries into the Surveillance, Epidemiology, and End Results (SEER) Registries sponsored by the National Cancer Institute. These registries cover approximately 10-12 percent of the U.S. population including both rural and urban residents. Cancer cases from the appropriate age group will be interviewed via telephone and their Vietnam experience compared to that of age matched controls selected from the same communities by random digit dialing.

The questionnaire for this study has been reviewed and cleared by the OMB. Data collection begin in 1985 and the names of identified Vietnam veterans are submitted to the Army and Joint Services Environmental Support Group for records review and assignment of an "Exposure Opportunity Index". This study should provide a good estimate of whether service in Vietnam and/or at least minimal exposure to Agent Orange is associated with an increased risk for Soft Tissue Sarcomas, Non-Hodgkins Lymphoma and certain other cancers 15 to 20 years later.

CDC - Birth Defects Study

The CDC Birth Defects Study was a Case-Control Study designed to determine if the fathers of babies with major birth defects were more likely to have served in Vietnam than fathers of healthy babies. The study was conducted among all identified severely affected cases from a population based Birth Defect Registry in the Atlanta, Georgia, metropolitan area and included almost 5000 major defects and 3000 normal babies born in the same hospitals at nearly the same time. Results of this study indicated that the risk for having a major birth defected child, diagnosed up to the first year, was no greater for Vietnam veterans than for other veterans, or for other men in general. In addition, there was no statistically significant increase in the relative risk for a Vietnam veteran fathering a baby with any individual type or group of defects compared to other men.

In addition to measuring the risks associated with the Vietnam experience per se, the investigators at CDC worked with the Department of Defense Army Agent Orange Task Force in assigning some measure of the likelihood for an opportunity for exposure to Agent Orange for as many Vietnam veterans as had available information. Two such indices (EOI) were created which were similar, but not identical. The analyses reported by CDC using these indices indicated an increased risk for fathering babies with three different defects with increasing opportunities for exposure on at least one of the indices. The three defects were spina bifida, cleft lip with or without cleft palate, and a group of neonatal neoplasms. Whether these findings are the result of chance occurrence when multiple comparisons are made, which is highly probable, cannot be determined with certainty. It is also quite possible that the indices themselves were sufficiently inaccurate as to render them uninterpretable, particularly since they were in the developmental stage at the time. It is not possible to make a definitive evaluation of these findings at this time.

At the suggestion of Congress, and as a matter of appropriate public interest, the Science Panel, through its Research Agenda Subpanel, is preparing a statement on the state-of-the-art of Reproductive Outcome research on the offspring of Vietnam veterans fathers. The purpose of this report will be to develop a research agenda of further research which needs to be done on this issue.

Soft Tissue Sarcoma - International Studies

The Science Panel reviewed international studies of the possible association between exposure to phenoxy acid herbicides and their contaminants and soft-tissue sarcomas. It was determined that these studies were inconclusive, that it would not be useful to engage in further in depth analysis of the already published data and that there are several studies currently underway that should enable a more definitive assessment of the possible association between soft tissue sarcoma and other cancers and exposure to phenoxy herbicides and contaminants to be made in the next several years.

NATIONAL CANCER INSTITUTE - CASE-CONTROL STUDY OF SOFT TISSUE SARCOMAS AND LYMPHONAS AND THEIR RELATIONSHIP TO HERBICIDE APPLICATORS IN KANSAS

The purpose of the Case-Control Study of these two cancers is to determine, by interview, whether cases of Soft Tissue Sarcoma and/or Lymphoma are more likely to have been occupationally exposed to phenoxy acid herbicides and contaminants than a matched comparison group. Cases were obtained from a population based tumor registry covering the whole state of Kansas and controls were matched for age, sex, race and residential area of the state. Kansas was chosen as a site for this study because, in addition to the existence of a tumor registry, the agricultural practices in Kansas wheat growing areas have included considerable application of 2,4,5-T without other concomittant pesticide use.

The Science Panel reviewed the original protocol for this study which is nearing completion under contract to the National Cancer Institute. The Science Panel is particularly interested in the outcome of this study since it should be useful in evaluating the possible associations between certain cancers and herbicide exposures which have been suggested from several studies conducted in Sweden.

National Cancer Institute - Study of Soft Tissue Sarcomas and Non-Hodgkins Lymphoma in Thirteen counties in Washington State

The Batelle Corporation, under grant from the NCI, is conducting a study of Soft Tissue Sarcoma and Non-Hodgkins Lymphoma in the 13 county area around Seattle, Washington which is covered by a population based Tumor Registry. The study will interview in depth for occupational exposure, residential history and home use of herbicides, especially 2,4,5-T. It is intended to verify such use from employment records, reported to be available in this region where much 2,4,5-T has been used. A comparison of the amount and rate of exposure of cancer cases will be made to a comparison group, the nature of which is unknown (to us) at present.

The Science Panel reviewed a very early version of this proposal in 1981, but was not involved in the formal review process. The Science Panel is interested in the outcome of this study since it should help in further evaluating the relationship between certain cancers and exposure to dioxin contaiminated herbicides.

AIR FORCE RANCH HAND STUDY

The purpose of the Ranch Hand Study is to determine whether the 1247 Air Force personnel who were involved in the spraying of Agent Orange (and other herbicides) in Vietnam were more likely to suffer ill health than a comparable group of Air Force personnel who were not involved in herbicide spraying activities. The aerial spraying of herbicide in Vietnam was code named Operation Ranch Hand and thus all of the Air Force personnel involved in the loading, operating and maintaining of the C123 Aircraft used in this operation were termed Ranch Handers. The comparison group consists of Air Force personnel who operated and maintained C130 aircraft in Southeast Asia and who were not involved in herbicide activities. The comparisons are matched to the Ranch Handers by age, race and military rank and specialty. The study will include comparing mortality from various causes between the Ranch Handers and the comparisons (since their service in Southeast Asia) with annual updates every year. It will also include comparing morbidity between the two groups based on an initial telephone interview and an extensive physical, laboratory and psychological examination every 3 to 5 years. The study is intended to continue for 20 years from 1981.

The Science Panel originally reviewed the protocol for the Ranch Hand Study in 1981. The study is of particular interest since the Air Force estimated at that time that many of the Ranch Hand personnel were exposed to Agent Orange at a rate 1000 times greater than almost any of the rest of the Armed Forces in Vietnam. The first Baseline Mortality Results from this study, published in 1983, indicated virtually no difference in mortality between the Ranch Handers and their comparisons through 1982. The Science Panel reviewed this report in the light of a critique which had been prepared by the Vietnam Veterans of America and suggested that a lay-language version of the report would be easier to understand than the rather detailed version which was released. The second interim report is scheduled for release in the very near future and is currently under review by the Advisory Committee for Special Studies.

Data collected during the interview and the first examination were released as the Baseline Morbidity Results in early 1984. The most interesting findings from this report included:

1. an increase in non-melanoma skin cancer among Ranch Handers. This finding will be further studied at the second examination to determine if exposure to sunlight has played a significant role since exposure to solar radiation is the acknowledged primary cause of skin cancer in the U.S.;

2. there was a significant increase in abnormal pulses of the extremities among the Ranch Handers. This will be further explored during the second examination since it is poorly understood and currently has no direct health related consequences; and

3. an increased number of minor birth defects (mostly birth marks) neonatal deaths and physical handicaps to children were reported by Ranch Hand parents than by comparisons. Each of these is currently being verified through the compilation of appropriate medical and vital records for all study subjects as requested by the Agent Orange Working Group. A progress report on this should be available imminently.

PROPOSED STUDIES OF INTEREST TO THE SCIENCE PANEL

Female Veterans Study

The Science Panel reviewed a proposal to study female Vietnam veterans which had been prepared by CDC. The proposed study would interview all, and examine 2000, of the approximately 7000 female veterans who served in Vietnam, who can be located, and who agree to participate. The Science Panel feels that, even though the study appears logistically feasible, it may not be the most efficient nor appropriate design to test possible adverse health effects among female Vietnam veterans. The Panel recommends that specific hypotheses relating Vietnam exposures and adverse health effects among female veterans be formulated, and then a suitable research design developed and evaluated.

Veterans Administration - Twin Study

A concept proposal for a study of identical twins - one of whom served in Vietnam and one of whom did not - was reviewed and approved by the Science Panel in 1982. The purpose of the study would be to compare physical and psychological health of the two members of an extremely closely matched pair of subjects who differed in their exposure to the Vietnam Experience - including possible exposure to Agent Orange. The final protocols for this study has subsequently been fully developed and we understand is currently under review.

THE STATE OF AGENT ORANGE RELATED RESEARCH IN THE FEDERAL GOVERNMENT

The FY 1985 Report of the Science Panel of the Cabinet Council Agent Orange Working Group

September 1985

The State of Agent Orange Related Research in the Federal Government
The FY 1985 Report of the Science Panel of the Cabinet Council Agent Orange Working Group

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The State of Agent Orange Related Research in the Federal Government
The FY 1985 Report of the Science Panel of the Cabinet Council Agent Orange Working Group

EXECUTIVE SUMMARY

The issue of possible adverse health effects in humans as a consequence of exposure to Agent Orange (AO) in Vietnam has attracted and maintained the attention of the nation for nearly a decade.

For the past four years, the Agent Orange Work Group (AOWG), a Cabinet Council working group composed of representatives from 12 different Federal agencies, has been evaluating the direction and extent of the government's scientific research in Agent Orange and related issues. When the AOWG was formed in 1981, it was clear from animal studies and the limited human studies that the toxic contaminant of AO, 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD), has the potential to cause a broad range of deleterious effects. Some concern was also expressed about the potential effects of the major components of Agent Orange: the herbicides 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) and 2,4-dichlorophenoxy acetic acid (2,4-D). The extent to which these effects were likely to appear in humans exposed to AO in Vietnam, however, was unknown.

Between 1981 and 1987, AOWG member agencies will have expended $150 million in AO-related research. The majority of these funds has been directed at closing the largest gap in our knowledge on AO: the effects of AO on humans. Ten major

epidemiological studies scheduled for completion by 1990, and five ongoing health surveillance projects should provide information on whether exposure to AO has affected the health of Vietnam veterans and for framing hypotheses which can be tested in follow-up studies if necessary. Additional resources have been expended to better characterize known toxic properties of 2,3,7,8-TCDD and AO, to investigate the toxic endpoints that are less well-studied, and to synthesize the expanding literature on this subject.

Based on the growing body of information in hand, the worst case scenarios envisioned by some as a consequence of exposure to AO are not being realized. Populations known or possibly exposed to AO which are being studied have not so far exhibited increased incidences of cancer, or death from other causes, or abnormally high rates of birth defects in their offspring. This optimism is tempered by the knowledge that other, less-well characterized effects of concern may be associated with 2,3,7,8-TCDD (e.g., immunotoxicity). Some effects (e.g., cancer) may not become manifest for several more years, due to a longer latency period.

The consensus of the Science Panel is that initiation of any new, major epidemiological study should await and be built upon the results of studies already underway. The time for broad, hypothesis-generating studies has passed; focused, hypothesistesting studies should characterize the future.

A large number of ongoing research projects designed to characterize the toxicity and mechanisms of action of 2,3,7,8-TCDD in laboratory animals will also help to identify possible adverse human health effects and will assist in the interpretation of epidemiologic study results.

September 1985

The State of Agent Orange Related Research in the Federal Government: The FY 1985 Report of the Science Panel of the Cabinet Council Agent Orange Working Group

I. Introduction

The controversy surrounding the tactical use of herbicides -- principally, Agent Orange (AO) -- in Southeast Asia during the Vietnam conflict has continued for more than a decade. Few environmental or occupational health issues have received the sustained national attention that has been focused on AO. The controversy has encompassed a broad range of issues, including questions on the actual use of the herbicide in Vietnam, the subsequent ecological effects, the procedures for disposing of surplus herbicides, and, most notably, the possible link to reported adverse health effects among Vietnam veterans.

As each of these different facets of the controversy came to light, additional government agencies were called upon to address the associated issues. Today, twelve agencies of the Federal Government are coordinating their efforts, under the leadership of the Agent Orange Working Group (AOWG), to seek resolution of the scientific, medical, legal and social problems surrounding the AO question. The scientific and medical issues are dealt with through the Science Panel of the AOWG which is composed of AOWG members and reports directly to the parent work group.

Section II of this report contains a brief description of the AOWG, its history and its mission. In Section III, there is a description of the state-of-the-science as of 1981 when the AOWG first was formed and which provided the basis for further research at that time. Section IV discusses the research that has been and is being conducted within the Federal government on AO-related matters. Although this report is not intended to be a thorough review of the state-of-the-science regarding AO or 2,3,7,8-TCDD, it does provide a brief overview of Federally sponsored research as reflected by these and other projects. This, together with an examination of implications of our state of knowledge by a group who have been involved for six years, is provided in Section V. Finally, Section VI contains a discussion of future directions for Federally-sponsored, AO-related research.

II. Brief History of the Agent Orange Working Group (AOWG)

On July 17, 1981, President Reagan formally established the Agent Orange Working Group as an entity reporting to his Cabinet Council. However, the AOWG traces its roots to December 11, 1979, when the White House formed the Interagency Working Group (IWG) to Study the Possible Long-Term Effects of Phenoxy Herbicides and Contaminants. The mission of IWG was to monitor, coordinate and set priorities among the pertinent Federal Government research activities, to design a research agenda, and to organize the means of ensuring that this research agenda was carried out.

In response to continuing concerns of veteran groups that exposure to herbicides in Vietnam could result in health problems, the President expanded the membership of the IWG, renamed the group (AOWG), and raised its status to Cabinet Council working group level. The IWG's mandate was reaffirmed with a stated emphasis on AO research. The current membership of AOWG is found in Appendix A.

In addition to assuming the mission of the IWG, the AOWG was charged with providing scientific guidance for the Congressionally mandated epidemiological study of Vietnam veterans, presumed to have been exposed to AO. The legislative history associated with the Act calling for the epidemiology study specifically refers to "...the importance of the provision directing the President to assure (preferably through an interagency task force) that the mandated study be fully coordinated with ongoing or future governmental studies..." The Act was later amended to include consideration of other than AO-related factors in investigating the health outcomes of Vietnam veterans.

The AOWG has formed a subcommittee, the AOWG Science Panel, to facilitate its consideration and evaluation of scientific questions related to AO. Every 12 to 18 months the AOWG collects a list of ongoing Federal research projects related to AO. This year, the work group is additionally providing a short analysis of this information and identifying possible directions for future research, by means of this report.

III. Basis for the Research Efforts Commencing in 1980

A. What was known

1. Effects in animals

Health concerns associated with the use of Agent Orange can be traced to experiments in the late 1960s which showed that a trace contaminant in AO -- 2,3,7,8-TCDD -- could generate birth defects in the offspring of pregnant mice exposed to low doses of the chemical. The 2,3,7,8-TCDD also caused death in laboratory animals at very small doses, for example, single doses of less than a millionth of a gram of this chemical resulted in death in guinea pigs. In some other species, e.g., hamsters, the lethal dose is more than a 1000-fold greater than that required to kill guinea pigs. In the late 1970s, animal experiments demonstrated that 2,3,7,8-TCDD is carcinogenic in rats and mice at very low levels. Further experimentation suggests additional toxic effects from low levels on a variety of other systems, including the liver, the reproductive system, the immune system and lipid metabolism.

2. Effects in humans

The severity of the toxicological responses and the wide range of sensitivity observed in animal studies heightened concerns about the possible effects in humans and their relative sensitivity to 2,3,7,8-TCDD. Partial answers to these questions have been ascertained from investigations of the consequences of occupational exposures associated with industrial accidents.

Information from such sources are never "clean"; that is, occupational settings and industrial accidents are generally marked by uncertain exposures and/or concurrent exposures to other chemicals. While these limitations make specific cause-and-effect determinations difficult, by 1980, the following human responses were known or thought to be associated with exposure to 2,3,7,8-TCDD or chemicals containing this compound.

a. Chloracne -- a persistent, acne-like condition which can be disfiguring, but is not life-threatening.

b. Soft tissue sarcoma -- a relatively rare form of connective tissue cancer.

c. Porphyria cutanea tarda -- a metabolic disorder, associated with changes in urine content and sensitivity of the skin to light.

In addition, case reports suggested an association between exposure to 2,3,7,8-TCDD and various toxic effects, e.g., liver dysfunction, abnormal lipid metabolism, neurologic problems and loss of libido.

B. What was not known

1. Effects in animals

Many researchers believe that the key to understanding the toxicity of 2,3,7,8-TCDD (and the toxicities of scores of chemically related substances) lies in understanding its mechanism of action in biological systems. By 1980, some scientists had suggested a hypothesis that linked the toxicity of 2,3,7,8-TCDD

to its chemical shape and the presence of certain "TCDD-receptors" in the cytoplasm of cells in target organs. Once combined with the toxicant, the TCDD-receptor complexes would move to the nucleus of the cell, where a series of reactions would be initiated, which would lead eventually to various toxic responses. Other scientists suggested that the key effect of 2,3,7,8-TCDD might be on the membrane of the cell.

In order to test either of these hypotheses and to understand the mechanism of action of 2,3,7,8-TCDD more completely, it was necessary to study its absorption, metabolism, and tissue distribution in whole animals, supplemented by in vitro experiments.

Additional toxic endpoints of concern needed to be investigated, e.g., neurotoxicity, behavioral effects, and mutagenicity. Further work was needed to characterize more fully the toxic endpoints already demonstrated, e.g., liver effects and immunotoxicity.

2. Effects in humans

In 1980, the biggest gap in our knowledge about AO clearly lay in the area of its effects on humans. In Congressional testimony, AOWG members emphasized this lack of information, pointing out that animal tests alone would never fully bridge this gap. Since few human studies had been completed, the results of animal studies and reports in the news media had heightened concerns of many Vietnam veterans

regarding their increased potential to sire children with birth defects due to their exposure to AO. Other veterans were worried about the possibility of an increased likelihood of contracting cancer due to their service in Vietnam. Still others were concerned about an association between Vietnam/AO and a broad range of adverse health effects, from specific debilitating diseases to general malaise.

One of the biggest impediments to a study of the effects of AO on Vietnam veterans was that the extent to which individuals had actually been exposed to AO during their military service was unknown. Additionally, no one knew how to gauge relative amounts of exposure among different individuals.

3. Information Management

In 1980, there were already hundreds of scientific papers written on AO and/or 2,3,7,8-TCDD, and the rate of publication of papers on the subject was expanding rapidly. There was a need to systematically capture this information and to assimilate it into an orderly, comprehensible form.

IV. Federal Research Related to AO: 1981-1987

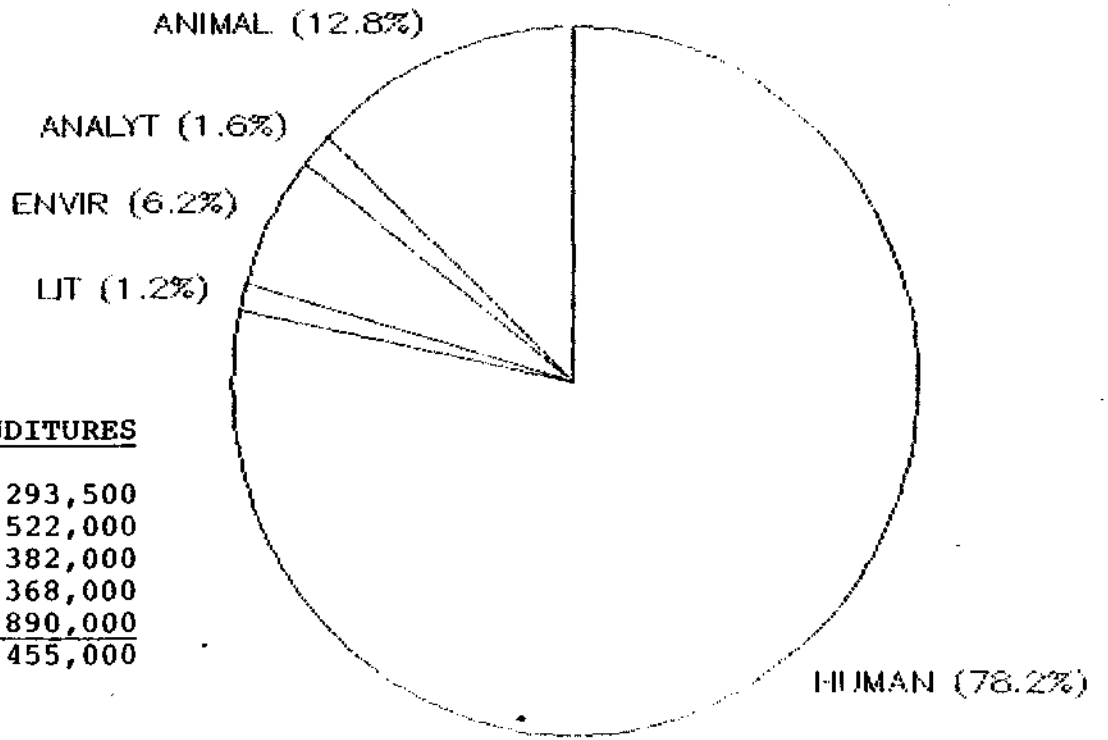
Between 1981 and 1987, the Federal government will have devoted more than $150 million to its attempts to address the gaps in the scientific data base identified in Section III. Figures I and II illustrate the proportions of these funds which were and are being expended by the various agencies for the different types of studies. Figures III-VII show

the breakdown of these expenditures for each agency by category of study, e.g., various human health effects and laboratory studies. Appendix B contains a complete project-by-project listing of this work from which the data for the Figures were drawn. Appendix C contains descriptions of the research supported by each agency and provides the basis for the discussion in the remainder of this section.

AGENT ORANGE/DIOXIN EXPENDITURES

AGENCY EXPENDITURES BY STUDY TYPE

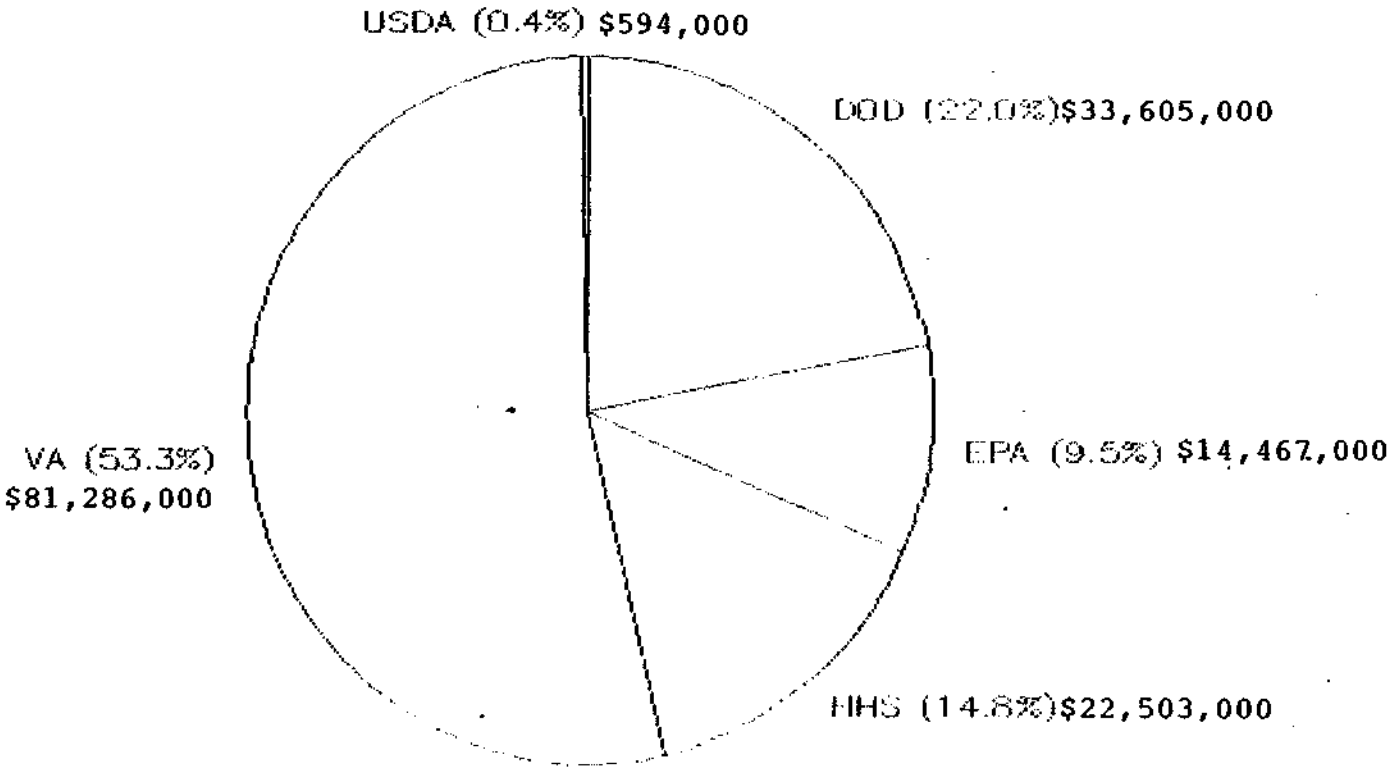
$152,455,000 TOTAL EXPENDITURES



STUDY TYPE	EXPENDITURES
HUMAN	$119,293,500
ANIMAL	19,522,000
ENVIRONMENT	9,382,000
ANALYTICAL	2,368,000
LITERATURE	1,890,000
TOTAL	$152,455,000

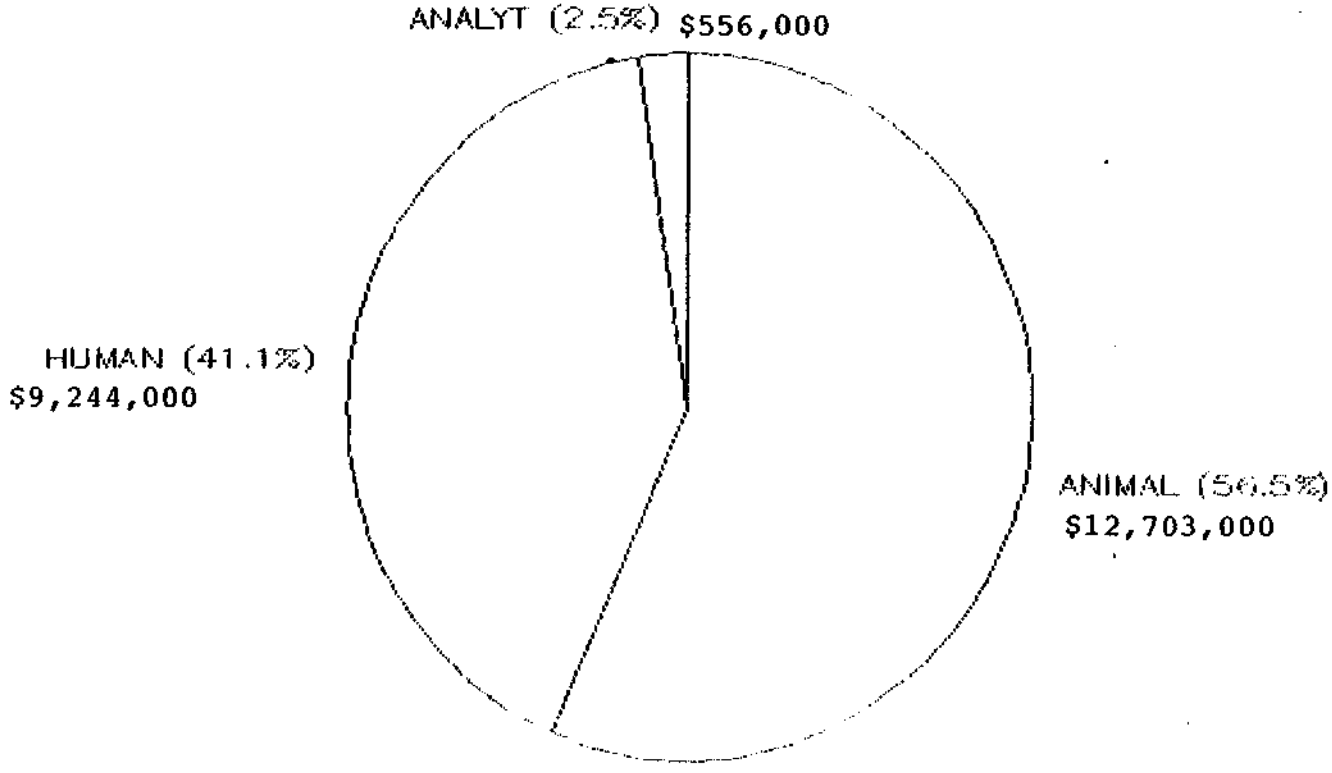
AGENT ORANGE/DIOXIN EXPENDITURES

$152,455,000 TOTAL COST



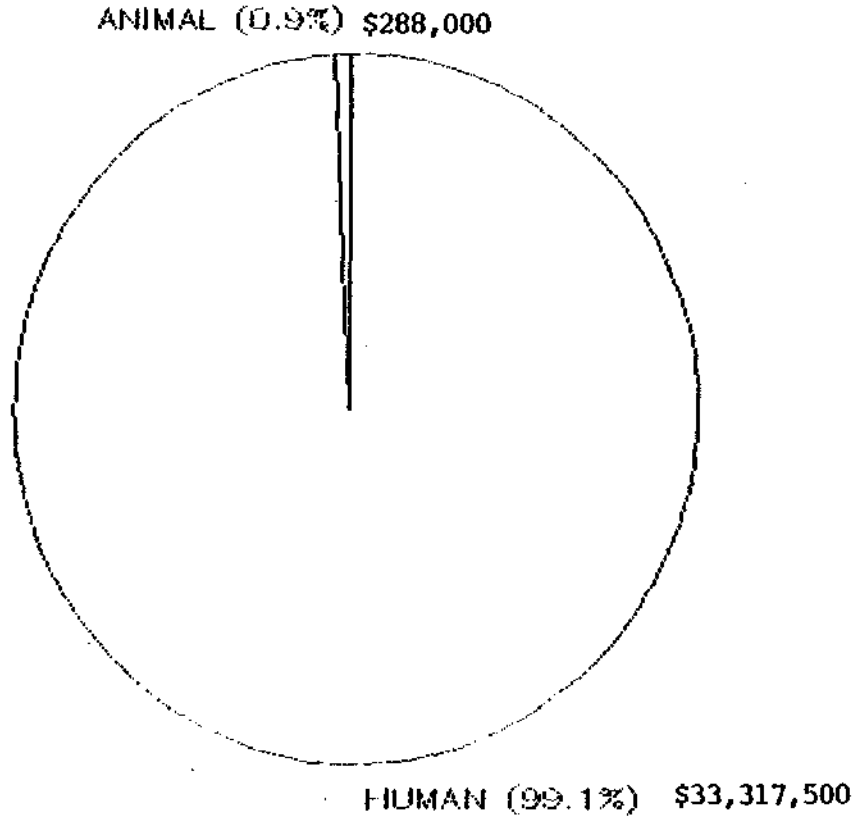
HHS A.O./DIOXIN EXPENDITURES

$22,503,000 TOTAL EXPENDITURES



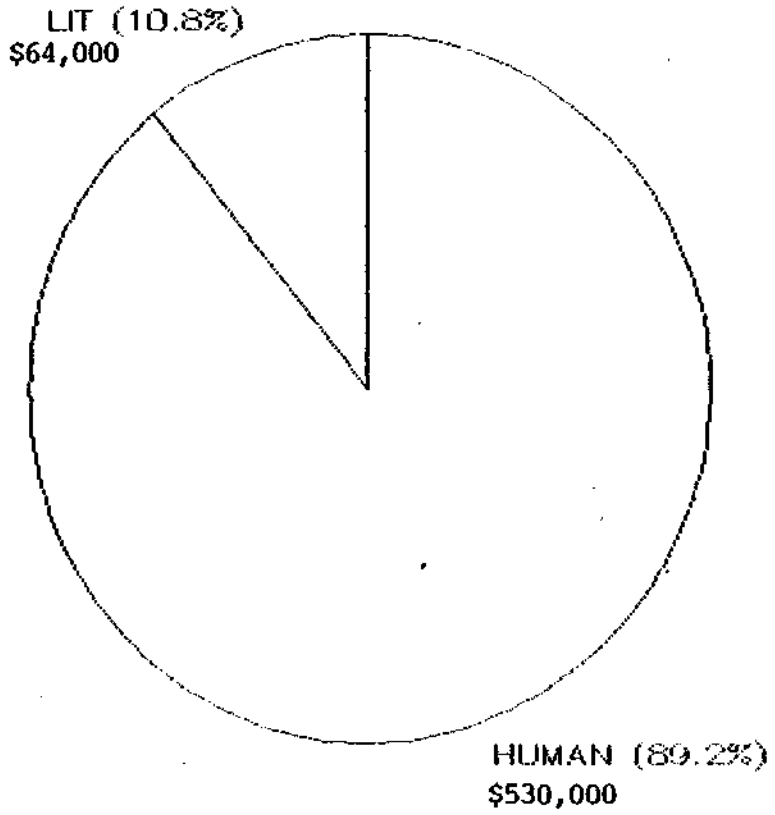
DOD A.O./DIOXIN EXPENDITURES

$33,605,500 TOTAL EXPENDITURES



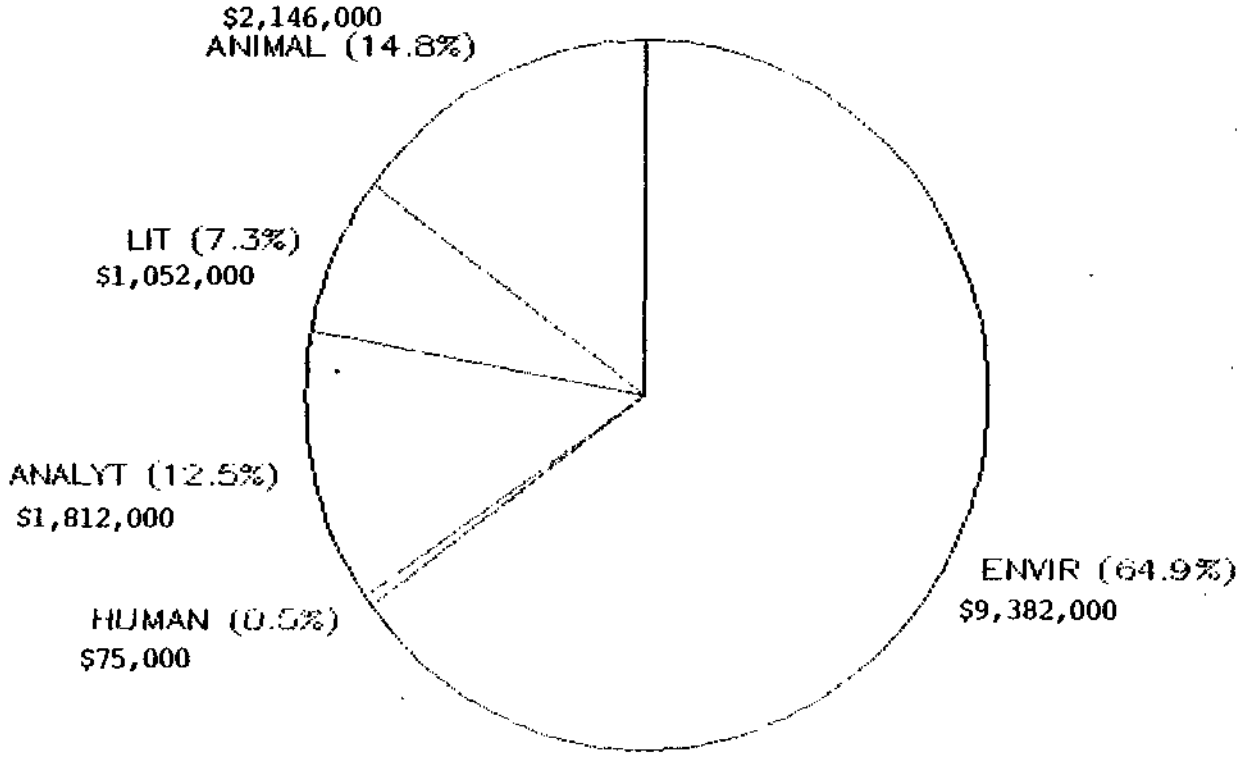
USDA A.O./DIOXIN EXPENDITURES

$594,000 TOTAL EXPENDITURES



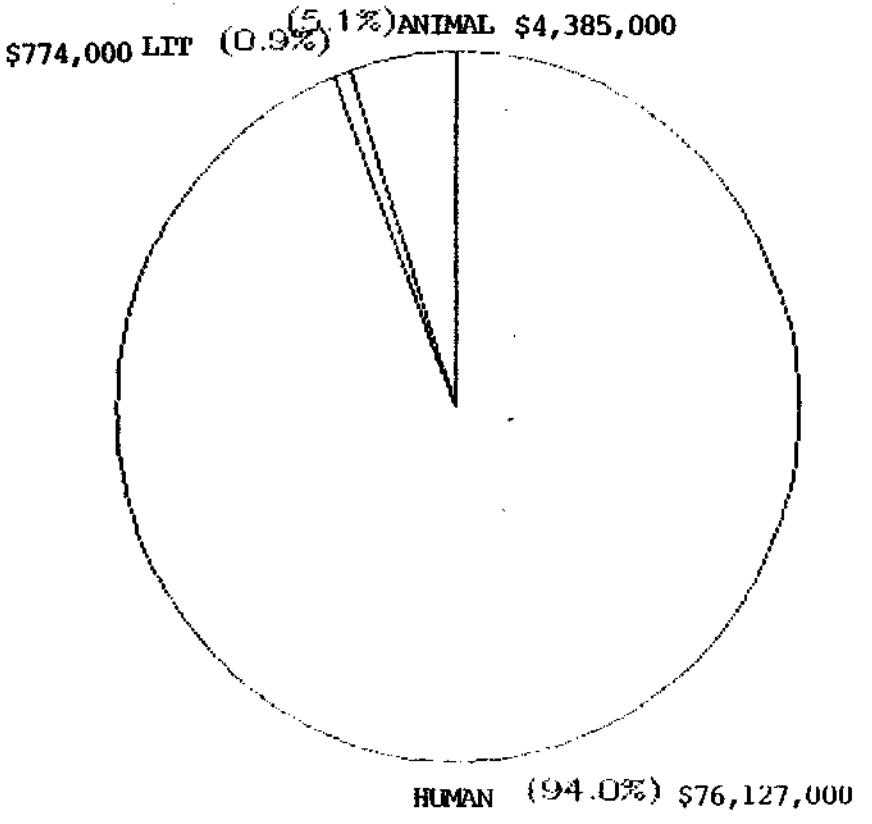
EPA A.O./DIOXIN EXPENDITURES

$14,467,000 TOTAL EXPENDITURES



V.A. A.O./DIOXIN EXPENDITURES

$81,286,000 TOTAL EXPENDITURES



A. Effects in animals

Over the past five years, hundreds of additional scientific papers have been published on the effects of AO and/or 2,3,7,8-TCDD on animals. Of special note was a study, expressly prompted by the concern of the veterans, that investigated the possible induction of certain birth defects in the offspring of male mice exposed to AO. This interest was prompted by the parallel to male soldiers exposed to AO in Vietnam, who were concerned about reproductive problems they might encounter. The results of the study indicated that exposure of male mice to the components of AO had no effect on their reproductive outcomes.

As the project titles in Appendix B indicate, research has continued in the previously studied areas of 2,3,7,8-TCDD animal toxicity; e.g., immunotoxicity, mutagenicity, lipid metabolism, and liver damage. Additional progress has been made in understanding the mechanism of action of 2,3,7,8-TCDD, its tissue distribution, and metabolism. New work has begun in certain behavioral endpoints.

In summary, the animal toxicology of 2,3,7,8-TCDD is increasingly well-characterized, although fundamental questions about the mechanisms of that toxicity and its relevance to humans remain unanswered.

B. Effects in humans

The major expenditures in Federally sponsored AO research over the past five years have been directed at the

TABLE 1: The Eleven Major Epidemiological Studies of U.S. Vietnam Veterans, Agent Orange and TCDD Exposure, and Vietnam Experience Currently Ongoing or Completed in the United States

Title	Responsible Federal Agency and Study Location	Type of Study	Total Study Population Size	Completion Date
Air Force Health Study	United States Air Force School of Aerospace Medicine, San Antonio, Texas	Matched Cohort Study of RANCH HAND Personnel and Controls, Mortality, Morbidity and Reproduction	2,500	a) Baseline Reports 1983 - 1984 b) Long-term follow-up planned
VA Mortality Study	Veterans Administration Agent Orange Projects Office, Washington, D.C.	Mortality Study of Vietnam-Era Veterans	75,000	Late 1985
Vietnam Experience Twin Study	Veterans Administration Medical Center, St. Louis, Missouri	Morbidity Study of Identical Twins	1,200	1986
Birth Defects Study	Centers for Disease Control, Atlanta Georgia	Case-Control Study of Anatomical Birth Defects	8,400	Completed August 1984
Agent Orange Epidemiological Study of Ground Troops	Centers for Disease Control, Atlanta Georgia	Three-Cohort Morbidity Study of Vietnam Veterans to determine the health effects of Agent Orange	18,000	1988
Selected Cancers Study	Centers for Disease Control, Atlanta, Georgia	Case-Control Study of Soft Tissue Sarcoma, Lymphoma and other Cancers	2,000	1989

TABLE 1: The Eleven Major Epidemiological Studies of U.S. Vietnam Veterans, Agent Orange and TCDD Exposure, and Vietnam Experience Currently Ongoing or Completed in the United States (Continued).

Title	Responsible Federal Agency and Study Location	Type of Study	Total Study Population Size	Completion Date
Vietnam Experience Epidemiologic Study	Centers for Disease Control, Atlanta Georgia	Matched Cohort Morbidity Study of Vietnam and non-Vietnam Veterans	12,000	1987
VA/AFIP Soft Tissue Sarcoma Study	Veterans Administration Agent Orange Projects Office, Washington, D.C.	Case-Control Study of Soft Tissue Sarcoma	250 cases 750 controls	Late 1986
NIOSH Dioxin Registry	National Institute for Occupational Safety and Health, Cincinnati, Ohio	Mortality Study of Workers at 12 Production Sites Where Dioxin Containing Products Were Manufactured	6,000	1986
NIOSH Industrial Morbidity Study	National Institute for Occupational Safety and Health, Cincinnati, Ohio	Morbidity Study of Workers at 2 Production Sites Where Dioxin Containing Products Were Manufactured and a Comparison Group	800	1988
NCI Kansas Soft Tissue Sarcoma Study	National Cancer Institute, Bethesda, Maryland	Case-Control of Soft Tissue Sarcoma	100 cases 300 controls	1986

TABLE 2: The Five Major Current Health Surveillance Projects of U.S. Vietnam Veterans, Agent Orange and TCDD Exposure.

Title	Responsible Federal Agency and Study Location	Type of Surveillance	Target Population	Status
VA Patient Treatment File Review	Veterans Administration Agent Orange Projects Office, Washington, D.C.	Review of VA hospital inpatient medical records	Vietnam era veterans who have been hospitalized in VA medical facilities	Ongoing
Agent Orange Register Review	Veterans Administration Agent Orange Projects Office, Washington, D.C.	Review of the records of the medical examinations at VA hospitals	Vietnam veterans who have reported to VA hospitals for an Agent Orange examination	Ongoing
A Review of the Soft Tissue Sarcoma Cases in Patient Treatment File for Vietnam Era Veterans	Veterans Administration Agent Orange Projects Office, Washington, D.C.	Review of pathology reports and the tissue specimens of patients diagnosed as having International Classification of Diseases (ICD) 171	Vietnam era veterans who have been hospitalized in VA medical facilities	Ongoing
AFIP Agent Orange Registry	Armed Forces Institute of Pathology, Washington, D.C.	Review of tissue specimens	Vietnam era veterans	Ongoing
VA/EPA Adipose Tissue Study	Veterans Administration and the Environmental Protection Agency, Washington, D.C.	500 samples of human fat	U.S. Vietnam era males	Ongoing

most critical need: studies of the potential effects of AO in humans. This work, coordinated through the AOWG, has been and is being conducted primarily by the Centers for Disease Control (CDC), the Department of Defense (DOD), and the Veterans Administration (VA). Epidemiological studies are complex and time-consuming projects, and, although many of these investigations are still in progress, all but one are scheduled for completion before the end of the decade. Table I briefly describes the epidemiological studies in progress.

The US Air Force is conducting a major investigation into the health of all identified individuals who were involved with the spraying of AO in Vietnam (Operation Ranch Hand), a group which were known to be exposed to AO. The mortality experience and the health status of the individuals in the cohort will be compared with that of other Southeast Asian veterans of the Air Force and followed for two decades to assess both the immediate and delayed results of exposure to AO.

In addition to the Ranch Hand study, ongoing human studies by the VA and CDC focus on health outcomes among Vietnam and Vietnam-era veterans. Investigations of both mortality and morbidity of Vietnam veterans are underway.

As noted in Section III, a major problem associated with human investigations has been estimating exposure of study subjects. This has attracted a significant portion

of the AOWG's time and attention, as well as the imagination and persistence of specified investigators, and of the personnel in the DOD Environmental Support Group in the US Armed Services. The uncertainty associated with obtaining an objective assessment of exposure to AO has influenced all of the epidemiological studies. The AO study being conducted by CDC will compare the health of cohorts of Vietnam veterans whose different proximities to AO applications have been obtained from detailed examination of herbicide application records and of daily records of troop movements and troop rosters. The Cancer and Mortality Studies will assign an index of opportunity for exposure to individuals based on quarterly reports of their assigned units' activities and proximity to herbicide applications during the period in which they were assigned to the unit. In some instances, however, individual AO exposures have been so difficult to estimate that investigators have had to assume that "service in Vietnam" is a surrogate for exposure to AO. Consequently, the effects of other aspects of the "Vietnam experience" have become even more difficult to distinguish from "AO exposure" per se.

In addition to studies focusing on Vietnam veterans, investigators are examining other populations which may have been exposed to AO-like materials. There are now "dioxin registries" of industrial workers who were involved in the

production or handling of 2,4,5-T and other chemicals which were contaminated with dioxins.

Some agencies are conducting health surveillance projects which, while lacking the rigor of formal studies, may provide information on possible links between AO exposure and/or Vietnam service and a variety of health effects. (See Table II.) Such information, if it points toward an association between exposure and adverse effects, will form the basis for hypotheses which can be tested in more rigorous studies.

In summary, during the past five years, major steps have been taken in our effort to address the critical gap in our understanding of AO. Over the next five years, we hope that the ongoing studies will produce sufficient information for us to both reach broad conclusions, and to more sharply focus our questions.

C. Other

1. Information Management

Since 1980, the VA has published six volumes of an annotated bibliography and review of the scientific literature related to the toxic effects of AO and related compounds. The VA has prepared a "lay summary" of this material to make these results more comprehensible to the interested non-scientific public.

2. Environmental Fate and Transport

Various agencies have conducted research on the question: what happens to 2,3,7,8-TCDD once it enters the environment?

The answer to this question is relevant to the potential exposure to humans. For example, studies by the Air Force and others have indicated that, once incorporated into the soil, 2,3,7,8-TCDD has a half-life of roughly a decade. In addition, studies by NIEHS and EPA suggest that the bioavailability (an index of the toxic potential of chemicals in a contaminated matrix) of 2,3,7,8-TCDD from different contaminated soils can vary widely.

3. Monitoring

A number of agencies have been active in developing more sensitive, more rapid, and/or less expensive methods for analyzing for 2,3,7,8-TCDD in different substances, e.g., soil, mother's milk, and human adipose tissue. These methods have expedited the agencies' search for 2,3,7,8-TCDD in various parts of our environment. In the future, it may be possible to use some of these methods to assist in determining who has been exposed to 2,3,7,8-TCDD-containing chemicals, such as AO.

V. Evaluation

Research mentioned in this report reflects a Federal investment of more than $150 million into the issue of the potential adverse human health effects of exposure to AO. The knowledge base, while by no means complete, is considerably broader and deeper than it was only four years ago when the AOWG came into existence.

Although considerable work remains to be done, the work completed to date generally supports an optimistic prognosis for the Vietnam veteran. The early results from these studies suggest that the projected worst case scenarios of the effects on veterans of service in Vietnam and/or possible exposure to AO have not been realized. While most of the studies are still in progress and their results will provide additional important information, the currently available data do not indicate the overwhelming adverse effects associated with such service or exposure that some had feared.

The results of several studies support this evaluation. First, baseline data from the Ranch Hand study indicate that the Vietnam veterans most likely to have been exposed to AO (those involved with the handling and application of the chemical) have not experienced a disproportionate number of serious adverse health effects when compared to other Air Force personnel with no known exposure to AO.

Second, in a health survey conducted by the VA, there were no significant associations found between cancer incidence and self-reported AO exposure, or other variables that should be related to herbicide exposure.

Third, a study conducted and published by the CDC and co-funded by CDC, VA and DOD, indicates that Vietnam veterans are at no greater risk of fathering deformed children than are their comparisons who have not been to Vietnam. (These results are consistent with a related study conducted in

Australia which found no evidence that Australian Army service in Vietnam increased the risk of fathering children with anomalies diagnosed at birth.)

Fourth, an animal study conducted by NIEHS suggested that AO exposed males are not likely to be the source of birth defects in offspring.

Between now and the end of the decade, more human health information will be generated on the AO problem than has been generated in all the years up to this time. While the limited data in hand should be encouraging to those concerned about possible adverse health effects to AO-exposed Vietnam veterans, it is still too early to make final statements. In particular, the potential for effects which manifest themselves only many years after exposure (e.g., cancer) have yet to be assessed fully. Also, effects which have not been so fully examined (e.g., immunotoxicity) may be found, and since the populations involved in some of the ongoing studies are larger than those in the completed studies, less common adverse effects may be discovered.

VI. Future directions

Since the early 1970s, the country has been sensitized to the possible presence of 2,3,7,8-TCDD in various environmental settings, including many in the United States. For example, over the past five years, 2,3,7,8-TCDD contamination has been reported at US locations from the forests of the Pacific Northwest to the streets of Newark, New Jersey. In the

early 1980s, the discovery of 2,3,7,8-TCDD contaminated soil at more than 40 locations in Missouri led to actions by EPA and CDC to limit human exposure to the contamination at some of these sites.

This increased attention has been accompanied by suggestions that additional human studies should be undertaken to investigate the possible deleterious effects of exposure to 2,3,7,8-TCDD contaminated material, such as AO. Populations within the US and additional cohorts of Vietnam service personnel have been mentioned as likely subjects of study. During the past year, however, the Science Panel has reached the conclusion that the human studies and surveillance of records which are already underway should be sufficient to detect the important human effects. Additional major epidemiological studies, associated with either Vietnam or domestic exposure, should profit if they await the results of the studies already underway before being initiated. Future studies should build on the information being gathered, i.e., testing specific hypotheses suggested by the current studies. In short, there is a consensus in the Science Panel that broad, hypothesis-generating studies are already underway; future studies should be focused to test hypotheses generated from completed and ongoing studies.

We now recognize that the "AO problem" has always been a subset of both the overall "Vietnam experience problem" and the larger "dioxin problem". The latter also encompasses

domestic contamination situations mentioned peviously, the panoply of "dioxin-like" chemicals emitted from combustion sources, and the problem of destroying 2,3,7,8-TCDD once it has been discovered in the environment. The results of such investigations may provide additional insights into the AO problem, as the AO research described in this report will reciprocate by shedding light on the larger "dioxin" question.

APPENDIX A

Agency Membership in Agent Orange Work Group

Department of Health and Human Services (Chair)
- Centers for Disease Control
- Center for Environmental Health; National Institute of Occupational Safety and Health
- National Institute of Environmental Health Sciences
- Public Health Service
- National Cancer Institute

ACTION

Council of Economic Advisors

Department of Agriculture

Department of Defense

Department of Labor
- Office of Occupational Safety and Health

Department of State

Enviromental Protection Agency

Office of Management and Budget

Office of Policy Development

Office of Science and Technology Policy

Congressional Office of Technology Assessment (Observer)

Veterans Administration

APPENDIX B

PROJECT-BY-PROJECT LISTING OF AGENCY AO-RELATED RESEARCH EFFORTS*

*The following tables list AO and related research studies sponsored by the Federal Government beginning in 1980. Studies carried out by one Agency, but funded by another have been listed under the Agency funding the study. Projects related to the investigation and clean-up of 2,3,7,8-TCDD contaminated sites have not been included.

DEPARTMENT OF AGRICULTURE HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS		STUDY PERIOD	TOTAL $ 1981-87
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING		
A CASE CONTROL STUDY OF THE RELATIONSHIP BETWEEN EXPOSURE TO 2,4-D AND SPONTANEOUS ABORTIONS IN HUMANS				X			X	1980-1981	365,000
EXPOSURE OF FOREST WORKERS TO GROUND APPLICATIONS OF 2,4-D					X		X	1981-1984	165,000

DEPARTMENT OF AGRICULTURE OFFICE OF SCIENTIFIC RESEARCH LAB/LITERATURE STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
BIOLOGICAL AND ECONOMIC ASSESSMENT OF 2,4,5-T AND SILVEX				X	X		1977-1983	64,300

DEPARTMENT OF DEFENSE/AFIP HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS		STUDY PERIOD	TOTAL $ 1981-87
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING		
ARMED FORCES INSTITUTE OF PATHOLOGY MORPHOLOGIC STUDIES/VIET VETS			X				X	1980-1986	350,000

DEPARTMENT OF DEFENSE/AIR FORCE HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS			
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING	STUDY PERIOD	TOTAL $ 1981-87
PROJECT RANCH HAND EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDE ORANGE (AIR FORCE HEALTH STUDY)	X	X	X	X			X	1981-1999	29,600,00

DEPARTMENT OF DEFENSE/AIR FORCE OFFICE OF SCIENTIFIC RESEARCH LAB/LITERATURE STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
2,3,7,8-TCDD INDU ED IMMUNOSUPPRESSION	X					X	1985-1987	62,600
MECH OF CELLULAR MEMBRANE EFFECTS OF TCDD	X					X	1984-1987	225,000

DEPARTMENT OF DEFENSE/ARMY ENVIRONMENTAL SUPPORT GROUP HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS		STUDY PERIOD	TOTAL $ 1991-97
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING		
VA SOFT TISSUE SARCOMA			X			X		1985	12,000
VA MORTALITY STUDY	X						X	1984-1987	561,000
CDC BIRTH DEFECTS STUDY				X		X		1983-1984	225,000
CDC EPIDEMIOLOG. STUDY	X	X	X	X	X	X		1984-1988	750,000
VA TWIN STUDY		X		X				1985-1987	75,000
VA ADIPOSE TISS. STUDY					X			PENDING	-
AFI SARCOMA STUDY			X					1984-1989	86,000
CDC SELECTED CANCERS			X				X	1984-1989	72,000
VA CHLORACNE		X						1984-1989	55,000
DIOXIN WORKERS		X				X		1984	12,000
VA PATIENT TREATMENT FILES		X						1984-1989	47,000
SERVICES HERBS TAPES					X			1982-1989	172,000
MISCELLANEOUS SUPPORT CDC VIETNAM EXPERIENCE STUDY	X	X	X	X	X	X		1980-1989	1,377,500
CDC VIETNAM EXPERIENCE STUDY							X	1984-1985	224,000

ENVIRONMENTAL PROTECTION AGENCY HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS			
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING	STUDY PERIOD	TOTAL $ 1981-87
REPORT OF ASSESSMENT OF A FIELD INVESTIGATION OF SIX-YEAR SPONTANEOUS ABORTION RATES IN THREE OREGON AREAS OF RELATION TO FOREST 2,4,5-T SPRAY PRACTICES				X		X		1979	0
NORTHWEST HUMAN MILK STUDY					X	X		1980	0
NATIONAL MONITORING OF HUMAN ADIPOSE					X		X	1983-1995	75,000
NEBRASKA ADIPOSE TISSUE STUDY					X	X		1980	
RETROSPECTIVE STUDY OF DIOXINS AND FURANS IN ADIPOSE TISSUE OF VIETNAM-ERA VETERANS (VA/EPA)					X		X	1982-1989	VA FUNDIN

ENVIRONMENTAL PROTECTION AGENCY LAB/LITERATURE STUDIES

EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
ASSESS OF PCB TRANSFORMER/ CAP FIRES			X		X		1984-1985	140,000
UPTAKE OF DIOXINS BY FISH	X					X	1984-1987	909,000
MICROB. DISSIM. OF 2,3,7,8-TCDD		X			X		1980	
POTENTL FOR 2,3,7,8-TCDD TRANSPORT IN SOILS		X				X	1984-1987	812,00
BACTER DECOMP OF TCDD		X				X	1982-1987	486,00
MISSISSIPPI CATFISH STUDY	X				X		1980	
EXPOS ASSESS MTHDS FOR TCDD AND OTHER DIOXINS				X		X	1984-1987	667,00
OF ENV. SAMPLES .DS AND CDFS		X			X		1982-1984	290,00
BIOAVAIL. OF FR. WATER FISH FOR TCDDS	X				X		1982-1984	250,00
OREGON MONKEY STUDY	X				X		1980	
EVAL OF MUNIC. WASTE COMBUSTORS		X			X		1982-1984	300,00
QUALITY ASSUR. SUPPORT			X			X	1984-1985	1,162,00
REGION X DEER & ELK STUDY	X				X		1980	
UPTAKE OF DIOXINS BY PLANTS AND LARGE ANIMALS		X				X	1984-1987	435,00
LA. CRAYFISH/CATFISH STUDY	X				X		1980	
EVAL OF LARGE SCALE COMBUSTION SOURCE		X			X		1982-1983	400,00
RISK ASSESS APPROACH TCDD AND OTHER DIOXINS				X		X	1984-1987	335,00
.AL DIOXIN STUDY		X				X	1984-1985	4,600,00
BEEF FAT PHASE II	X				X		1980	

ENVIRONMENTAL PROTECTION AGENCY LAB/LITERATURE STUDIES

EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
EVAL UV PHOTOLYSIS/ APEG CHEM DETOX		X				X	1984-1987	607,000
HEALTH ASSESS OF PCDDS & PCDFS				X		X	1985	50,000
BIODEG AND CARBON ADSORPTION OF TCDD		X			X		1980	0
INVEST OF IN SITU STABIL. TECHNOLOGY		X				X	1984-1987	397,000
SORPTION/DESORPTION OF TCDD		X				X	1984-1987	670,000
METHODS ANALYS. ENVIR. OF TCDD BY MASS. SPECT.			X			X	1984-1985	300,000
PHARMACO. OF TCDD IN MONK. & HEALTH ASSES. OTHER DIOXINS	X					X	1984-1987	837,000
MONOCLON. ANTIBOD. METHOD OF DIOXIN ANALYSIS			X			X	1984-1985	200,000
INACTIVE MINES FOR REPOS. OF DIOXIN SOIL		X				X	1984-1985	185,000
ROUND ROBIN SURVEY-METHODS DIOXIN ANALYSIS IN ADIPOSE			X			X	1985	10,000
WISCONSIN MONKEY STUDY	X				X		1980	0
PHOTOCHEMISTRY		X				X	1986-1987	200,000
BIOAVAILABILITY TO ANIMALS	X					X	1985-1986	150,000

HEALTH AND HUMAN SERVICES/CDC HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS		STUDY PERIOD	TOTAL $ 1981-87
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING		
CDC BIRTH DEFECTS AND MILITARY SERVICE IN VIETNAM STUDY				X			X	PUBLISHED AUG. 1984	1,504,000
CDC EPIDEMIOLOGIC STUDY OF GROUND TROOPS EXPOSED TO AGENT ORANGE DURING THE VIETNAM CONFLICT	X	X	X	X	X		X	SEPT 1989	VA FUNDING
DEVELOPMENT OF TCDD REFERENCE STANDARDS FOR LAB ANALYSIS OF HUMAN TISSUES					X	X		1984-1985	EPA FUNDIN
DEVELOPMENT OF LAB METHODS FOR TCDD ANALYSIS OF HUMAN [illegible] TISSUES AND [illegible] ULTRALOW [illegible] LEVELS					X	[illegible]		1984-1985	EPA FUNDIN
EXPOSURE STUDIES OF MO RESIDENTS OF TCDD-CONTAMINATED AREAS									
PILOT STUDY		X					X	1984-1985	EPA FUNDIN
PILOT STUDY FOLLOWUP		X			X		X	1985-1986	EPA FUNDIN
ADIPOSE TISSUE TESTING					X		X	1985-1986	EPA FUNDIN
REPRODUCTIVE OUTCOMES				X			X	1985-1986	EPA FUNDIN
ASSESSMENT OF HEALTH RISK OF EXPOSURE TO 2,3,7,8-TCDD IN SOIL IN A RESIDENTIAL COMMUNITY (TIMES BEACH, MO)					X	X		1984	EPA FUNDIN
DETAILED CURRENT LITERATURE REVIEWS WITH PUBLISHED REPORTS ON THE STATE OF SCIENTIFIC KNOWLEDGE OF THE HEALTH EFFECTS OF TCDD					X		X	1975-1985	140,000

HEALTH AND HUMAN SERVICES/NCI HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS			
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING	STUDY PERIOD	TOTAL $ 1981-87
LUNG CANCER - STRUCTURAL PEST CONTROL WORKERS	X						X	1984-1986	100,000
CONTROL STUDY OF LYMPHOMA AND SOFT TISSUE SARCOMA			X			X		1981-1982	487,000
NCI PESTICIDE WORKERS			X				X	1983-1985	870,000

HEALTH AND HUMAN SERVICES/NIEHS LAB/LITERATURE STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
DED-WEED.LV-69: SALMONELLA	X				X		1980	[illegible]
2,4-D: DROSOPHILIA	X				X		1981	7,400
2,4,5-T: DROSOPHILIA	X				X		1981	7,4[illegible]
2,4,5-T: N-BUTYL ESTER: SALMONELLA	X				X		1981	1,20
2,4-D, N-BUTYL ESTER: SALMONELLA	X				X		1981	1,20
2,4,5-T: SALMONELLA	X				X		1980-1981	1,20
CYTOGENETICS	X				X		1982	4,2[illegible]
2,4,5-T: CYTOGENETICS	X				X		1982	4,20
DIBENZOFURAN: CYTOGENETICS	X				X		1981	4,15
2,4-D: SALMONELLA	X				X		1980-1981	1,200
2,7-DICHLORODIBENZO-P-DIOX: SALMONELLA	X				X		1982	1,20[illegible]
DIBENZOFURAN: SALMONELLA	X				X		1980	[illegible]
2,4-D, DIMETHYLAMINE SALT: SALMONELLA	X				X		1980	
PENTACHLOR. & DIOXIN CONTAM IN PCP			X		X		1984	200,00[illegible]
NEUROTOXICITY OF 2,4-D IN RODENTS	X				X		1980-1981	27,00[illegible]
PEST. & TRANS. ACROSS BIL. LIP. MEM.	X				X		1980-1987	987,00[illegible]
ILL. & TOX. [illegible] LIVER	X					X	1980-1986	741,00[illegible]
OCCUPTL. & ENVMTL. HLTH. CTR. GRANT	X				X		1980-1984	95,00[illegible]

HEALTH AND HUMAN SERVICES/NIEHS LAB/LITERATURE STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1991-97
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
ALTER. OF CELL-SURF. MEMBRANE FOR DI TOX	X					X	1985-1989	415,000
EFFECTS ON NUTRIENT ASSIMILATION	X					X	1982-1986	760,000
BIOAVAILABILITY OF TCDD (RAT) DERMAL AND ORAL	X				X		1983-1984	110,000
TOXICANT DERES ENDOCRINE HEME BIOSYNTH	X					X	1985-1987	316,000
DI-EPITH CELL INTERACT. MECH AND ASSAY	X					X	1985-1997	219,000
.RE-TOXICITY RELAT.	X					X	1980-1984	35,000
MOLECULAR TOXICOLOGY OF TCDD	X					X	1991-1996	462,000
IMMUNOSUPPRESSION BY IN UTERO EXPOS	X				X		1990	0
ARACHIDONATE PRODTS IN DI AND PCB TOX	X					X	1985-1987	497,000
IMPLCTNS. OF LOW LVL. EXP. TO DIOXIN	X				X		1990-1992	258,000
TOC. MOT. OF TETRACHLOROBENZENE AND DIOXIN	X				X		1990-1993	214,000
GENTC. IND. OF PLE. REP. IN LIVER TOX	X					X	1980-1986	1,144,000
CHL. DIB-P-DIOX. MECH. OF TOX.	X					X	1982-1987	546,000
MOLCR. MDLS. OF DIOX. BNDG. PROTEINS			X		X		1993-1985	90,000
...HEXACHLORO-DIBENZO-P-DIOXIN	X				X		1990	0
MCH. FOR TOX. OF CHL. DIBENZODIOX.	X				X		1981-1987	471,000

HEALTH AND HUMAN SERVICES/NIEHS LAB/LITERATURE STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
TER. OF TCDD CLFT. PAL. INDC. (MICE)	X					X	1983-1985	400,000
DISPOSIT OF TCDD FTL. DIST. IN MICE	X					X	1984-1985	50,000
PRE-DIOX. IN PCP BIOCH., EF., & TOX	X				X		1980-1982	172,000
ATMC. EM. SPCT. FOR DIOXIN TR. ANLYS.	X					X	1983-1986	344,000
SYNTH. OF 6 CHLOR DIBENZO-P-DIOX			X		X		1982	61,000
MOLECULAR BASIS OF DIOXIN TOXICITY			X			X	1983-1985	120,000
S.. / OF TETRACHLORO-DIBENZO-P-DIOX	X				X		1990	0
ROLE OF TCDD RECEPTOR IN TUMOR PROMO	X					X	1985-1989	400,000
TOXIC AND ANOREXIC EFFECTS OF TCDD	X					X	1985-1987	456,000
MECHANISMS OF TCDD TOXICITY	X					X	1985-1987	200,000
MECHANISMS OF IMMUNOSUPPRESSION	X					X	1984-1985	130,000
BIOASSAY OF TETRACHLORO-DIBENZO-P-DIOXIN	X				X		1980	0
QUAN. ANAL. OF TCDD BY MASS SPECT.			X		X		1981	25,000
TXC HLS WST IN VTR. BIASY. DVLMT.	X				X		1982-1984	181,000
M.. ..MS OF D.. ..OXICITY	X					X	1985-1988	253,000
THEORETICAL MOLG OF A DIOXIN RECEPTOR			X		X		1983-1984	25,000
MECHANISMS OF TOXICITY OF DIOXIN	X					X	1985-1989	740,000

HEALTH AND HUMAN SERVICES/NIEHS LAB/LITERATURE STUDIES

STUDY EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
ENVIRMTL HLTH SCI CNTR GRANT	X					X	1980-1987	597,000
DIOXIN NMR STUDY			X		X		1984	35,000
EFFECTS ON INTESTINAL CELLS	X				X		1981-1982	4,000
HEXACHL BENZ DISPOSIT	X				X		1981-1984	75,000
INTL. RES/EXPOS TO PHENOXY ACID HERB	X				X		1981-1983	456,000
MEMBRANE/LP RECEPTOR NRSA	X					X	1984-1987	36,000
LIPID ASSIMILATION NRSA	X				X		1981-1984	36,000
2-TCDD DISP IN MICE & G.P.	X				X		1980-1983	200,000
2,3,7,8-TCDF METABOLISM IN RATS, MICE & G.P.	X				X		1981-1985	100,000
CONTROL OF GENE EXPRESSION BY DIOXIN	X					X	1985-1990	743,000
TCDD EFFECTS ON STEROID HORMONE SYNTHESIS	X					X	1985-1988	204,000

HEALTH AND HUMAN SERVICES/NIOSH HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS		STUDY PERIOD	TOTAL $ 1981-87
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING		
NIOSH HEALTH HAZARD EVAL AND LEUKEMIA CLUSTER IN MADISON COUNTY, KENTUCKY ALLEGEDLY ASSOCIATED WITH PENTACHLOROPHENOL TREATED AMMUNITION BOXES			X			X		1981-1984	> 615,00
NIOSH HEALTH HAZARD EVAL AND TECHNICAL ASSISTANCE		X					X	1983-1989	—
NIOSH DIOXIN REGISTRY AND MORTALITY	X		X				X	1980-1987	1,228,00
NIOSH DIOXIN REGISTRY MORBIDITY & REPRO OUTCOME STUDY		X	X	X			X	1985-1988	4,095,00
NIOSH SOFT TISSUE SARCOMA INVESTIGATION (TECH. ARTICLE)			X			X		1981-1983	4,00

VETERANS ADMINISTRATION HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS			
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING	STUDY PERIOD	TOTAL $ 1981-87
VIETNAM VETERANS MORTALITY STUDY	X						X	1982-1989	2,334,00
EPIDEMIOLOGY STUDY (CDC)	X	X	X	X	X		X	1983-1989	67,694,00
BIRTH DEFECTS (CDC)				X			X	1981-1983	488,00
TWIN STUDY: VIETNAM EXPERIENCE TWIN STUDY (VETS I)		X		X			X	1982-1987	
TWIN STUDY: VIETNAM EXPERIENCE TWIN STUDY (VETS II)		X						SUSPENDED	3,359,00
VA/AFIP SOFT TISSUE SARCOMA			X				X	1984-1989	302,00
VA/AFIP SOFT TISSUE SARCOMA T TREATMENT FILE		X	X				X	NO FUNDING	-
TCDD IN BODY FAT OF VIETNAM VETERANS AND OTHER MEN		X			X	X		1980	-
RETROSPECTIVE STUDY OF DIOXINS AND FURANS IN ADIPOSE TISSUE OF VIETNAM-ERA VETERANS (VA/EPA)					X		X	1982-1989	810,00
CASE CONTROL STUDY OF LYMPHOMA			X				X	1985-1989	150,00
FEMALE VETERAN SURVEY	X						X	1985-1988	480,00
COHORT MORTALITY STUDY OF VIET VETS	X						X	1985-1989	370,00
PTF/VIETNAM SERVICE INDICATOR						X		1982-1984	140,00

VETERANS ADMINISTRATION HUMAN HEALTH STUDIES

STUDY EFFORT	TYPE OF STUDY					STATUS		STUDY PERIOD	TOTAL $ 1981-87
	MORTALITY	MORBIDITY	CANCER	REPRO-DUCTION	ANALYTICAL	COMPLETED	ONGOING		
INVESTIGATOR INITIATED RESEARCH: CHRONIC EFFECTS OF HERBICIDE EXPOSURE ON TESTICULAR FUNCTION IN VIETNAM VETERANS		X					X		
INVESTIGATOR INITIATED RESEARCH: FAT TISSUE ANALYSIS FOR 2,3,7,8-TCDD (DALLAS)					X		X	1980-1989	INCLUDED BELOW
INVESTIGATOR INITIATED RESEARCH: FAT TISSUE ANALYSIS FOR 2,3,7,8-TCDD (SAN ANTONIO)					X		X		

VETERANS ADMINISTRATION LAB/LITERATURE STUDIES

EFFORT	TYPE OF STUDY				STATUS		STUDY PERIOD	TOTAL $ 1981-87
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING		
REVIEW OF LITERATURE ON HERBICIDES, INCLUDING PHENOXY HERBICIDES AND ASSOCIATED DIOXINS				X		X	1981-1989	439,000
INVESTIGATOR INITIATED RESEARCH: URINARY 6-HYDROXY CORTISOL: PHYSIOLOGICAL AND PHARMACOLOGICAL STUDIES (INCLUDING AGENT ORANGE)	X					X		
INVESTIGATOR INITIATED RESEARCH: EFFECT OF TCDD ON LIPID METABOLISM	X					X		
INVESTIGATOR INITIATED RESEARCH: MECHANISMS OF DIOXIN INDUCED TOXICITY USING THE CHLORACNE MO[illegible]	X					X		
INVESTIGATOR INITIATED RESEARCH: BEHAVIORAL TOXICITY OF AN AGENT ORANGE COMPONENT: 2,4-D	X					X	→ 1980-1989	4,385,000
INVESTIGATOR INITIATED RESEARCH: EFFECTS OF 2,3,7,8-TETRACHLORODIBENZODIOXIN ON HEPATOBILIARY FUNCTION IN ANIMALS	X					X		
INVESTIGATOR INITIATED RESEARCH: MECHANISM OF TCDD ABSORPTION AND TOXICITY ON LIPID AND LIPOPROTEIN METABOLISM	X					X		
INVESTIGATOR INITIATED RESEARCH: METABOLISM OF THE HERBICIDES PRESENT IN AGENT ORANGE AND AGENT WHITE	X					X		
INVESTIGATOR INITIATED RESEARCH: TCDD EXPOSED RHESUS MONKEYS: EFFECTS ON BEHAVIOUR AND STRESS HORMONES	X					X		
INVESTIGATOR INITIATED RESEARCH: NEUROMUSCULAR TOXICITY OF AGENT ORANGE	X					X		

VETERANS ADMINISTRATION LAB/LITERATURE STUDIES

S. _FFORT	TYPE OF STUDY				STATUS			
	ANIMAL	ENVIRONMENTAL	ANALYTICAL	LITERATURE	COMPLETED	ONGOING	STUDY PERIOD	TOTAL $ 1981-87
INVESTIGATOR INITIATED RESEARCH: EFFECTS OF LOW DOSE TCDD ON MAMMALIAN CHROMOSOMES AND LIVER CELLS	X					X		
INVESTIGATOR INITIATED RESEARCH: MECHANISM OF PORPHYRIA CAUSED BY TCDD AND RELATED CHEMICALS	X					X	→ 1980-1989	INCLUDED ABOVE
INVESTIGATOR INITIATED RESEARCH: EFFECTS OF AGENT ORANGE ON SLEEP	X					X		
INVESTIGATOR INITIATED RESEARCH: UPTAKE AND METABOLISM STUDIES AND PHARMACOL & TOXICOL	X					X		
MONOGRAPHS				X		X	1982-1987	136,000
L ME TASK FORCE				X		X	1983-1987	199,000

APPENDIX C

AGENCY SUMMARY STATEMENT OF AO-RELATED RESEARCH EFFORTS

ENVIRONMENTAL PROTECTION AGENCY

Research Program Associated with
Chlorinated Dibenzo-p-dioxins (CDDs) and Dibenzofurans (CDFs)

The US Environmental Protection Agency (EPA) has been concerned with CDDs/CDFs, particularly 2,3,7,8-TCDD, since the early 1970s. Much of the early work was related to 2,3,7,8-TCDD as a contaminant in the herbicde 2,4,5-T and included analytical methods development and its application to monitoring data.

While the Agency's research work with humans has been limited, it has been important. In the late 1970s, a controversial epidemiological study triggered immediate regulatory action by the Agency. During the same period, the Agency conducted an investigation of 2,3,7,8-TCDD in the human milk of mothers living in areas in which 2,4,5-T had been used. No confirmed positive residues were detected in any of 100 samples. The Agency has detected trace amounts of 2,3,7,8-TCDD in some human adipose tissue samples. Ongoing collaborative efforts with the Veterans Administration is aimed at analyzing samples of human adipose tissue collected during the 1970s to determine whether or not Vietnam service personnel have greater residues of 2,3,7,8-TCDD than do a comparable group of individuals who did not go to Vietnam. In addition, EPA has conducted assessments of the potential human risks associated with exposure to 2,3,7,8-TCDD and some of the other CDDs/CDFs. These "ballpark" risk estimates have been useful in reaching regulatory decisions.

During the 1980s, the EPA research program for CDDs/CDFs has focused on environmental and risk management concerns. Specifically, Congress directed the Agency of conduct a National Dioxin Study, the aim of which is the investigation of potential "hot spots" across the country and the determination of background levels, if any, of 2,3,7,8-TCDD in the environment. This current effort builds on more limited, but more focused, Agency efforts searching for 2,3,7,8-TCDD in envivonmental samples. In an attempt to conduct such investigations more quickly and inexpensively, the Agency has sponsored research to develop new methods of analysis of CDDs/CDFs. In order to better understand the significance of reports of CDDs/CDFs in the environment, EPA is conducting studies in the environmental transport and fate of these compounds, with a particular emphasis on the bioavailability and possible movement into the human food chain. Large-scale combustion is under special investigation as a possible source of CDDs/CDFs in the environment.

A major thrust of recent EPA efforts has been in the direction of controlling, managing, and/or destroying CDDs/CDFs once they are found in the environment. Methods have been found which successfully destroy 2,3,7,8-TCDD in contaminated soil and liquids. Procedures are being developed to minimize the emission of CDDs/CDFs from combustion sources.

RANCH HAND EPIDEMIOLOGIC STUDY

In October 1978, the United States Air Force (USAF) Surgeon General made the commitment to the Congress and to the White House to conduct an epidemiologic study of the possible adverse health effects arising from the herbicide exposure of Air Force personnel who conducted aerial dissemination missions in Vietnam (Operation Ranch Hand). The purpose of this epidemilogic investigation is to determine whether long-term adverse health effects exist, and whether they can be attributed to occupational exposure to herbicides and their contaminants. The study protocol for this effort incorporates a matched cohort design placed in a non-concurrent prospective setting. The study approach includes mortality, morbidity, and follow-up elements linked tightly in time in order to produce the most data in the shortest period of time. The study addresses the question: Has there been, or are there currently, or will there be any adverse health effects among former Ranch Hand personnel caused by repeated occupational exposure to 2,4,5-T containing herbicides and the contaminant, TCDD?

A mortality determination on 1,247 Ranch Handers and 6,171 comparison subjects was made.

The Baseline Mortality Report was released in June 1983.

Data analysis showed that the mortality experience of the Ranch Hand group is nearly identical to that of the comparison group. Analyses showed that officers are living longer than enlisted personnel in both Ranch Hand and comparison groups. This difference between officers and enlisted personnel was statistically significant in the comparison group whereas it was not in the Ranch Hand cohort. A contrast of the Ranch Hand and comparison groups to the 1978 DoD Life Table showed significantly less mortality for Ranch Hand officers, comparison officers and comparison enlisted men, however; there was not a statistically significant favorable mortality rate for Ranch Hand enlisted personnel.

The Ranch Handers showed a relative paucity of overall cancer but an excess of disgestive disorder deaths, both statistically nonsignificant. No soft tissue sarcoma deaths were detected in either group.

The first annual Mortality Report Update was issued in December 1984. As was the case in the first mortality report, the current mortality analyses did not reveal any statistically significant differences in mortality between the exposed and comparison groups.

As was reported in the baseline mortality study, the Ranch Hand officers had a nonstatistically significant though slightly lower death rate than their comparisons, Ranch Hand flyers had a nonstatistically significant though slightly lower death rate than comparisons, and Ranch Hand ground personnel had a slightly higher but nonstatistically significant death rate than comparisons.

The herbicide/dioxin exposure index described in the morbidity report was applied to the data, and no relationship between exposure and mortality experience was identified.

As was also noted in the baseline mortality study, analyses consistently demonstrated significantly better survival in the Ranch Hand officers than Ranch Hand enlisted members, as was the case with comparison officers and comparison enlisted personnel. Cause-specific analyses did not demonstrate any increased Ranch Hand mortality for accidents, suicide, homicide, malignancy or circulatory system disease. No unusual patterns of malignancy were observed in either the Ranch Hand or comparison groups, a finding which would be expected from the small number of deaths to date.

In February 1984, the Air Force released its Baseline Morbidity Report. The morbidity analyses disclosed numerous medical findings, most of a minor or undetermined nature that will require detailed follow-up. At this time, there is insufficient evidence to support a cause and effect relationship between herbicide exposure and adverse health in the Ranch Hand group.

The physical examinations and the questionnaire data were analyzed by major medical organ system. The study assessed the general physical health, malignancy, and fertility/reproductive, neurological, psychological, hepatic (liver), immunology, dermatologic, cardiovascular, hematologic, pulmonary, renal and endocrine systems.

There were not statistically significant differences in the occurrence of malignant or benign systemic tumors between the groups. There were no cases of soft tissue sarcoma in the Ranch Handers and only one in the comparison group. There were no cases of digestive cancers in the Ranch Hand Group. Significantly more nonmelanotic skin cancer (predominantly basal cell carcinoma) was noted in the Ranch Hand group, but these analyses have not yet been adjusted for sunlight exposure. Such skin cancer is the most common neoplasm in the white population in the United States and excessive exposure to sunlight is a major cause of these cancers. There was no evidence that the skin cancers were related to herbicide exposure. Up to the sample size limits of the study, there were no consistent data that showed that the Ranch Handers were developing uncommon cancers, or cancer in unusual sites, or at an unusual age.

Measurement of fertility and reproductive systems showed mixed results.

There were no significant differences in fertility/infertility, miscarriages, still births or live births.

There was no significant disparity between groups for the classifications of severe or moderate birth defects. By parents' reports, however, significantly more minor birth abnormalities (rashes, birth marks, etc.) were reported for the Ranch Hand offspring. If these are excluded, there are no significant differences in birth defects.

No cases of chloracne were diagnosed clinically or by biopsy. A thorough questionnaire analysis of acne showed no significant differences between the groups.

Data from the Ranch Handers (1,045) and the original comparison (773) subjects who completed the physical examinations are the primary focus of this report. Further physical examinations and questionnaires will be administered at the 3 (1985), 5, 10, 15 and 20 year points.

The mortality and morbidity reports have been reviewed and approved by the Advisory Committee on Special Studies Related to the Possible Long-Term Health Effects on Phenoxy Herbicides and Contaminants prior to release.

CENTERS FOR DISEASE CONTROL

Agent Orange Projects

The epidemiologic studies of the health of Vietnam veterans ("the Agent Orange Projects") being conducted by the Centers for Disease Control (CDC) are proceeding on schedule.

Under the terms of the Interagency Agreement that transferred responsibility for these studies to CDC from the Veterans Administration, CDC is solely responsible for all decisions related to the design, conduct, analysis, and scientific interpretation of the results of the study. Data for the studies is being collected by contractors under protocols and guidelines written and monitored by CDC. The data are transmitted to CDC in computer-readable formats.

The overall CDC effort comprises three separate but related investigations: two are retrospective cohort studies; the third is a case-control study.

Vietnam Experience and Agent Orange (cohort) Studies

The cohort studies will interpret data collected from a selected population of Vietnam era veterans to determine whether there are long-range health effects associated with military service in Vietnam (the Vietnam Experience component), or with exposure to Agent Orange (the Agent Orange component). Selected veterans who agree to participate are assigned to one of two Vietnam Experience cohorts on the basis of whether they served in Vietnam or another country during 1966-71. Assignments to one of

three Agent Orange component groups is made on the basis of opportunity of exposure to the herbicide. Up to 43,000 veterans will be interviewed by telephone about matters that may have influenced their health. Up to 10,000 of the men will be given comprehensive medical examinations.

Data collection for the cohort studies began in January 1985 and will be ongoing through 1987. The members of the Vietnam Experience cohorts will be identified, interviewed and examined first; then the members of three Agent Orange cohorts. As of June 23 the CDC interview contractor, Research Triangle Institute, Inc., had completed 6115 interviews. The first of the main study medical examinations were conducted earlier this month at the Albuquerque, NM facilities of another contractor, Lovelace Medical Foundation.

Mortality findings for the Vietnam Experience component are scheduled for publication in April 1986, and for the Agent Orange component in December 1987. Morbidity and summary findings for both components are to be published by September 1988.

Selected Cancers (case-control) study

This component assesses the risk of lymphoma, soft tissue sarcoma, nasal and nasopharyngeal cancer, and primary liver cancer among Vietnam veterans. Other types of cancers can be added to the study later if appropriate. Cases are male patients who have actually had these tumors, and who could have been in the military during the Vietnam conflict. The control group is made up men of the same age and from the same geographic

areas as the case group, but without the tumors. The cases are identified by tumor registries under contract to CDC. Controls are identified by another contractor using a random digit dialing technique. The tumor registries collect both case and control data.

Interviews for the Selected Cancers Study component were begun in February 1985 and will continue through about June 1989. CDC is presently contracting with six tumor registries for case ascertainment, and expects to announce one or more additional contracts this summer. Findings from the case-control investigation are scheduled for publication in September 1989.

CENTERS FOR DISEASE CONTROL

Birth Defects Study

In August 1984 the Centers for Disease Control (CDC) published the results of a two year study of Vietnam veterans' risks for fathering babies with birth defects. The most important conclusion to be drawn from this study is that the data collected contain no evidence to indicate that Vietnam veterans have had a greater risk than other men for fathering babies with defects when all types of serious structural birth defects are combined. This CDC study cannot prove that Agent Orange or some other factor associated with service in Vietnam was or was not associated with the occurrence of rare types of defects, defects in the babies of selected individuals, or defects in the babies of small groups of veterans. The conclusion, however, that Vietnam veterans have not fathered, at higher rates than other men, babies with defects when all types of birth defects are combined is based on relatively strong evidence.

VA/AFIP Soft Tissue Sarcoma Study

The possibility that exposure to phenoxy herbicides may induce rare forms of cancer in humans such as soft tissue sarcoma (STS) has been suggested from recent studies in Sweden. Subsequently, there is much concern in the United States that many veterans who served in Vietnam might have had a significant exposure to the phenoxy herbicides including Agent Orange and, therefore, might be at increased risk of developing STS.

In view of the concern raised by many veterans and conflicting findings in the scientific literature, the VA, in collaboration with the Armed Forces Institute of Pathology (AFIP), is conducting a case control study in which 250 individuals with STS are compared with 750 individuals without STS with respect to Vietnam service, probable Agent Orange exposure and other host and environmental risk factors.

The study is conducted in two phases. Phase I of the study will investigate whether service in Vietnam during 1965-1971 increased the risk of developing STS. Military service information, in particular Vietnam service status, for each case and control patients will be obtained from a review of the patient's military personnel records archived at the National Personnel Records Center in St. Louis, Missouri.

Phase II of the study will investigate other host and environmental risk factors for the development of STS based on information obtained from telephone interviews with the subjects or their next-of-kin. Information on risk factors such as occupational and non-occupational exposure to phenoxy herbicides, ionizing radiation asbestos, arsenic, vinyl chloride, and genetic synodromes will be obtained from the interviews and analyzed individually and jointly with respect to the risk of developing STS.

As of July, 1985, 58% of the study subjects (616/1,066) have been located and have completed the telephone interview. Data collection will be completed by March, 1986 and the final report is expected in late 1986.

VA Mortality Study

The Vietnam Veterans Mortality Study is designed to assess mortality patterns of U.S. servicemen in the Army or Marines who served during a portion of the Vietnam era. A sample of 75,000 veterans deaths has been selected from the VA BIRLS files. For each of the deaths, military service and cause of death information are being collected and coded. The two types of data will be merged and analyzed to compare the mortality experience of veterans who served in Vietnam with veterans of the same era who did not serve in Vietnam. Various analytical approaches are planned including classical proportionate mortality ratio (PMR) analyses as well as categorical data analyses.

As of August 1985 the military records search and abstracting have been completed for 98% of total cohort of 75,000. Ninety nine percent of the expected 72,000 death records have been received. However, about 15% of the records received did not include the cause of death information. Extensive tracing efforts have been made using both internal records and records maintained by other government agencies for all veterans whose VA claims folders lacked the cause of death information.

Completeness, accuracy and consistency of data on numerous variables (e.g., age, race, year of death, cause of death, branch of service, rank, MOSC, years of active duty, separation year, length of service in Vietnam, industry, occupation) are being checked in preparation for analysis. The final report is expected in late 1985.

JOHN H. GIBBONS
DIRECTOR

Congress of the United States
OFFICE OF TECHNOLOGY ASSESSMENT
WASHINGTON, D.C. 20510

STAFF MEMO

May 14, 1985

TO: Executive Secretary
Cabinet Council Agent Orange Working Group

FROM: Office of Technology Assessment
Observers, Cabinet Council Agent Orange Working Group

RE: Status Report

The Office of Technology Assessment (OTA) is mandated by Public Law 96-151 to oversee the epidemiologic studies of the health of Vietnam veterans now being carried out by the Centers for Disease Control (CDC). In addition, OTA responds to requests from Committee Chairmen and Ranking Minority Members of Committees for review and comment on various documents related to Agent Orange. Listed below are the letters, reports, and testimony that OTA provided between January 1983 and May 1985.

March 1983 — Letter report to Committees on Veterans' Affairs and Appropriations Committees describing transfer of epidemiologic study from the Veterans Administration to the CDC. Made favorable comment on CDC's outline of the study.

June 1983 — Testimony, Senate Committee on Veterans' Affairs about CDC's study plan. Optimistic and positive comments.

July 1983 — Letter report to Committees approving CDC protocol in principle, and asking for consideration of some OTA suggestions. Included 41 page review of protocols. Copy to VA.

February 1984 — Letter report to Committees approving revised CDC protocol. Noted CDC's careful consideration of OTA's and other reviewers' comments. Copy to VA.

May 1984 — Review of United States Air Force's Ranch Hand Health Study. Judged to be a reassuring study in that no excess of serious health conditions was found

in excess in Ranch Hands, but noting some items of concern. Staff Memorandum, 17 pages.

September 1984 Letter review for Committees of CDC's report "Vietnam Veterans' Risks for Fathering Babies with Birth Defects." Commented that study was well-done and accepted conclusions that there was no increased risk of fathering babies with birth defects as a result of service in Vietnam.

October 1984 Testimony, House Committee on Veterans' Affairs about CDC birth defects study. Restated positive comments about overall quality of study and the conclusion that there is no excess risk of fathering babies with birth defects associated with Vietnam service. Stated that the information about exposure to Agent Orange was so inherently uncertain that no conclusions could be drawn about any possible association between exposure and risks of birth defects.

December 1984 Letter report to Committees about progress in CDC studies of the health of Vietnam veterans.

February 1985 Meeting of OTA Agent Orange Advisory Panel to consider issues reported in March and April reviews described below.

March 1985 Letter review of proposed study of twins, one of whom had served in Vietnam, to determine effects of Vietnam service and exposure to Agent Orange on health. Recommended study not be done. Copy to VA.

April 1985 Review of CDC's plans for estimating exposure to Agent Orange in study of veterans' health. Recommended that greater effort be expended on locating company-level units, and that efforts be made to improve communication between CDC and the Army's Environmental Support Group, or to maintain records of unit movements and locations. Staff Memorandum, 6 pages.

Staff Memorandum review to Committees of Ranch Hand Mortality Update and a report of mortality among Vietnam veterans living in Massachusetts. Agreed that there are no discernible differences in mortality between Ranch Hands and comparisons. The excess of soft tissue sarcoma deaths among Vietnam veterans in Massachusetts was out of context of other soft tissue sarcoma studies, completed and ongoing. No action was suggested because of number of studies to be completed soon. 10 pages.

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
WASHINGTON, D.C. 20503

APR 30 1985

MEMORANDUM FOR : Charles Baker
Chairman, Agent Orange Working Group

FROM : Annette E. Rooney
Member of the Resource Panel
Agent Orange Working Group

SUBJECT : Preliminary Report on Federal Activities and Studies Related to Agent Orange

Enclosed is a preliminary summary report of Federal activities and studies relating to Agent Orange compiled from data submitted last May and subsequently updated.

Data for the Enrivonmental Protection Agency (EPA) for 1985 through 1989 is still under review and a revised submission will be forthcoming, from which a corrected report will be submitted.

This report provides the number of studies and funds provided in fiscal years 1980-1984, 1985, 1986, 1987-1989, and total by agency and type of study. The primary focus of this data collection effort was on studies relating to Agent Orange exposure, with information requested on studies involving herbicides and dioxin. However, this report is not intended to provide a complete accounting of all herbicide- and dioxin-related activities.

During the month of May, I will be asking each agency to verify the information used to generate this report before submitting a final report to you.

Enclosure

APR 30 1990

PRELIMINARY

FEDERAL ACTIVITIES AND STUDIES RELATED TO AGENT ORANGE
(# of activities and thousands of $ by agency and by study type)

	1980-84		1985		1986		1987-89		Total	
AGENCY	#	$	#	$	#	$	#	$	#	$
VA	14	87,287	9	12,738	11	6,160	10	8,814	16	114,999
DOD	11	12,566	12	4,091	10	5,343	9	16,140	15	38,140
HHS	59	10,502	28	3,975	16	2,841	12	3,140	71	20,458
EPA	24	7,313	2	3,350	0	0	0	0	25	10,663
Total	108	117,667	51	24,154	37	14,344	31	28,094	127	184,259

	1980-84		1985		1986		1987		Total	
Study type	#	$	#	$	#	$	#	$	#	$
Agt Orange	28	92,863	14	16,229	13	10,644	11	24,036	32	143,772
Herbicides	5	992	1	50	1	20	0	0	5	1,062
Dioxin	61	16,846	27	7,266	15	2,909	11	3,138	73	30,159
Support	14	6,966	9	609	8	771	9	920	17	9,266
Total	108	117,667	51	24,154	37	14,344	31	28,094	127	184,259

DEPARTMENT OF THE AIR FORCE
HEADQUARTERS UNITED STATES AIR FORCE
BOLLING AFB, D.C. 20332

19 APR 1985

Dr. Peter Beach
AOWG Executive Secretary
Director of Veterans Afairs
Office of the Under Secretary
Room 632-F HHH Building
200 Independence Avenue, S. W.
Washington, D. C. 20201

Dear Dr. Beach

Please find at Attachment 1 a summary of key Air Force Ranch Hand activities since 1983. I have included the Baseline Mortality Report, June 1983, so the series would be complete.

I have also included as additional attachments cover pages and full executive summary of key documents.

Please call me if I can be of any additional assistance.

Sincerely

Robert A Capell

ROBERT A. CAPELL, Lt Col, USAF, BSC
Assistant for Bioenvironmental Engineering
Office of the Surgeon General

5 Attachments
1. Executive Summary
2. Extracts Mortality Baseline Report, 1983
3. Extracts Morbidity Baseline Report - 1984
4. Extracts Mortality Update - 1984
5. Abstract - Reproductive Outcome Draft Report - 1984

Executive Summary

Air Force Ranch Hand Activities

1983 - 1985

1. Report Title: An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides - Baseline Mortality Study Results - 30 June 1983

2. Report Title: An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides - Baseline Morbidity Study Results - 24 February 1984

3. Report Title: An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides - Mortality Update - 1984 - 10 December 1984

4. Report Title: An Epidemiologic, Reproductive Outcome Update - Draft Report-Submission Date - 17 December 1984

PROJECT RANCH HAND II

AN EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDES

BASELINE MORTALITY STUDY RESULTS

30 JUNE 1983

Prepared for:
The Surgeon General
United States Air Force
Washington, D.C. 20314

Approved for public release; distribution unlimited

EPIDEMIOLOGY DIVISION
DATA SCIENCES DIVISION
USAF SCHOOL OF AEROSPACE MEDICINE (AFSC)
BROOKS AIR FORCE BASE, TEXAS 78235

A-1

EXECUTIVE SUMMARY
Baseline Mortality Study

The Ranch Hand II epidemiologic study uses a matched cohort design in a nonconcurrent prospective setting, incorporating mortality, morbidity, and follow-up studies. The purpose of this report is to present the baseline mortality study results.

Since 1979, a detailed population ascertainment process has enumerated a total of 1269 Ranch Hand personnel who served in Vietnam during the period of 1962-1971. As described in the protocol, this total is believed to comprise the entire exposed study population. The eligibility of each Ranch Hander was verified by a hand review of his personnel record. A comparison group was formed by identifying all individuals assigned to selected Air Force organizational units with a mission of flying cargo to, from, and in Vietnam during the same period. All Ranch Hand and comparison subjects designated as killed in action were removed from the study population. By a computerized nearest neighbor selection process, up to 10 comparison individuals were matched to each Ranch Hander by job category, race, and age to the closest month of birth. A hand record review of the matched comparison sets revealed that on the average, 8.2 comparison individuals were fully suitable for study. From each matched comparison set, five individuals were randomly selected for the mortality study, yielding a 1:5 design. Every Ranch Hander and his set of comparisons will be the subjects of annual mortality updates throughout the entire 20 years of the follow-up study so that emerging mortality patterns or disease clusters may be detected with maximal sensitivity. Each living Ranch Hander and his first and willing comparison match were selected to participate in a comprehensive physical examination and an in-home interview; the results of this study will be presented in a subsequent report in late 1983.

A mortality determination on 1,247 Ranch Handers and 6,171 comparison subjects was made, sequentially using the data sources of the Air Force, Veterans Administration, Social Security Administration, Internal Revenue Service, and personal contact efforts. As of December 31, 1982, 50 Ranch Hand and 250 comparison subjects had died (certified on/before April 27, 1983). Death certificates were obtained on all 300 deceased subjects and were coded by an Air Force nosologist (ICD, 9th ED). All codings were verified by the National Center for Health Statistics. Autopsy results are currently being sought for future analyses.

Statistical analyses of noncause specific death emphasized survival curve estimates, linear rank procedures, relative risk estimates, and standardized mortality ratios (SMRs). Cause specific analyses were limited to relative risk estimates because of small cell sizes. In addition to these approaches, three other data bases were contrasted to the Ranch Hand population, where possible; the 1978 US White Male Mortality experience, the 1978 Department of Defense (DoD) Nondisability Retired Life Table, and the mortality experience of the West Point Class of 1956. These additional comparison groups have substantial comparability or sample size limitations, rendering conclusions to the weakest order. Analyses with these "external" comparison groups were accomplished to crudely define the healthy worker effect and to determine if the Ranch Hand group mortality was drastically out of line with that of other military populations.

Data analysis showed that the mortality experience of the Ranch Hand group is nearly identical to that of the comparison group. Analyses showed that officers are living longer than enlisted personnel in both Ranch Hand and comparison groups. This difference between officers and enlisted personnel was statistically significant in the comparison group whereas it was not in the Ranch Hand cohort. A contrast of the Ranch Hand and comparison group to the 1978 DoD Life Table showed significantly less mortality for Ranch Hand officers, comparison officers and comparison enlisted men, however, there was not a statistically significant favorable mortality rate for Ranch Hand enlisted personnel. This pattern of mortality was also seen in a contrast of the Ranch Hand and comparison groups to the 1978 U.S. white male mortality experience. That is, highly favorable mortality differentials for Ranch Hand officers, comparison officers and comparison enlisted personnel were observed, but not for Ranch Hand enlisted. This trend is consistent with the self perceptions of differential herbicide exposures reported by many of the Ranch Hand subjects. The reason(s) for these observations are speculative at present, but may include the related items of sample size, socioeconomic differences, access to medical care, and health education and possible herbicide effects. Cause specific analyses were statistically nonsignificant. The Ranch Handers showed a relative paucity of overall cancer but an excess of digestive disorder deaths, both statistically nonsignificant. No soft tissue sarcoma deaths were detected in either group. Analyses of both the Ranch Hand and the comparison groups to the 1978 US White male mortality experience showed highly significant favorable findings. Most of these differences are speculatively attributed to the healthy worker effect. A contrast of the Ranch Hand and comparison groups to the 1978 DoD Life Table showed significantly less mortality for Ranch Hand officers and comparison officers and enlisted men. The West Point comparison showed nonsignificant SMRs of 0.530 and 0.778 for the Ranch Hand officers and the comparison group officers, respectively. Overall, the limitations of the statistical power calculations in most of these analyses were substantial in most analyses due to 1) the low mortality rate (4%) in the Ranch Hand and comparison groups to date, 2) the inherently small group of Ranch Handers (as described in the study protocol), and 3) the observed relative risks which approached unity in most categories.

This baseline mortality report can in no way be regarded as conclusively negative because this small, young, and relatively healthy cohort may not have yet reached the latency period wherein attributable fatal disease might be expected and detected within limited power boundaries of this study. Future commitments for the annual mortality updates include detailed covariate analyses for disease risk factors, herbicide exposure, and confounding industrial chemical exposures. Further, subsequent morbidity reports will include full spectrum, disease specific analyses, e.g., cancer (fatal, ongoing, cured) in an effort to enhance study sensitivity to emerging herbicide effects, if they occur.

AIR FORCE HEALTH STUDY
(PROJECT RANCH HAND II)

AN EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDES

BASELINE MORBIDITY STUDY RESULTS

24 FEBRUARY 1984

Prepared for:
The Surgeon General
United States Air Force
Washington, D.C. 20314

George D. Lathrop, Colonel, USAF, MC
William H. Wolfe, Lieutenant Colonel, USAF, MC
Richard A. Albanese, M.D., GM-15
Patricia M. Moynahan, Colonel, USAF, NC

Approved for public release; distribution unlimited.

USAF SCHOOL OF AEROSPACE MEDICINE
Aerospace Medical Division (AFSC)
Brooks Air Force Base, Texas 78235

EXECUTIVE SUMMARY

BASELINE MORBIDITY STUDY

The Ranch Hand II epidemiologic study uses a matched cohort design in a nonconcurrent prospective setting, and incorporates mortality, morbidity, and follow-up studies. The purpose of this report is to present the baseline morbidity study.

The morbidity study design matched each living Ranch Hander (by age, job, and race) to the first living and compliant member of a randomly selected comparison mortality set of 5 individuals, producing a 1:1 contrast. The comparison group was formed from numerous flying organizations which transported cargo to, from, and within Vietnam, but were not involved in aerial spray operations of Herbicide Orange. Of the potential study participants, 99.5% were located. Early in the physical examination phase of the study, it was discovered that 18% of the entire comparison group was ineligible to participate because of inappropriate selection. Thereafter, study eligibility was certified only after a hand-review of personnel records. Next-in-line compliant comparisons entered the study as replacements after fully completing the questionnaire and physical examination. Statistical analyses of these replacement individuals later showed that they differed from the original comparisons in a variety of subtle and often opposite ways. As a conservative measure to avoid possible bias by the inclusion of the replacements in the analyses, a management decision was made to base the statistical tests in this report primarily upon contrasts of the Ranch Hand group to the original comparison group.

The preponderance of data was obtained from the in-home interviews and the physical examination, each conducted under contract to the Air Force by Louis Harris and Associates, Inc., New York NY, and the Kelsey-Seybold Clinic, P.A., Houston TX, respectively. All contacts with the participants were carried out with utmost professionalism and sensitivity. Other morbidity data sources included reviews of medical records, military personnel documents, and birth certificates; in-home questionnaires and telephone questionnaires of the study participant's wives, former wives and, occasionally, their next-of-kin. All aspects of the study were voluntary. As a contract requirement, data collection personnel were blind as to the exposure status of the participants. Ninety-seven percent of the Ranch Handers and 93% of the comparisons participated in the in-home interview. For the physical examination, 87% of the Ranch Handers and 76% of the comparison group participated, a total of 2,272 individuals. This differential attendance at the examination may have introduced a potential participation bias that, in a military population predominantly engaged in flying duties, is multifactorial and complex. All study phases were monitored by stringent quality control standards. Statistical analyses of the data consisted primarily of log-linear models, logistic regression techniques, generalized linear models, matched covariate analyses, and Kolmogorov-Smirnov, chi-square, and t tests.

The physical examination and the in-home questionnaire data were analyzed by major organ system. In terms of general health, more Ranch Handers perceived themselves to be in fair or poor health than did their comparisons. No

group differences were detected for hematocrit or percent body fat determinations. Unadjusted group differences in sedimentation rate were not observed; however, significantly more young comparisons had abnormalities in sedimentation rate than did their Ranch Hand counterparts. There were no statistically significant differences in the occurrence of malignant or benign systemic tumors between the groups. One case of soft tissue sarcoma was found in a comparison member. Significantly more nonmelanotic skin cancer was noted in the Ranch Hand group, but these analyses have not yet considered (adjusted for) sunlight exposure, the prime etiology of these cancers. Such nonmelanotic skin cancer (predominantly basal cell carcinoma) is the most common neoplasm in the White population of the United States. Up to the statistical limits of the study there were no consistent data that showed that the Ranch Handers were developing uncommon cancers, or cancer in unusual sites, or at an unusual age. Measures of fertility and reproductive outcome showed mixed results. It is emphasized that the fertility and reproductive results are preliminary at this time as they are based largely upon subjective self reports that await full medical record and birth certificate verification. Four measures of fertility: number of childless marriages, couples with the desired number of children, the infertility index and the fertility index, showed no difference between the Ranch Hand and comparison groups. A semen specimen obtained from those willing and able to provide one showed no group differences with respect to total sperm count or percent abnormal sperm. There were no significant findings in conception outcomes for miscarriages, stillbirths, induced abortions, or live births. For live birth outcomes no differences were observed for prematurity, learning disability, or infant deaths. There was no significant disparity between groups for the classifications of severe or moderate birth defects. By parental history, however, Ranch Hand offspring showed significantly more minor birth defects (birth marks, etc). Reported neonatal deaths and physical handicaps were also significantly excessive in the Ranch Hand group when contrasted to the total comparison group. All fertility and reproductive findings in the Ranch Hand group showed inconsistent relationships to the herbicide exposure index. Medical records and birth certificates are currently being chronicled for complete verification of all historical findings. A comprehensive neurological examination showed no consistent abnormalities in the cranial nerves, peripheral nerves or central nervous system function of the Ranch Handers. As expected, there was a profound influence of diabetes and alcohol in both groups upon numerous neurological tests. Detailed psychologic data were obtained on all participants at both the in-home interview and the physical examination. It is emphasized that the majority of psychological data was derived from self reported responses during interview and has not been fully assessed for the effect of differential reporting. A variety of subjective deficits (fatigue, anger, fear, anxiety, etc) were significantly more common in the high school educated Ranch Handers. Educational level significantly and consistently influenced most subjective test results. In sharp contrast, more objective performance testing by the Halstead-Reitan battery and IQ testing did not reveal any significant intergroup differences. The roles of overreporting and the Post Vietnam Stress Syndrome in these analyses have not as yet been assessed. Liver function tests and clinical history data showed mixed results. Ranch Handers had some elevated liver enzyme tests and lower cholesterol levels. More Ranch Handers were found to have hepatomegaly and verified histories of prior hepatic disease than their counterpart comparisons. Exposure to alcohol, degreasing chemicals, and industrial chemicals in general, influenced

the liver test results. Ranch Handers reported significantly more symptoms resembling porphyria cutanea tarda than the comparisons, but these data have not been verified by medical record reviews nor were they substantiated by laboratory testing or by physical examination. Exposure index analyses were essentially negative. In the dermatologic evaluation, no cases of chloracne were diagnosed clinically or by biopsy. A thorough questionnaire analysis of acne showed that the incidence, severity, duration, and anatomic location did not differ between groups, and suggested that the historical occurrence of chloracne was highly unlikely in the Ranch Handers. Evaluation of the cardiovascular system showed equal proportions of abnormalities in blood pressures, electrocardiograms, past electrocardiograms, and heart sounds in both groups. Ranch Handers are not having premature heart attacks or generalized heart disease. However, the Ranch Handers showed significant deficits in 2 specific peripheral leg pulses and all leg pulses as a group. These puzzling findings were highly correlated with age and smoking patterns, and verified past heart disease. The assessment of the immune system by laboratory testing was compromised by excessive test variability. An independent review committee determined which test data were suitable for statistical analysis. As an unexpected finding, the test data were significantly influenced by the age and smoking history of the participant; no group differences were detected after adjustment for these factors. A hematologic test battery revealed three red cell abnormalities in the Ranch Hand group, but these were difficult to place into a clinical or epidemiologic context. Evaluation of renal, pulmonary, and endocrine functions generally disclosed small and inconsistent proportions of abnormalities between groups, and were deemed clinically unimportant. An unrefined assessment of all summed and weighted organ system abnormalities by group did not show an aggregation of multisystem disease or malfunction.

Any interpretation of these study data, in whole or in part, must carefully consider the methodical steps required for a proper inference of causality. It is specifically pointed out that many group differences were largely based upon subjective data, and that a subtle effect of differential reporting is suggested but has not been fully evaluated. For objective data, group differences were generally within normal ranges and were not correlated to the herbicide exposure index, nor fell within the expected latency periods following Vietnam service. The proposed clinical end points of dioxin exposure, chloracne, soft tissue sarcoma, and porphyria cutanea tarda, were not found in the Ranch Hand group (study power limitations recognized). Overall, substantial credence is given to the objective study findings, particularly after observing the consistent duplication of the classical effects of risk factors such as age, smoking, alcohol, etc., in almost all clinical areas. Additional work with these baseline data is still required in the areas of data base refinement, statistical testing and bias analysis, exposure index refinement, establishment of the follow-up examination requirements, and collaboration with other dioxin research studies.

This baseline report concludes that there is insufficient evidence to support a cause and effect relationship between herbicide exposure and adverse health in the Ranch Hand group at this time. The study has disclosed numerous medical findings, mostly of a minor or undetermined nature, that require detailed follow-up. In full context, the baseline study results should be viewed as reassuring to the Ranch Handers and their families at this time.

PROJECT RANCH HAND II

AN EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDES

MORTALITY UPDATE - 1984

10 DECEMBER 84

William H. Wolfe, Colonel, USAF, MC

Joel E. Michalek, PhD

Richard A. Albanese, M.D.

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Patricia M. Moynahan, Colonel, USAF, NC

Prepared for:
The Surgeon General
United States Air Force
Washington, D.C. 20314

EPIDEMIOLOGY DIVISION
DATA SCIENCES DIVISION
USAF SCHOOL OF AEROSPACE MEDICINE (AFSC)
BROOKS AIR FORCE BASE, TEXAS 78235

Project Ranch Hand II Mortality Update - 1984

EXECUTIVE SUMMARY

BACKGROUND

The purpose of the Ranch Hand II Study is to determine whether those individuals involved in the aerial spraying of herbicides in Vietnam during the Ranch Hand operation have experienced any adverse health effects as a result of their participation in that program. The study evaluates both mortality (death) and morbidity (disease) in these individuals over a 20-year period of time after the studies were initiated.

The baseline mortality study was released in June 1983 and the baseline morbidity study in February 1984. Neither study demonstrated health effects which could be conclusively attributed to herbicide or dioxin exposure. The reader is referred to reports of the studies for further details (1, 12).

METHOD

The present study report describes the second mortality analyses. Deaths in the 1256 Ranch Hand and 6171 comparison subjects were determined, using the data sources of the Air Force, Veterans Administration, Social Security Administration, Internal Revenue Service, and personal contacts. As of 31 December 1983, 54 Ranch Handers and 265 comparison subjects had died. Death certificates were obtained on all subjects. Autopsies were conducted on 157 of the individuals who had died. Results have been obtained for 104 of these autopsies to confirm the death certificate findings. Autopsy reports for the 53 others have been requested, but have not yet been obtained.

Extensive statistical analyses were accomplished, as detailed in the report, to compare the death experience in the Ranch Hand population with the comparison group. In addition, death experience in these groups was compared to the 1978 U.S. White Male Mortality experience, the 1978 Department of Defense Nondisability Retired Life Table, the mortality experience of the West Point Class of 1956, the USAF active duty personnel, and the active U.S. Civil Service population.

RESULTS

As was the case in the first mortality report, the current mortality analyses did not reveal any statistically significant differences in mortality between the exposed and comparison groups. The percentages dead in each major category are summarized below.

	Percent Deaths	
	Ranch Hand	Comparison
Rank		
Officers	3.2	4.0
Enlisted	4.9	4.5
Occupation		
Flying	3.6	4.7
Ground	5.1	3.9

Note: None of the above differences between the Ranch Hand and Comparison groups are statistically significant.

	Ranch Hand	Comparison
Total Overall	4.3	4.3

As was reported in the baseline mortality study, the Ranch Hand officers had a nonstatistically significant though slightly lower death rate than their comparisons, Ranch Hand flyers had a nonstatistically significant though slightly lower death rate than comparisons, and Ranch Hand ground personnel had a slightly higher but nonstatistically significant death rate than the comparisons.

The herbicide/dioxin exposure index described in the morbidity report was applied to the data, and no relationship between exposure and mortality experience was identified.

As was also noted in the baseline mortality study, analyses consistently demonstrated significantly better survival in the Ranch Hand officers than Ranch Hand enlisted members, as was the case with comparison officers and comparison enlisted personnel. Cause-specific analyses did not demonstrate any increased Ranch Hand mortality for accidents, suicide, homicide, malignancy or circulatory system disease. No unusual patterns of malignancy were observed in either the Ranch Hand or comparison groups, a finding which would be expected from the small number of deaths to date.

When compared to the 1978 U.S. White male population, the Ranch Hand officers, comparison officers, and comparison enlisted are living significantly longer than expected. Although Ranch Hand enlisted are also living longer, the difference is not significant. A similar pattern was seen in analyses using the DOD retired population. All groups had a mortality experience similar to the civil service population. As would be expected from the fact that individuals in the active duty population who develop severe chronic disease are medically retired, all groups in this study had an increased mortality when compared to the Air Force population currently on active duty. Both Ranch Hand and comparison officers had mortality similar to the West Point group.

CONCLUSION AND RECOMMENDATION

Continued mortality surveillance is recommended, since the study groups are still relatively young and healthy. While sufficient time may have elapsed for some clinically significant conditions to occur, additional time is necessary for other conditions, which may possibly be attributable to herbicide exposure, to develop. At this time, however, there is no evidence of increased mortality as a result of herbicide exposure in those individuals who accomplished the Ranch Hand spray operations in Vietnam.

ABSTRACT OF REPRODUCTIVE OUTCOME

DRAFT REPORT, 17 December 1984

Abstract:

This report was written in response to requests from the Office of Science and Technology Policy, the Chair - Agent Orange Working Group and by direction of the Air Force Deputy Surgeon General. It was intended as an "interim" analysis of the data and not as a definitive answer to the birth defects issue.

Since the release of the baseline morbidity report in February 1984, birth defects and neonatal deaths reported by study participants during the baseline questionnaire have been verified by record review. This verification was accomplished by the review of birth and other medical records, birth certificates and death certificates. Since not all data can be verified for at least an additional 24 months, these interim analyses were based on the verification of the positive reports only. Verification of negative responses to the birth defect and neonatal death questions have not as yet been completed.

The draft report was submitted to the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants. Their comments have been received and will be discussed with them in a forthcoming visit to the Ranch Hand Office. This interim assessment will then be forwarded to the OSTP through the Chair, AOWG.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date APR 26 1985

From Director, National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control (CDC)

Subject Status Report

To Peter E. M. Beach, Ph.D.
Executive Secretary, Cabinet Council Agent Orange Working Group
Office of the Secretary

This is in response to your request of April 9 for a brief accomplishment summary and update of NIOSH research, activities, Congressional testimony, and/or published findings since 1983. Attached is a chart which summarizes our research in the format provided by the Cabinet Council Agent Orange Working Group.

A. Research

1. A major effort has been devoted to the NIOSH Dioxin Registry and Mortality Study of 6,000 production workers at 14 companies. This study will be completed in FY 1986.

2. A morbidity study of workers from two companies and of appropriate comparison groups has been designed and reviewed by peer reviewers and by the Science Panel of AOWG. This study, which will begin in late FY 1985 or early FY 1986, will include complete medical examinations of the workers and the comparison persons. It will also include a questionnaire survey of workers' wives to address reproductive outcomes.

B. Activities

Medical officers and industrial hygienists of NIOSH's Hazard Evaluation and Technical Assistance Branch have provided assistance to employees, companies, Federal and State agencies regarding the types of protection needed by workers involved in the cleanup of dioxin-contaminated sites and the safety of workers employed at companies in which dioxin was found in buildings and soil. A NIOSH Current Intelligence Bulletin was issued which summarizes research, the currently known hazards, and NIOSH recommendations regarding the isomer (attached).

C. Congressional Testimony

No new testimony was delivered after 1983.

D. Published Findings (attached)

An Evaluation of Reports of Dioxin Exposure and Soft Tissue Sarcoma Pathology in U. S. Chemical Workers. Fingerhut M, Halperin W, Honchar P, Smith AB, Groth D, and WO Russell. In Banbury Report 18: Biological Mechanisms of Dioxin Action, 1984, Cold Spring Harbor Laboratory.

An Evaluation of Reports of Dioxin Exposure and Soft Tissue Sarcoma Pathology Among Chemical Workers in the United States. Fingerhut M, Halperin W, Honchar P, Smith AB, Groth D, and WO Russell; Scand. J. Work Environ. Health 10 (1984) 299-303.

The NIOSH Occupational Dioxin Registry. Fingerhut M, Marlow D, Honchar P, Halperin W. In Public Health Risks of the Dioxins, Proceedings of a Symposium. 1984. The Rockefeller University, New York City.

Review of Exposures and Pathology Data for Seven Cases Reported as Soft Tissue Sarcoma Among Persons Occupationally Exposed to Dioxin-Contaminated Herbicides. Fingerhut M, Halperin W, Honchar P, Smith AB, Groth D, and W Russell. In Public Health Risks of the Dioxins, Proceedings of a Symposium. 1984. The Rockefeller University, New York City.

A Case-Control Study of Leukemia Among Federal Employees at the Blue Grass Ordnance Depot. (Internal Report - available through National Technical Information Service.) Fingerhut M, Honchar P, Skaggs J, and J Bothe.

J. Donald Millar, M.D.
Assistant Surgeon General

7 Attachments

FEDERALLY SPONSORED HUMAN STUDIES RELATED TO AGENT ORANGE

Agency Study Title	Type of Study: Mortality	Morbidity	Cancer	Reproduction	Analytical	Status: Completed	Ongoing	Estimated Completion Date
NIOSH								
Dioxn Registry and Mortality Study	X		X				X	1986
Dioxin Morbidity Study		X	X	X			To begin late FY85 or early FY86	1989
Technical Assistance to Employees, Companies, Agencies, States		X					X As needed	
Soft Tissue Investigation						X		1984
Investigation of leukemia cluster in Madison County, Kentucky						X		1984

DEPARTMENT OF THE ARMY
US ARMY & JOINT SERVICES ENVIRONMENTAL SUPPORT GROUP
1730 K STREET N.W. ROOM 210
WASHINGTON, DC 20006-3868

REPLY TO
ATTENTION OF

DAAG-ESG 30 April 1985

MEMORANDUM FOR EXECUTIVE SECRETARY CABINET COUNCIL AGENT ORANGE WORKING GROUP

SUBJECT: Status Report

Please find attached an Executive Summary (1 page) and a narrative description of the significant activities of the U.S. Army and Joint Services Environmental Support group. The period covered is from 1 August 1983 to 30 April 1985.

R. S. Christian

RICHARD S. CHRISTIAN
Director

Encl
as

EXECUTIVE SUMMARY

29 April 1985

DoD/ESG Status Report. Since August 1983 the Department of Defense has supported the Agent Orange Working Group in the following subject areas:

- Abstraction of Personnel Data
- Support for VA & VARO adjudication cases
- CDC Sponsored health studies
- Federal Court Litigation
- Congressional Requests for data
- Vietnam Veteran requests for data

R.S. CHRISTIAN/DAAG-ESG/653-1829

Significant Activities of the U.S. Army and Joint Services Environmental Support Group (ESG) 1 August 1983 to 30 April 1985

1. Background. The Army Agent Orange Task Force (AAOTF) was created on 21 May 1980, and is within the command structure of the U.S. Army's The Adjutant General (TAG). On 26 April 1982, The Secretary of Defense designated the U.S. Army as lead agency for all Department of Defense (DoD) initiatives and responses concerning the on-going controversy and resulting studies stemming from the use of herbicides in the Vietnam War. January 1984, the AAOTF and Army Nuclear Test Personnel Review were administratively combined as the U.S. Army and Joint Services Environmental Support Group, reporting directly to The Adjutant General.

2. One of the conditions frequently reported by Vietnam veterans is a broad-ranging psychological unrest related to their war experiences which has, in many cases, greatly disrupted their lives. The diagnosis has been reorganized by the medical community and is classified as Post Traumatic Stress Disorder (PTSD). Symptoms vary, but include bitterness, alienation, sleeplessness, inability to develop close relationships, guilt at having survived an experience that many did not, flashbacks to combat situations and serious consideration to suicide, as well as drug and alcohol abuse. The expansion of ESG responsibilty grew rapidly in the spring of 1983 when the VA Administrator, the Honorable Harry N. Walters, requested that the Secretary of Defense provide data needed to adjudicate VA cases. By the end of 1983, over 174 PTSD cases had been received by ESG. The number of cases has continued to grow through 1984 and on into 1985. For calendar year 1984 some 364 cases had been received and since the start of the calendar year 1985, some 185 cases have been received. Further, the average case takes 20 hours per research to review.

3. The CDC Birth Defects Study was to determine whether Vietnam veterans exposed to Agent Orange had a greater likelihood than those not exposed, of fathering a child with a birth defect. The ESG provided CDC with exposure opportunities on 526 thoroughly researched individual cases. On 15 August 1984 CDC released the Birth Defects Study.

4. In addition to the work stated above, ESG continues to play a vital role in providing military data for scientific studies. They include the VA Mortality Study; a study comparing the mortality experience of Vietnam veterans with Vietnam era veterans who did not serve in Vietnam, a Soft Tissue Sarcoma Study; case-control study of tissue sarcoma (a rare cancer); and Armed Forces Institute of Pathology (AFIP), studying the relationship between various medical diagnosis and service in Vietnam. Since 1983 the ESG has worked closely with the Armed Forces Institute of Pathology by verifying service participation of over 2700 individuals. And in coordination with the VA's chloracne study on Vietnam veterans the ESG has provided detailed information on all requests made (13).

5. In response to Senator Cranston's questions at Senate hearings during the spring of 1983, the ESG conducted a search of service personnel and organizational records to determine how many women served in Vietnam. The search revealed that the women who served in Vietnam could be broken down as follows: Army 4675, Navy 423, Marine Corps 36, and Air Force 771. On 27 March 1984 we provided the Senator the above figures.

6. During the spring of 1983 ESG began to gear up for its support of CDC when then the draft protocol for the Agent Orange studies was released. During the rest of the year coordinated work between ESG and CDC proceeded at a steady pace. An ESG team went to the National Personnel Records Center in St. Louis during August 1983 and randomly selected groupings of Vietnam era personnel service records. This was done to develop study and control cohorts for CDC's pilot Vietnam experience study. The study was completed and forwarded to CDC in 29 September 1983. Also, initial ESG pre-test activities were began under the CDC Agent Orange study. A prototype battalion study was computed and provided CDC on 12 October 1983. By 1 March 1984 initiation of ESG support for the CDC's Agent Orange studies began and through out the year meetings were held to define many research details and to develop quality control standards. ESG completed research for the Vietnam Experience Study by examing 47,850 records qualifying 23,824 on 9 April 1985. To date 33 Battalions including the companies have been researched for tracking covering a 2 year period between 1967 and 1968.

7. Since August 1983 litigation publicity and its side effects in the media have left its mark on ESG. Seemingly, each time a court room event occurred there would be a measurable surge in correspondence inquires from Vietnam veterans and veteran organizations.

8. Early 1984 saw ESG heavy into litigation support. Between 29 February 1984 and 9 March 1984 15 attorneys and para-legals involved in Agent Orange related litigation worked on ESG furnished documents. They reviewed and copied records pertinent to litigation being heard in the Eastern District Court of New York. In May of 1984 a settlement was worked out between veterans and chemical companies. The decision triggered an avalanche of requests for information from the veterans and continues to date.

9. Agent Orange requests for assistance from veterans totaled 5,384 for the year 1984 and 5,000 for 1985 (through 15 April).

10. On 19 December 1983, Congressman Fortney H. (Pete) Stark, CA, wrote to Secretary of the Army Honorable John O. Marsh, Jr. requesting Department of the Army assistance in locating veterans who served with the 570th Supply Company, Long Binh, Republic of Vietnam and who may have been involved in fighting the chemical fire that occurred in November 1967. His objective was to have a health poll conducted on those veterans to see if they suffer any adverse health effects as a result of exposure to those chemicals. The Adjutant General's Office (ESG) assigned action to conduct research into the unit and personnel records of the 570th in an attempt to:

(1) determine which individuals were with the unit at the time of the fire and (2) provide home addresses of those individuals. An extensive research effort ensued (320+ man hours) culminating in TAGO providing a roster of all individuals assigned to the 570th, identifying those who were with the unit at the time of the fire, and providing last known home addresses. At the request of Congressman Stark, this data was provided to the VA who was tasked with conducting the health survey/poll. On 28 March 1985 TAGO provided a final response to Congressman Stark.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 22 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Dr. Peter Beach
AOWG Executive Secretary
Room 632-F
Hubert H. Humphrey Building
200 Independence Avenue, N.W.
Washington, D. C. 20201

Dear Peter:

Attached you will find a draft of the EPA response to your request for an agency update on activities related to the work of AOWG.

As you know, we have collectively run around the block several times in various attempts to identify the breadth of activities which are of concern to AOWG. In the strictest sense, EPA has no activities that deal with Agent Orange. In the broadest sense, we have a large number of activities associated with phenoxy herbicides and their contaminants.

In the attached, I have tried to summarize our activities in a format that highlights those that are most relevant to the concerns of AOWG. I would appreciate feedback from you as to the breadth and depth of what is presented here. With such guidance, we will be able to provide you the best type of report to meet your needs.

Sincerely yours,

Donald G. Barnes
Science Advisor to the
Assistant Administrator
for Pesticides
and Toxic Substances

Enclosure

UPDATE ON ACTIVITIES OF INTEREST TO
THE AGENT ORANGE WORK GROUP (AOWG)

The Environmental Protection Agency

EXECUTIVE SUMMARY

While EPA has never had any direct involvement with Agent Orange, during the past two years the Agency's involvement with 2,3,7,8-TCDD and other "dioxins" broadened and deepened.

The long-running legal proceedings over the herbicide 2,4,5-T, and its 2,3,7,8-TCDD contaminant, ended with the cancellation of all registrations for manufacture and use of 2,4,5-T in this country.

The national concerns raised by the discovery of 2,3,7,8-TCDD in Times Beach, Missouri and elsewhere are being addressed in a National Dioxin Study, scheduled for completion in December, 1985. By that time, thousands of samples will have been collected and analyzed in an attempt to assess the presence and significance of 2,3,7,8-TCDD and certain other "dioxins" in the US environment.

Research continues in the areas of health effects and risk assessment, environmental effects, control/disposal technologies and monitoring. The goal is to provide more precise information about the risks posed by the presence of CDDs and CDFs in the environment.

In addition, the Agency has taken regulatory action on certain pesticides and industrial wastes which are contaminated with CDDs and CDFs. Current plans call for examining additional commercial chemicals for the presence of these substances. A major petition from environmentalists, calling for the Agency to increase its activities in the area of "dioxins", is now a matter of discussion in court.

UPDATE ON ACTIVITIES OF INTEREST TO
THE AGENT ORANGE WORK GROUP (AOWG)

The Environmental Protection Agency
April, 1985

I. Introduction

The Environmental Protection Agency (EPA) has been involved with the deliberations of the AOWG since the work group was first formed in 1979. While EPA has never dealt with Agent Orange (AO) per se, the Agency regulates the domestic production and use of the components of AO; specifically, 2,4,5-trichlorphenoxyacetic acid (2,4,5-T) and 2,4-dichlorophenoxyacetic acid (2,4-D). It is 2,4,5-T that is contaminated with 2,3,7,8-tetratchlorodibenzo-p-dioxin (2,3,7,8-TCDD). 2,3,7,8-TCDD, in turn, exhibits a range of toxic effects in animal studies at quite low doses and has been a focus of concern relative to exposure to AO. 2,3,7,8-TCDD is sometimes referred to "dioxin", an inexact term that invites and receives misinterpretation.

EPA has been involved with 2,4,5-T and 2,3,7,8-TCDD since the early 1970s. In 1979, the Agency issued an emergency suspension against the use of 2,4,5-T on forests and rights-of-way, due to the concern for the potential for adverse health effects associated with exposure to 2,4,5-T and its 2,3,7,8-TCDD contaminant. In 1980, an administrative hearing was initiated under procedures outlined in the Federal Insecticide, Fungicide and Rodenticide Act to examine the Agency's proposal to cancel all registrations of 2,4,5-T (and silvex, a related herbicide, which is also contaminated with 2,3,7,8-TCDD).

In the late 1970s and early 1980s, the Agency became aware that a range of chlorinated dibenzo-p-dioxins (CDDs) and dibenzofurans (CDFs) were associated with the emission of certain combustion sources and other chemical compounds; e.g., municipal waste combustion and incinceration of polychlorinated biphenyls (PCBs). Despite results of studies on these two combustion sources in the early 1980s, concerns about CDDs/CDFs and combustion remained.

During the early 1980s, the Agency began a series of investigations of sites in the state of Missouri where 2,3,7,8-TCDD contaminated waste oil had been sprayed as a dust control agent. The discovery of dozens of such contaminated sites raised the question of appropriate methods of clean-up and disposal. In addition, concerns were expressed elsewhere in the country that "other Missouris" might exist and should be investigated. These concerns resulted in the formation of a Dioxin Strategy and its implementation in the National Dioxin Study.

Buttressing all of these activities has been an active research program aimed at answering questions related to the

detection of CDDs/CDFs in the environment, an assessment of the human health and environmental risks posed by the materials, and approaches to cleaning up the environment once CDD/CDF contamination has been found.

A number of other matters related to CDDs/CDFs have occurred during the past two years which have a less direct bearing on the concerns of AOWG; e.g.,

a. the Agency's regulatory actions on pentachlorophenol
b. the Agency's regulatory actions on wastes containing CDDs and CDFs
c. the Agency's response to a petition by the Environmental Defense Fund and the National Wildlife Federation.

II. 2,4,5-T Hearings

In _____, 19__, the Dow Chemical Co., principal party in the 2,4,5-T cancellation hearings announced that it was dropping out of the hearings, voluntarily requesting that the Agency cancel all its registrations for 2,4,5-T and silvex. In February, 1985 the presiding judge found that there was no longer an active party to contest the cancellation; therefore, he ruled in favor of the Agency so that there are no longer any registrations for the production and use of 2,4,5-T in the country. (Some provision was included in the judgment that permits the use of existing stocks.)

It should be noted that despite the presentation of risk-based information over a period of many years, the proceedings terminated without a ruling on the merits of the case. Therefore, the scientific issues remain.

III. National Dioxin Study

In December, 1983 the Agency released its Dioxin Strategy, the major focus of which was 2,3,7,8-TCDD. It contains seven "tiers" of activities designed to assess the impact of 2,3,7,8-TCDD in the U.S. environment. High priority is given to sites of previous manufacturing, processing and formulation of 2,3,7,8-TCDD containing chemicals, such as 2,4,5-T, and includes the investigation of disposal of any associated wastes. Also included are sites where these chemicals were previously used. An important feature of the Strategy is the study of "background levels" of 2,3,7,8-TCDD in the environment; e.g., soils and fish. The issue of CDDs/CDFs from combustion sources is also addressed through the investigation of a range of combustion sources which have not been examined previously. This will provide a context in which to assess the significance of the known presence of CDDs/CDFs in the combustion of municipal wastes.

During 1984 and 1985, the Agency has been implementing the Dioxin Strategy through the conduct of the National Dioxin Study. This Study will culminate in a report to Congress in December, 1985. EPA headquarters is coordinating the collection of thousands of samples by its regional offices for analysis for the presence of 2,3,7,8-TCDD. To date, ___ manufacturing sites

have been examined with about __% of them revealing detectable levels of 2,3,7,8-TCDD, at a level of detection of _____. Samples have included soil, fish, air, wildlife, and wastes. Sites which are found to be contaminated to levels of concern will be directed to our Superfund program for further consideration.

As a special study affiliated with the National Dioxin Study, our Chicago office, in with the State of Michigan and the Dow Chemical Co., conducted an investigation of possible 2,3,7,8-TCDD contamination in Midland, Michigan, one of the sites of previous manufacture of chemicals contaminated with 2,3,7,8-TCDD. Assessment of the data from this study by CDC and EPA resulted in an announcement in March, 1985 that none of the public areas of Midland examined were currently contaminated at levels of 2,3,7,8-TCDD which raise special concerns.

IV. Research

In conjunction with the National Dioxin Study, the Agency has expanded its breadth and depth of studies related to CDDs and CDFs.

A. Health Effects and Risk Assessment

While much is known about the effects of 2,3,7,8-TCDD, the Agency is looking in greater detail at the way in which this chemical is manifests its toxicity. Using monkeys a model, EPA is examining the extent and rate of distribution of 2,3,7,8-TCDD throughout the body, including pregnant females and their off-spring. Through the Superfund program, EPA is providing funding to NIOSH for the conduct of epidemiological studies of individuals who have been involved with the manufacture of 2,3,7,8-TCDD contaminated chemicals. Further, the Agency is exploring methods for assessing the significance of CDDs and CDFs other than 2,3,7,8-TCDD. This accumulating knowledge about CDDs and CDFs is being synthesized into hazard assessment documents which, when coupled with suggestions for estimating the extent of exposure in different situations, will provide guidance on assessing the risks associated with exposures to these compounds.

This range of activities from animal studies to human studies to risk assessment methodology should provide the Agency with a firmer base for drawing conclusions about the likely health affects that might be seen in exposed populations as a consequence of CDDs and CDFs.

B. Environmental Effects

Within the past two years, conflicting data have been published regarding the bioavailability of the 2,3,7,8-TCDD in contaminated soil. EPA has funded additional work in an attempt to resolve this issue. Further, the Agency sponsored a workshop for outside experts who were charged with developing a research agenda to fill in the gaps that exist in our knowledge about the transport, fate, and effects of 2,3,7,8-TCDD in the environment. Uptake studies have already begun using plants, fish, and large

animals. In the case of fish, the Agency has published results showing that fish exposed to incinerator flyash that is contaminated with the entire range of CDDs and CDFs will selectively absorb and/or retain 2,3,7,8-TCDD. Given EPA's special concerns with dumpsites, the Agency is funding studies to investigate the potential of 2,3,7,8-TCDD to leach through soil.

These studies are designed to provide information on what might happen to 2,3,7,8-TCDD once it enters the environment, with an emphasis on how it might indirectly reach humans.

C. Control/destruction technologies

As noted above, EPA is confronted with serious problems once 2,3,7,8-TCDD (and other CDDs and CDFs) are identified in the environment. Means must be available to isolate or reclaim the contaminated area in an acceptable manner. Approaches which are being considered include the following:

1. Combined treatment with UV radiation and chemical detoxification
2. Field testing of high temperature incineration
3. Investigation of in-situ stabilization techniques
4. Applicability of abandoned mines as repositories

The goal of this research is to expand the arsenal of safe and effective methods for disposing of CDDs/CDFs once they are found.

D. Monitoring methods

The basis of most quantitative information about CDDs and CDFs in the environment is analytical results. Since the levels of these substances in the environment are generally so low, it is important to have proven methods of analysis which are both sensitive and selective.

To this end, EPA, a leader in the development of the gas chromatography/mass spectroscopy method of analysis that is the state-of-the-art today, is adapting those procedures to quantify 2,3,7,8-TCDD and other CDDs and CDFs in a variety of matrices, including wastes and human adipose tissue. In addition, work continues on the development of sensitive, inexpensive method of analysis based on monoclonal antibodies.

V. Other matters

During 1984, EPA took regulatory action under FIFRA to limit the amount of HxCDD found as a contaminant in the widely used wood preservative, pentachlorophenol (PCP). In a separate, but related, action the Agency has listed wastes from certain chemical production/formulation processes which, because they are likely to give rise to CDDs and/or CDFs, are subject to special handling and disposal requirements under the Resource Conservation and Recovery Act (RCRA).

In 1984, the Environmental Defense Fund (EDF) and the National Wildlife Federation (NWF) petitioned the Agency to take a broad range of actions related to CDDs and CDFs. The Agency responded by denying most points of the petition on the technical

grounds, noting, however, that many of the concerns were already being addressed. For example, EPA is investigating other commercial chemicals which might be contaminated with chlorinated and/or brominated dibenzo-p-dioxins and dibenzofurans. EDF and NWF have since filed suit in Federal court to pursue their petition.

ACTION

WASHINGTON, D.C. 20525

April 15, 1985

MEMORANDUM

TO : Dr. Peter Beach, Chairman
Cabinet Council Agent Orange Working Group

FROM : Tom Carhart, Director
Veterans Grants

SUBJECT: Status Report

We have, to date, performed no direct activities or research, provided no Congressional Testimony or published no findings on the subject of Agent Orange. However, there are 48 subsidiary VVLP organizations located across the country, formerly funded by HHS, and DOL. Many of these private corporations are actively involved in disseminating information on Agent Orange, and assisting in referring veterans to appropriate service organizations for claims and related issues. The sources for this information are varied, some no doubt more accurate than others.

We appreciate ACTION's presence on the CCAOWG, and look forward to continued close participation. We especially look forward to receiving materials that we can forward to our national network.

ARMED FORCES INSTITUTE OF PATHOLOGY
WASHINGTON, D.C. 20306

April 25, 1985

ADDRESS REPLY TO THE DIRECTOR
ATTN: AFIP-

Environmental/Drug Induced
Pathology Department

Honorable William Mayer, M.D.
Assistant Secretary of Defense
(Health Affairs)
The Pentagon, Room 3E346
Washington, D. C. 20301-1200

Dear Doctor Mayer:

This status report of the Agent Orange Registry (AOR) at the Armed Forces Institute of Pathology (AFIP) is made in response to a recent request from Captain Peter A. Flynn of your staff for an update of this Registry's activities made to Dr. Nelson S. Irey, who is Chairman of the Institute's Department of Environmental and Drug-Induced Pathology, and in charge of the Institute's Agent Orange Registry.

The AOR is studying current illnesses of veterans who served in Vietnam as reflected in surgical specimens obtained in the operating room. Over the past six years the AFIP has accessioned 4300 veterans' cases in this Registry. Most of these have been sent from Veterans Administration pathologists, with the excellent cooperation of and coordination with the VA Central Office here in Washington. The quality of these morphologic studies have been considerably enhanced by utilizing the consultative resources of the entire professional staff of the AFIP.

This Agent Orange Project is divided into three phases. The first phase has been completed, and the second and third phases are near initial completion. It is estimated that an analysis of the first 2300 cases can be completed within the next several months. This will permit an initial report on two aspects of the Agent Orange problem: a comparison of diseases in Vietnam veterans with non-Vietnam veterans; and a determination of the relative risk associated with service in Vietnam.

Phase One consisted of a study of 1700 Vietnam veterans, looking for clusters of similar cases, and also for unusual or unique diagnoses. A report on the first 1200 of the cases was made to the Committee on Veterans' Affairs of the United States Senate on 17 Nov., 1981. The thrust of this report was that there was no significant clustering and that no unique diagnoses were evident in these 1200 cases.

Phase Two consists of a morphologic study of about 1300 cases divided into a group of veterans who had served in Vietnam, and a group of veterans without Vietnam service. Some of the cases in this phase came from Phase One if certain criteria were met, including confirmation of service in Vietnam furnished by the Adjutant General's Office of DOA.

Phase Three consists of a statistical study of about 350 cases selected from Phase Two. The purpose of this part of the Project is to make an estimate of the relative risk of developing disease(s) associated with service in Vietnam. This part of the study is being made in conjunction with a statistician consultant who is a member of the Staff of the School of Public Health, Johns Hopkins Hospital.

In summary comparative morphologic studies are being made on Vietnam and non-Vietnam veterans. In addition, relative risk assessment studies are also being conducted. The anticipated initial report soon to be made will be followed by subsequent reports as additional cases are added to the series.

Please do not hesistate to contact us, if questions arise.

Sincerely yours,

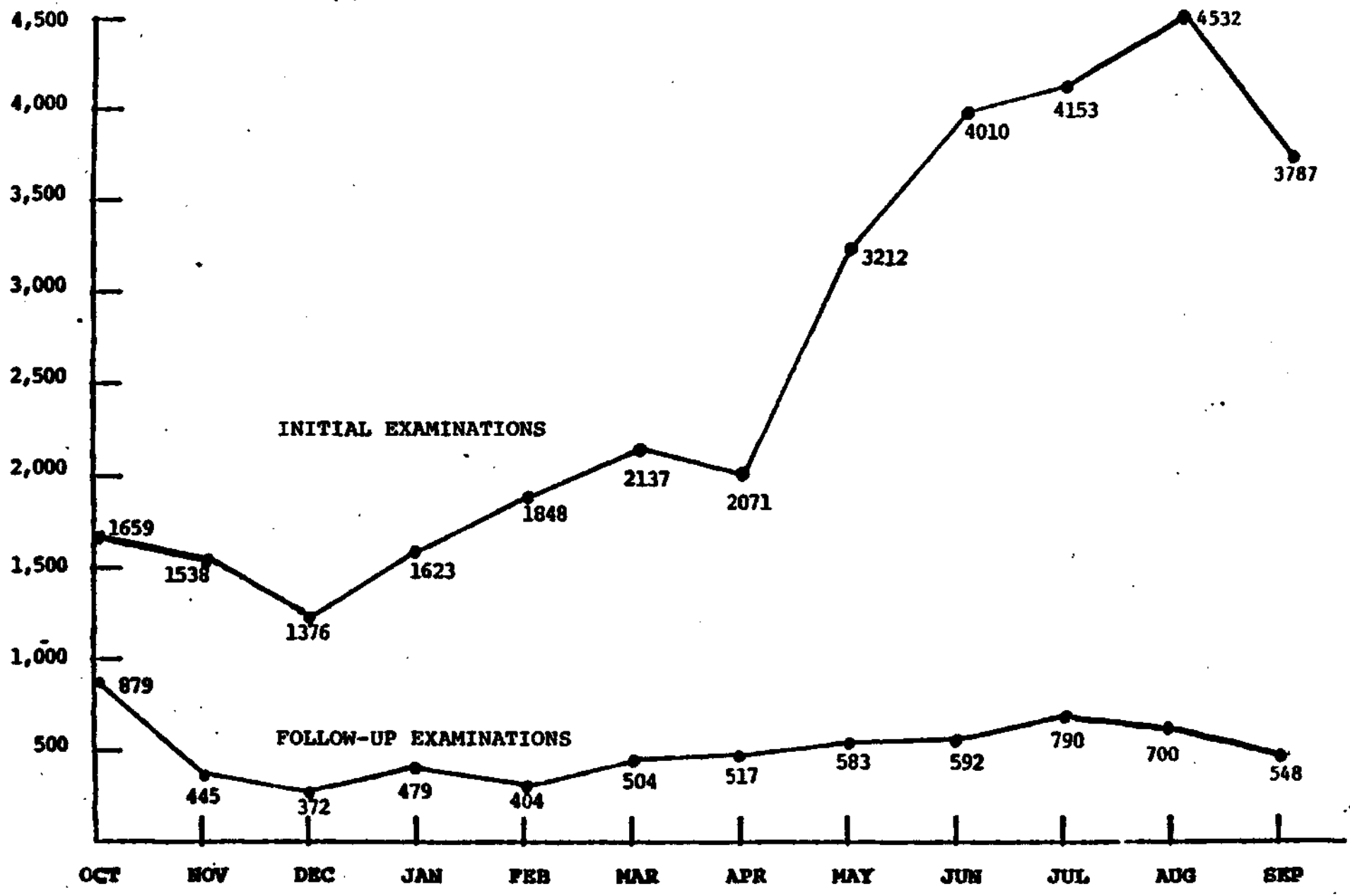
Robert R. McMeekin, M.D.
Colonel, MC, USA
The Director

PUBLIC LAW 97-72
INPATIENT ADMISSIONS/OUTPATIENT VISITS
(FY's 1982 - 1984)

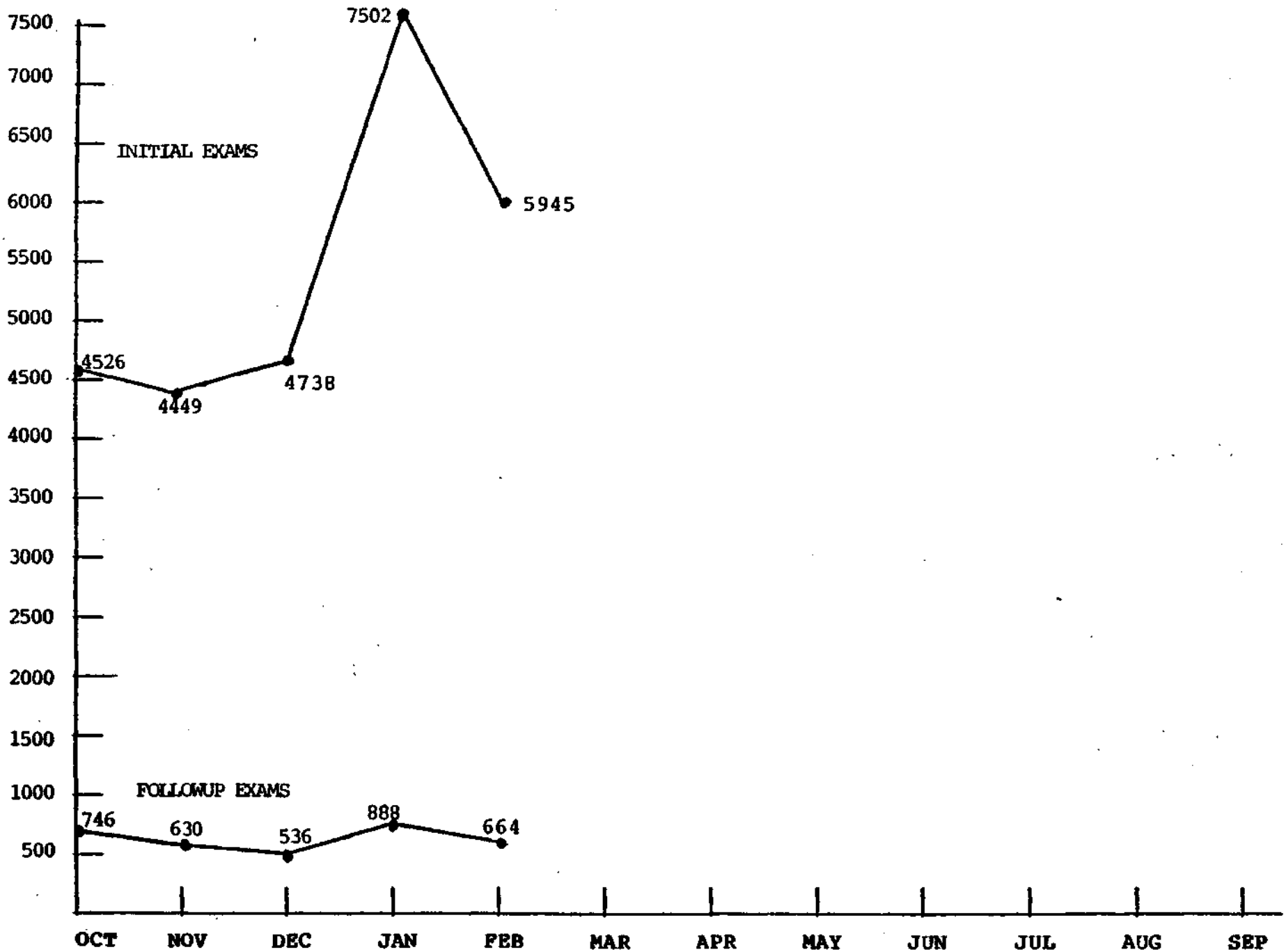
	FY 1982	FY 1983	FY 1984	CUMULATIVE TOTALS FY 1982-1984
INPATIENT ADMISSIONS:	9,400	10,900	3,800	24,100
OUTPATIENT VISITS:	369,000	432,000	444,000	1,245,000

AGENT ORANGE EXAMINATIONS

MONTHLY - FY 1984



AGENT ORANGE EXAMINATIONS MONTHLY - FY 1985



Alternate Methods for Assigning Agent Orange Exposure Status to Vietnam Veterans Exposure Opportunity Index (EOI)

Some time ago the Joint Services Environmental Support Group (then the Army Agent Orange Tast Force (AAOTF) began to develop methods to estimate potential exposure to Agent Orange among Vietnam veterans. The method to be used in the proposed Agent Orange Morbidity and Mortality Studies currently underway by CDC involves detailed day-by-day tracking of both military units and individuals while in Vietnam. Amassing the information necessary to do this requires considerable effort and yields simultaneous information on all of the members of a given military unit. The method is thus suitable for identifying cohorts, but is extremely inefficient for determining potential exposures of individuals selected by other means. Furthermore, the necessary records apparently do not exist for many units in Vietnam, particularly non-Army units, and is the major reason why the CDC Epidemiological studies are confined to veterans of the Army.

In order to obtain some information on the possible exposure to Agent Orange of veterans identified through other sources, an alternative method was proposed by the AAOTF.

The Science Panel was briefed on, and reviewed in depth the alternative procedures for assigning Exposure Opportunity Indices (EOI) to Vietnam veterans. These procedures are based on the place, time and job specialty of veterans while in Vietnam as indicated in personnel records, military unit quarterly reports and herbicide application records from Vietnam. The method was proposed by the Department of Defense, and was developed by the Army and Joint Services Environmental Support Group in conjunction with the investigators of the CDC Birth Defects Study. Even though the alternative method is somewhat subjective and confounds combat status with exposure to herbicide, all of the members of the Science Panel agree that the method as developed, can provide an individual estimate of the relative likelihood for at least some exposure to Agent Orange while in Vietnam. Attempts to establish whether such exposures are capable of compromising health status is the business of ongoing health and mortality studies.

AGENT ORANGE LITIGATION

In 1979, a class action was commenced in the United States District Court, Eastern District of New York, charging the United States and a major portion of the chemical industry with deaths and injuries to tens of thousands of Vietnam veterans who came in contact with herbicides used in the war in Southeast Asia. The suit also claimed that as a result of the veterans' exposure, their children suffer severe birth defects. After five years of numerous motions and extensive discovery, a settlement amount of $180,000,000 was negotiated between the plaintiff-veterans and the defendant-manufacturers and approved by Chief Judge Jack B. Weinstein on June 11, 1984.

Following this settlement, a $10 billion class action was filed against the United States on behalf of the servicemen, their wives and children. The class action alleged, among other things, failure to warn, and pre-induction, in-service, and post-discharge negligence. At the same time, the defendants expressed their intention to press third-party contribution and indemnity claims against the United States, to recover all costs associated with their defense of the litiga- tion, including the amount of the settlement.

The United States moved to dismiss the plaintiffs' class action and, on December 10, 1984 Judge Weinstein denied class certification and dismissed all claims brought by the service-men. The Court also found that there is no credible medical or scientific evidence supporting claims of male-mediated birth defects or miscarriages, but reserved final judgment on these claims for ninety-days. The United States will also seek dismissal of all third-party claims pending against it.

Judge Weinstein has established a 28 member advisory board to advise the Court on how the settlement trust fund proceeds might be best utilized. The Justice Department has refused to allow federal personnel to participate in any way in the settlement process. Judge Weinstein has reserved final approval of the settlement pending review of the settlement distribution plan and resolution of all counsel fee disputes.

Veterans Administration Advisory Committee On Environmental Hazards

The Veterans Administration Advisory Committee on Environmental Hazards and its Scientific Council were created by the Veterans' Dioxin and Radiation Exposure Compensation Standards Act, P.L. 98-542, enacted on October 24, 1984. The functions of this Committee and its Council are not perceived to encroach on, or duplicate the efforts of the Agent Orange Working Group (AOWG).

The Veterans Administration Advisory Committee is distinguished from the Agent Orange Working Group in that the Agent Orange Working Group is solely concerned with risk assessment and the Veterans Administration Advisory Committee and its Scientific Council are concerned with risk management.

P.L. 98-542 requires, inter alia, that the VA Administrator prescribe regulations on adjudicating claims based on dioxin and radiation exposure after considering the recommendations of an advisory committee and its scientific council.

The Advisory Committee on Environmental Hazards created by the Act consists of fifteen members appointed by the VA Administrator. Eleven of these, of whom none may be from the Armed Forces, the VA, or Defense and not more than three may be federal employees, are appointed in consultation with the Director, NIH. These members must include three authorities on dioxin, three on ionizing radiation, and five on epidemiology or a related field. These eleven members also constitute the Scientific Council of the Committee. The Council is divided into two eight member panels which will, respectively, evaluate studies on dioxin and radiation exposure. The Scientific Council reports to the Committee and to the Administrator directly.

The balance of the Committee is made up of four individuals from the general public with special concerns regarding exposure to dioxin or radiation. The Chief Medical Officer and Chief Benefits Director of the VA are ex officio members.

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Administration

Synopsis of Scientific Literature on Phenoxy Herbicides and Associated Dioxins

No. 1 - (Volumes I-IV)

Department of
Medicine and Surgery

VA CONTRACT NO: V101(93)P-953

SYNOPSIS OF SCIENTIFIC LITERATURE ON PHENOXY HERBICIDES AND ASSOCIATED DIOXINS

Prepared for Contracting Officer's Technical Representative:
Barclay M. Shepard, M.D.
Director, Agent Orange Projects Office
Department of Medicine and Surgery
Veterans Administration
810 Vermont Avenue, N.W.
Washington, D.C. 20420

Submitted by:
Clement Associates, Inc.
1515 Wilson Boulevard
Arlington, Virginia 22209

PREFACE

In October 1981, the Veterans Administration published the first two volumes of a comprehensive report entitled *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins*. A continuation of this important effort resulted in the preparation and publication in April 1984 of volumes III and IV. At this point it was thought that a summary in layman's terms, with emphasis on health effects would be helpful to the general public's understanding of the complex and often controversial issue of Agent Orange. Consequently this summary has been prepared to fill that need. It should be noted that this synopsis includes only that body of scientific literature published through December 1983, and therefore does not include the results of more recent research such as the study of birth defects conducted by the Centers for Disease Control and published in August 1984. Also not included is the mortality study of Australian Vietnam-era veterans published in September 1984. The results of these and other more recent reports will be summarized in a similar synopsis currently being developed by the VA for publication in the near future. It is hoped that these lay-language summaries will serve as useful supplements for assisting non-technically oriented readers in understanding both the significance and impact of such literature and thereby assist in the ultimate resolution of the many and varied issues related to the phenoxy herbicides and associated dioxins.

Agent Orange Projects Office
Veterans Administration
Washington, D.C.
1985

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1. Introduction

For the past several years the Veterans Administration, in response to the concerns of veterans who served in the war in Vietnam, has been conducting or sponsoring research on the health effects of Agent Orange, the principal herbicide used by U.S. military forces in that country and to which some American military personnel were exposed.

In April 1984, under contract to the Veterans Administration, Clement Associates, Inc., a research firm in Arlington, Virginia, completed a two-volume survey of the extant scientific literature on the health effects of Agent Orange. The material that follows is a lay summary of that survey and is published because the Veterans Administration believes that it will be of interest to Vietnam veterans and others who have been following the Agent Orange issue.

2. What is Agent Orange?

"Agent Orange" is a name that has come to be used to describe a particular type of chemical herbicide that was used in military operations in Vietnam from 1965 to 1971. The name came from the orange stripe that identified the 55-gallon drums in which the herbicide was shipped and stored. Agent Orange was not a single chemical compound but rather a mixture of chemicals containing equal amounts of the two active ingredients, 2,4-D and 2,4,5-T. These weed-killing chemicals enjoyed extensive commercial and private use in the United States and in many countries around the world from the 1940s well into the 1970s. 2,4-D is still used extensively in this country and abroad.

Like many industrial chemical mixtures, the Agent Orange that was manufactured during the Vietnam era contained small quantities of impurities. These impurities included chemicals used in the production of 2,4-D and 2,4,5-T as well as by-products which developed during the manufacturing process. Some of the impurities were a family of closely related compounds known as polychlorinated dibenzodioxins which, as a group, have often been called "dioxins."

One of these dioxins, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin or TCDD, has been extensively tested in experimental animals and is believed to be the most toxic member of the dioxin family. TCDD is one of the contaminating dioxins in 2,4,5-T. In the remainder of this report the term dioxin will be used to refer to any of a number of different polychlorinated dibenzodioxins, usually unidentified. The term TCDD will be used to designate the specific chemical 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Agent Orange was produced by several manufacturers in a number of chemical plants throughout the United States under contract to the Department of Defense, which specified the composition of the herbicide. Therefore the nature and amount of the active ingredients were the same regardless of the manufacturer. Although Defense Department specifications set an upper limit on the total amount of impurities that could be present in a batch of Agent Orange, it is certain that both the exact amount and the nature of these impurities varied from batch to batch, from year to year, and from manufacturer to manufacturer. Furthermore, since very little attention was paid to the importance of the impurities in Agent Orange until

late in the Vietnam experience, there is relatively little information available on the amount of the impurities contained in the herbicide shipped to Vietnam.

Agent Orange was somewhat different from commercial formulations of this class of herbicides made and marketed in the United States and in other countries around the world. In addition, we don't really know precisely all the types and amounts of the impurities that were present in Agent Orange, and furthermore we don't have any accurate way to find out. Because there is considerable evidence that the health effects of these herbicide mixtures depend heavily on the amounts and types of impurities such as dioxins which were present in the mixture, we can accept, only with reservations, information on health effects obtained from studies of people exposed to other herbicide preparations containing 2,4-D, 2,4,5-T, or both. If we hope to understand the health effects of Agent Orange with a high degree of certainty, it is essential to identify and study people who were exposed to Agent Orange.

3. Who was exposed?

The only individuals who are known to have been exposed to Agent Orange are those who were exposed during its manufacture and distribution or as a result of its use in Vietnam. Because Agent Orange was considered relatively safe at the time of its use, however, there were no systematic studies to determine how much Agent Orange might enter a person's system as a result of exposure in a manufacturing plant, during spraying operations or other applications, or from entering an area that had already been sprayed.

Another way of determining exposure is to depend on people's memory of when and how often they might have been exposed. Unfortunately, several different types of chemicals were manufactured in most of the plants that manufactured Agent Orange. In addition, several other herbicide mixtures as well as insecticides and other chemicals were used in Vietnam.

It would be very difficult for most individuals to know when they were exposed to Agent Orange specifically and how much exposure they received. The Air Force did keep records of most of the aerial herbicide spraying missions. By combining this information with data from records of the location of military units, the probability of exposure from aircraft spraying can be estimated. Those people who were actually involved in the handling and application of Agent Orange were undoubtedly among the most heavily exposed, but it is not possible to determine accurately the amount to which they were exposed.

4. What do we know about the health effects?

As one might guess from the information above, we don't have precise and direct information on the human health effects of Agent Orange itself. Scientists cannot identify people who were definitely exposed to known quantities of Agent Orange in order to compare such a group to people who were not exposed to Agent Orange or similar herbicides. Furthermore, Agent Orange as such was not tested in experimental animals at the time of its manufacture and use.

5. How do we determine the health effects?

Since we cannot study the human health effects of Agent Orange directly, we must use other techniques to learn what health effects might result from exposure to this material. Several methods are available and all of them have been used during the last 10 or 15 years. Each has limitations that make it difficult for scientists to reach definitive conclusions about the adverse human health effects of Agent Orange. Nevertheless, if scientists and health professionals review the entire body of information that has become available from all these approaches, certain patterns emerge.

It is now possible to begin reaching tentative conclusions about the health effects of Agent Orange. However, these conclusions are still somewhat uncertain. The results of studies which are currently in progress or planned will go a long way toward removing this uncertainty, but, for the general reasons described above and for specific reasons described below, it is quite likely that we may never be completely sure of what the health effects of Agent Orange are. This same uncertainty exists for many environmental health issues and is a result of the normal limitations of science.

One of the most promising approaches to studying the health effects of Agent Orange is to evaluate the health of people who may have been exposed to it as a result of the Vietnam experience and to compare their health with that of people who were not exposed to these herbicides. A few such studies have been conducted and several more are in progress. Some of the limitations of these studies have already been mentioned.

We don't have reliable records of everyone who was exposed, so assumptions are made such as "any veteran who served in Vietnam was exposed to Agent Orange" (Australian Veterans Health Study) or "any individual who was assigned to Operation Ranch Hand was heavily exposed to Agent Orange" (U.S. Air Force Epidemiology Study). These assumptions may lead to the inclusion in the "exposed" group of people who had very little exposure. If enough of these people are mis-classified as to exposure, scientists will not be able to detect any real health effects that might be present in those who were actually heavily exposed. In other words, the greater the mis-classification rate, the less reliable are conclusions regarding health effects of exposure.

Another serious limitation is that it is very difficult to select a group of "unexposed" people who can be closely matched with the people in the "exposed" group. Ideally, the two groups should be the same except for their potential exposure to Agent Orange. This means that individuals in both groups should not only be the same in age, weight, and sex, but they should also have similar smoking habits, diets, jobs, life styles, and places of residence. Another problem inherent in these studies relates to the widespread use in the United States of commercial herbicides that are similar to Agent Orange. In addition, dioxins are known to be present in other industrial chemicals in the environment. It is therefore very possible that some individuals in the "unexposed" group have actually been exposed to the ingredients of Agent Orange at other times and in other places.

Another problem with studies of people who were exposed to Agent Orange is that a relatively short period of time has elapsed since exposure took place. The phenoxy herbicides contained in Agent Orange were first used in Vietnam in 1962. Heavy use and potentially heavy exposure to Agent Orange did not begin until three years later, so the time that has elapsed since most veterans were exposed has been about 15 to 20 years. Certain adverse health effects such as cancer, heart disease, and respiratory problems that result from exposure to chemicals may take many years to develop. Increased cancer rates due to smoking or exposure to toxic chemicals have been shown to reach a peak 20 to 30 years after exposure. Thus, a lack of evidence of increased rates of cancer and heart disease in populations exposed to Agent Orange might suggest that exposure to Agent Orange does not increase the risk of developing these diseases. On the other hand, it might be that they haven't had time to appear in sufficient numbers to be detected.

The studies of populations who were probably exposed to Agent Orange as a result of the Vietnam experience have not yet provided clearcut answers to questions about its health effects. This is the result of some of the limitations described above. Furthermore, future studies of this type will not be capable of answering all these questions. It is therefore necessary to ask, "Where else can we look for these answers?" One potentially valuable source of information is the study of human populations with exposure to commercial herbicidal mixtures that were similar, but not identical, to Agent Orange. A number of such studies are available. Most are of workmen who sprayed herbicides on the job, but some are of populations who lived in areas where herbicides containing 2,4-D and 2,4,5-T were used. Most of these studies are subject to the same limitations as those of the people exposed to Agent Orange.

In all of these studies, the determination that a person is or is not exposed is based largely on that person's memory of past events or, in many cases, simply on where the person lived or worked. Also, people may be included in the exposed group who worked at a job or lived in an exposed area for only a few weeks. On the other hand, people may be included in the unexposed group if they are currently working in jobs or living in areas where they are not exposed to herbicides but who may have been exposed to herbicides in some previous job or place of residence, perhaps even without knowing it. Either type of error decreases the ability of scientists to detect possible effects of exposure to the chemical.

Other potential sources of information about the health effects of Agent Orange are studies of humans who were exposed to some of the components of Agent Orange. There are a number of groups of people throughout the world who were exposed to dioxins as a result of industrial accidents or unintentional release of dioxin into the environment. Several of these groups have been followed for a number of years and much information has been gathered. It is difficult, however, to judge how relevant these findings are to people exposed to Agent Orange. The specific dioxins to which these people were exposed were not always completely or accurately identified, and they may be somewhat different from those found in Agent Orange.

One of the most widely publicized incidents in which humans were exposed to dioxins was the explosion of a chemical reactor at the ICMESA plant near Milan, Italy, in July 1976. A cloud of chemicals containing relatively large quantities of dioxins blanketed a portion of the small town of Seveso immediately downwind of the plant. In succeeding weeks many persons living in Seveso showed signs of dioxin exposure, the most prominent being chloracne, a form of acne which includes the appearance of blackheads around the eyes and ears and in some cases covers much of the body.

No direct measurements were made of the chemicals in the accidental gas cloud itself but it has been possible to estimate the dioxin exposure of people in different areas by three independent methods. The first was a calculation of the distribution of the dioxin based on the nature of the chemical reaction, the quantity of ingredients, and the wind direction and speed at the time of the accident. The second method recorded biomedical changes, such as the death of birds and other wild and domestic animals and the appearance of chloracne in people. These changes were then correlated with the geographic location of each person or animal affected. The third method, performed somewhat later, was the actual analysis of the soil for dioxin. This gave results which were judged to be in agreement with those of the other two methods. In addition, reports by the exposed individuals provided supplementary and confirmatory information.

In the areas with the most intense exposure, animals and birds died; humans did not. People experienced a variety of symptoms shortly after the explosion including weakness, headache, loss of appetite and weight, insomnia, impotence, nausea and abdominal pain. There was also a burning sensation and an eruption of the skin, but the role of dioxin, as opposed to other more caustic chemicals suspected of being present in the cloud, is unclear. The symptoms cleared up within a brief period but one characteristic skin change, chloracne, persisted. Chloracne was present, especially in children under the age of 14. In the most heavily contaminated areas about 20 per cent of the children developed the skin disorder. The changes gradually cleared over the ensuing months.

Early after the exposure there were laboratory results suggesting changes in liver function, but the test results did not differ a great deal from those obtained in an unexposed, control population. Within a year after the exposure careful examinations showed some problems with the nerves controlling muscle function. These changes apparently disappeared within the following two or three years.

It is not clear that the exposure to dioxin had any effect on the pregnancy rate, the miscarriage rate or the birth rate since there are no good statistics from nearby communities with which to compare the exposed populations. There is no convincing evidence that the dioxin caused birth defects, interfered with growth, disturbed resistance to disease or increased the death rate. Some details of these results may be questioned because of the difficulties encountered in collecting the data. It is reasonable, however, to say that the Seveso accident did not result in a very serious or life-threatening effect on the health of exposed persons, at least in the near-term. It is too soon to draw final conclusions regarding possible delayed effects.

A final potential source of information about the adverse health effects of Agent Orange includes studies using experimental animals. Care must be taken in interpreting the results of animal studies because animals may respond quite differently from humans in the way they absorb chemicals, in the distribution of these chemicals in the body, in the way the chemicals

are broken down or stored in the body, and in the way they are eliminated. Differences in body size, diet, lifespan, and the way individual organs function may also cause animals to respond differently from humans. For these reasons responsible scientists are reluctant to base predictions of human health effects on animal studies unless the chemical has been tested in several species of experimental animals and there is a good basis for believing that the test animals are similar to humans in the way they respond to the chemical.

For reasons noted earlier, Agent Orange when it was first used was not tested in experimental animals and, because the amount and identity of the impurities in Agent Orange varied, it cannot be exactly reproduced for studies in experimental animals now or in the future. It is therefore necessary to rely on the results of experimental studies of herbicide mixtures similar to Agent Orange as well as studies of individual components of Agent Orange such as 2,4-D, 2,4,5-T and TCDD to serve as a basis for predicting the human health effects of Agent Orange.

The remainder of this report on the health effects of Agent Orange summarizes the information available as of early 1984 from all the types of studies described above. The section that follows provides a discussion of each of the suspected or potential health effects and in each case the available evidence is evaluated as a whole. For more detailed information regarding specific studies the reader is urged to refer to the *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins,* Volumes I, II, III and IV, published by the Veterans Administration.

6. Summary of the studies on health effects

Cancer

To date only one systematic study of cancer in military personnel exposed to Agent Orange in Vietnam has been published. In this study of Air Force personnel who were engaged in Operation Ranch Hand (the herbicide spraying operation in Vietnam), there was no increased occurrence of serious or life-threatening forms of cancer, but a greater incidence of a type of skin cancer was found in the exposed group compared to a control group of military personnel who were not exposed to Agent Orange. This type of skin cancer is a very common, localized form that is known to be associated with exposure to sunlight. Further studies need to be done to determine whether Ranch Hand personnel were more likely to have been exposed to sunlight than were the members of the comparison group. There was also a slightly increased incidence of cancer of the mouth and throat in the Ranch Hand group, but this excess is so small that it may be due to chance.

Two other reports are available on cancer in Vietnam veterans but in neither report was there any confirmation of exposure nor were matched control groups used. In one survey, based on Vietnam veterans who registered with the VA's Agent Orange Registry, a somewhat higher proportion of mouth and throat cancer and of lymphoma (cancer of the lymphatic system) was found compared to the same proportion of cancers among U.S. males aged 25 to 39. In the other report, a physician in Atlanta reported three cases of soft-tissue sarcoma (a rare cancer) among his patients. All three of these patients had served in Vietnam but no other information was given about them.

Comparisons between groups exposed to the herbicides or to dioxins and unexposed groups have shown no overall increase in cancers. Attention has centered on certain types of cancers.

There have been 11 reports of studies of cancer in men who were employed in jobs that involved the spraying of herbicides similar to Agent Orange. Eight of these studies were limited to men who sprayed herbicides containing 2,4-D or 2,4,5-T. The other three studies were of workers exposed to agricultural chemicals in general, including herbicides. These three studies are not discussed here because of the uncertainty regarding exposure. The eight remaining reports are also based on groups of workers whose exposure was of doubtful duration and intensity. Two of the eight studies of 2,4-D or 2,4,5-T indicated that there was an association between exposure and the incidence of soft-tissue sarcoma. A third study showed an association between exposure and lymphoma, and one study showed an association between exposure and stomach cancer. Another of these eight reports described five cases of lymphoma with cutaneous (skin) lesions seen in an English hospital. Four of the five patients worked with 2,4-D or 2,4,5-T. A case-control study reported an association between herbicide exposure and cancer of the nose and throat. The remaining three reports showed no association between exposure and any form of cancer, although one suggested a slight association with soft-tissue sarcoma.

Of seven studies on populations exposed to dioxins either in the workplace or in the environment, two showed an increased incidence of cancers. A study of workers exposed to dioxin as a result of a reactor explosion in a 2,4,5-T manufacturing plant in Germany in 1953 showed an excess of stomach cancer. Another study of the residents of Midland County, Michigan, where Dow Chemical Company has a large plant, revealed an increased incidence of soft-tissue sarcoma in women between 1960 and 1980. This finding is unlikely to be related to dioxin exposure, however, because the excess cancer was seen only in women and several of the people with soft-tissue sarcoma had lived in Midland County only a short time before the diagnosis of cancer and had little or no connection with the company.

Three separate reports describe two cases of lymphoma and three cases of soft-tissue sarcoma in workers who may have been exposed to dioxin. These are isolated case reports, and they contained little evidence of dioxin exposure. Two studies of workers occupationally exposed to dioxin revealed no excess incidence of any form of cancer.

None of the studies of cancer in humans exposed to Agent Orange, related herbicides, or dioxins provides an answer to the question of whether Agent Orange might cause cancer in humans. When all the reports are taken together, however, certain patterns appear that provide suggestive evidence that exposure to dioxin-contaminated herbicides may be associated with an increased incidence of cancer. Thus, seven reports suggest a relationship between such exposure and soft-tissue sarcoma. Four reports point to a possible connection with lymphoma. Two studies show an association with stomach cancer and three reports suggest a possible association with cancer of the mouth, nose, or throat.

The results of animal studies lend support to the hypothesis that dioxins and dioxin-contaminated herbicides may cause cancer in humans. Six studies of the potential for TCDD to cause cancer in animals were positive when relatively large doses were given. TCDD painted on the skin of mice caused cancers related to soft-tissue sarcomas. Four studies in which rats were given TCDD by mouth showed that the rats developed cancer of the liver, mouth and nose, tongue, adrenals, and thyroid. In two studies in which TCDD was given to mice by mouth, liver and thyroid cancers resulted. Several studies suggest that when TCDD is given to mice with other cancer-causing chemicals, it increases the response to those cancer-causing chemicals.

As yet there have been no published studies which show that Agent Orange or similar commercial herbicides have a demonstrated potential for causing cancer in laboratory animals. A few studies designed to measure the effect of 2,4-D and 2,4,5-T on rats and mice have been negative for cancer, but these studies were not adequate to detect a small increase in cancer in the treated animals. The current evidence, though far from conclusive, justifies continued surveillance of people who have been exposed to dioxin and dioxin-contaminated herbicides in order to confirm or deny an increased incidence of cancer which can be attributed to that exposure.

Reproductive effects

The various possible causes of reproductive abnormalities are difficult to determine because there are fairly high rates of birth defects, stillbirths, miscarriages, and sterility in all populations. For example, between three and six percent of all children are born with some kind of defect. The percentage varies depending upon how serious a disturbance has to be before it is recorded as a defect. In addition, some defects are not noted at birth, but show up later in childhood or beyond.

Two systematic studies of reproductive performance and outcome among men who may have been exposed to Agent Orange in Vietnam have been published. In the first of these the Australian government sponsored a study to see whether birth defects were related to the father's service in Vietnam. No association was found, although there was a slightly increased risk of heart defects and Down syndrome among the children of Vietnam veterans.

In the study of Operation Ranch Hand personnel discussed in the cancer section above, a small increased incidence of miscarriages following Vietnam service was found among the wives of the Ranch Hand group when compared to wives of the control group. The same difference, however, was observed for pregnancies occurring prior to Vietnam service. There were also slight increases in deaths of newborn babies and minor birth defects. There may have been slight increases in learning disabilities and physical handicaps among children of Ranch Hand personnel. The significance of these findings is not clear because most of the increases are very small, and many of these differences disappear if the data are analyzed differently. In addition, these differences were based on self-reporting and at the time of the initial report had not been confirmed by a review of medical records.

Two studies have been reported of men who were exposed to herbicides similar to Agent Orange. A study of wives and children of herbicide sprayers in New Zealand showed no increases in birth defects, stillbirths, or miscarriages when compared to the population of New Zealand as a whole. There was a very small increase in the incidence of heart defects, but this may have been due to chance. Another study of children born to the wives of men who sprayed herbicides for the Long Island Railroad showed no increase in major birth defects but two relatively minor birth defects—minimally deformed feet and tear duct obstruction—were seen in excess.

Several studies have been conducted to ascertain whether there are increased incidences of spontaneous abortions, stillbirths, or birth defects in areas where herbicides similar to Agent Orange have been heavily used. In these situations there is the potential for exposure of both parents as opposed to exposure of only the father as in the four studies discussed above.

One of these general population studies gained a great deal of publicity in the late 1970s when it was asserted that women living in the vicinity of Alsea, Oregon, experienced a higher rate of miscarriage than did women living in other parts of Oregon where herbicides were not commonly used. Careful review of this study by expert scientists has resulted in a consensus that the results were misinterpreted and that the study did not show the claimed effect.

More recently, a study of people living in an area of New Zealand where herbicides containing 2,4,5-T were often used revealed an increase in the occurrence of clubfoot in children in the area. Other small and perhaps insignificant increases were found in heart defects and malformations of the penis. A study conducted in Hungary looked at the rate of five major birth defects in that country's general population over a five-year period in which the use of 2,4,5-T increased greatly. No changes in the rates of these birth defects were found.

Four studies have been conducted of men exposed to dioxin as a result of working in plants where 2,4,5-T was manufactured. None of these studies showed a clearcut effect on reproductive outcomes. Two of them did show a slight increase in spontaneous abortions in the wives of the workers. Two studies of the population exposed to dioxin as a result of the ICMESA accident at Seveso suggest that there may have been an increase in birth defects (particularly of the heart) and an increased incidence of spontaneous abortions in the year following the accident, but their validity is questionable because the reporting of birth defects and abortions was generally unreliable.

The studies of the reproductive effects of 2,4-D, 2,4,5-T, and TCDD in experimental animals are of limited usefulness in helping to predict the reproductive effects of Agent Orange in male Vietnam veterans. In almost all of the animal studies, the herbicide or dioxin was given to pregnant females rather than to male animals. In the one study in which the mixture found in Agent Orange was fed to male mice, it had no effect on reproductive performance or on the offspring. In two studies, relatively uncontaminated 2,4,5-T and TCDD were fed to both male and female rats and reproductive performance and outcome were recorded for three successive generations. These studies showed that both 2,4,5-T and TCDD decreased the number of live births and the weight of newborn animals, as well as causing an increase in birth defects of the kidneys. Numerous studies in which TCDD was given to pregnant females in relatively large

doses indicate that it can cause defects in the developing fetus. TCDD causes birth defects in pregnant rats, mice, rabbits, and monkeys when given by mouth or injection. It also causes an increase in the number of spontaneous abortions and a decrease in birth weight of newborn animals.

In summary, no study of reproduction in humans exposed to Agent Orange conclusively shows an adverse effect which has been caused by the herbicide. Scientists believe, however, that people with known exposure to TCDD-contaminated chemicals should be observed for possible adverse reproductive effects.

Enzyme effects

One of the best studied effects of dioxins in experimental animals is the ability of these compounds, especially TCDD, to alter the activity of certain enzymes. Enzymes are proteins that serve as catalysts in the formation or breakdown of various chemicals in the body. In some cases many enzymes are involved in the alteration of just one chemical, whereas other enzymes are capable of acting upon an entire class of chemicals.

It is very difficult to study the effects of chemicals on enzyme activities in humans. Most enzymes are located in tissues where metabolic activity is greatest, such as the liver, lungs, intestines, brain, and reproductive organs, and these tissues are the least accessible to study. Furthermore, there are large differences among people in their baseline metabolic activity. About the only approach available is to look at the levels of chemicals produced by enzyme reactions that appear in the blood or urine and determine whether they are different in people exposed to a specific compound when compared to people who are not exposed to that compound.

Only a few studies of enzyme activities have been conducted in animals which have been fed or otherwise dosed with 2,4-D and 2,4,5-T. These studies suggest that these compounds do not cause major alterations in enzyme activities, and some of the small effects seen may be the result of contamination of these chemicals with small amounts of dioxin. A number of studies of TCDD, on the other hand, have shown that it alters the activity of some enzymes in experimental animals.

The best studied effect is an increase in the activity of an enzyme known as aryl hydrocarbon hydroxylase (AHH). AHH is important because it makes certain chemicals more soluble in water and, thus, more likely to be excreted in the urine. Very small amounts of TCDD cause large increases in the activity of this enzyme in rabbits, mice, rats, guinea pigs, hamsters, birds, fish, and monkeys. In several studies in which living cells were taken from humans and allowed to grow in a culture medium, the addition of TCDD to the culture caused an increase in AHH activity in the cells.

It is interesting that in two studies of human populations exposed to dioxin as a result of industrial accidents (one at Seveso and the other at a 2,4,5-T manufacturing plant in England), scientists found elevated levels of d-glutaric acid in the urine of exposed people. This chemical

is believed to be formed by enzymes that are very closely associated with AHH. This finding adds support to the theory that TCDD may stimulate AHH activity in humans.

What are the health implications of stimulation of AHH activity? This is a difficult question to answer because the role of AHH is not yet fully understood. Evidence from animal experiments and some human evidence indicate that some of the aryl hydrocarbons that are altered by AHH are cancer-causing. Some experiments in which TCDD was given to animals several days before they were exposed to cancer-causing aryl hydrocarbons showed that it protected the animals against cancer. Thus, TCDD caused an overall health benefit.

Unfortunately, the picture is much more complicated than that because, if TCDD is given to animals at the same time as the aryl hydrocarbon rather than a few days earlier, the TCDD binds to the site of the AHH enzyme that is responsible for changing the aryl hydrocarbon and prevents the AHH enzyme from doing its job. Thus, administration of TCDD with aryl hydrocarbon causes more cancer than does the aryl hydrocarbon itself.

An additional complication is that there is evidence that AHH catalyzes other tranformations and that some of them may convert inactive chemicals into toxic ones. In the absence of complete information, the fact that TCDD stimulates AHH activity must be viewed as a potentially adverse effect.

Animal studies have also shown that TCDD alters some enzymes that are involved in the manufacture of heme, the portion of the hemoglobin molecule that binds oxygen in red blood cells. Animal studies indicate that TCDD *decreases* the activity of an enzyme known as uroporphyrinogen decarboxylase in the liver. This results in a decrease in the amount of heme synthesis and a build-up of the chemicals known as porphyrins from which heme is formed. As the porphyrin level builds up, more porphyrins are excreted in the urine.

A number of animal experiments have shown that the pattern and amount of porphyrins excreted in the urine changes after treatment with TCDD. Two studies of workmen exposed to dioxin have shown increased urinary excretion of porphyrins. The Air Force study of personnel involved in Operation Ranch Hand has also shown that there are more men with abnormally high porphyrin levels in the exposed group than in the comparison group, although this finding correlates more strongly with alcohol use than it does with potential exposure to Agent Orange.

Interference with porphyrin metabolism may result in a condition known as porphyria cutanea tarda (PCT) in which the skin blisters and later becomes dry and brittle, particularly on exposure to sunlight. Workers who were exposed to dioxins as a result of two industrial situations developed this condition but in both instances the men were also exposed to another chemical known to cause PCT.

The available medical evidence indicates that there are no lasting adverse human health effects that result from alterations in porphyrin metabolism due to exposure to TCDD. The body adjusts by producing sufficient heme to meet the oxygen-carrying needs of the body. PCT is a relatively rare manifestation of changed heme metabolism and may be caused by

other external factors, such as alcohol consumption. There is also a known genetic factor which influences the development of PCT. PCT resulting from exposure to such chemicals as dioxins and similar compounds is reversible and disappears after exposure.

Another enzyme activity for which there is indirect evidence of interference by dioxins is related to the conversion and storage of fats. Studies of workmen exposed to dioxins showed increased blood levels of fat molecules known as triglycerides. Although elevated levels of some triglycerides are known to be associated with heart disease, to date there is no conclusive evidence of an association between heart disease and dioxin exposure.

Although it appears that dioxins have the ability to alter the functions of a number of enzymes, at present none of these alterations has been shown to be associated with any serious or irreversible adverse health effects in humans. However, any influence that substantially alters the way the body handles internal and external chemicals must be viewed with concern. It should be remembered that as in the case of most of the effects of these chemicals, the active herbicide ingredients 2,4-D and 2,4,5-T by themselves are not known to affect the enzyme system in humans.

Effects on the immune system

Unlike such well-studied and relatively well-understood systems of the body as the cardiovascular and digestive systems, there is still much of the "immune system" which is not well understood. It is currently the subject of intensive research to better understand its chemistry, mechanisms, and functions. The immune system is involved in a large and complex array of processes that defend the body against foreign chemicals, disease-causing bacteria, viruses, foreign cells from outside the body, and abnormal cells from within the body. Virtually all of the body's organs and tissues participate in these processes to a greater or lesser extent.

Because of the lack of basic knowledge in some areas, it is difficult to assess the impact of chemicals on the immune system. One problem is that the system functions in many different ways. A chemical to which the body is exposed may activate only one or two of dozens of known defense mechanisms. Therefore, it may be necessary to run a large number of different tests to detect these changes. Since many of these tests are very complex and some require the examination of body tissues, it is especially difficult to study altered immune function in humans.

Two additional factors make it difficult to detect such changes in humans. First, there are tremendous differences among people in the manner in which their immune systems operate. For example, there is a wide variation in the way different people manifest an allergic reaction, which is one of the ways the immune system functions. Second, many activities of the immune system have no obvious or external manifestations. It is usually not possible to assess a person's immune function by a simple physical examination. These changes in immune function may only be reflected by subtle variations in indirect indicators, such as increased susceptibility to infections or increased sensitivity to materials that cause allergic reactions. One result of these problems is that the effect(s) of chemicals on the immune system of humans may

be very subtle and difficult to detect. Highly specialized and complex tests are often needed to detect these changes.

There is no evidence that 2,4-D or 2,4,5-T by themselves alter the immune function of animals. There have been no studies of humans exposed to Agent Orange or similar herbicides that show an adverse effect on the immune system, and there have been no reports of increased allergies or of increased susceptibility to infection, either of which might indicate altered immunity. On the other hand, there have been no studies reported that were designed specifically to look for such an effect in humans soon after exposure.

There is considerable evidence, on the other hand, that TCDD interferes with the functioning of the immune system in experimental animals. When TCDD is given to animals, a common effect is a decrease in the size of the thymus, an organ that is involved in the immune system. This effect occurs at doses lower than those that cause changes in other organs. At even lower doses, TCDD interferes with the ability of the animal to produce certain types of white blood cells in response to the presence of foreign materials in the blood stream. In some studies, this effect is paralleled by decreased resistance to bacterial and viral infections.

It appears that TCDD has the ability to suppress the immune system in unborn animals when the TCDD is given to pregnant females. Sensitivity decreases in newborns but significant effects can still be seen in adult animals treated with TCDD. In fact, immune suppression is the most sensitive indicator of TCDD exposure in mice, occurring at doses below those that cause changes in enzyme activity. Furthermore, although immune function improves after exposure ends, it remains relatively depressed for a very long time in experimental animals.

Most studies of humans who have been exposed to dioxins have not included tests of immune function. There has been a study of children who lived in the heavily contaminated area of Seveso, Italy. The results of this study showed that these children had higher levels of certain immunologically active blood components than did children from uncontaminated areas. The body also produced more white blood cells in response to certain foreign materials. These results suggest that exposure to dioxins *stimulated* immune function in these children rather than depressing it, as seen in the animal experiments. This finding is not inconsistent, however, with experimental findings that some chemicals which depress immune function at high doses may actually stimulate immune functions at low doses.

Another study of workers exposed to dioxin as the result of an industrial accident has been reported to have shown *decreased* immune function in the exposed workers 10 years after the accident, but this study has not been published and cannot be independently reviewed. These results, taken together, fall far short of providing convincing evidence that dioxin exposure can cause altered immune function in humans. Nevertheless, the evidence of such effects in experimental animals provides some basis for concern that exposure to dioxin may adversely affect immune function in humans.

Chloracne

Chloracne is a skin condition that is known to result from exposure to a group of structurally similar compounds in which chlorine atoms are bound to an aromatic hydrocarbon. One of

these compounds is TCDD. As its name suggests, chloracne, is similar in appearance to the common forms of acne that affect teenagers and usually appears within a few weeks after exposure to the chemical that causes it.

The first sign of chloracne may be excessive oiliness of the skin. This is accompanied or followed by the appearance of numerous blackheads. In mild cases the blackheads may be confined to the area around the eyes extending along the temples to the ears. In more severe cases blackheads may appear in many places on the body. The blackheads are usually accompanied by fluid-filled cysts and by an increased or darker growth of body hair. The skin may become thicker and flake or peel. In severe cases, the acne may result in opens sores and permanent scars. The condition fades slowly after exposure. Minor cases may disappear altogether, but more severe cases may persist for years after the exposure.

It is well known that chloracne can result from exposure to dioxins. In seven reported situations where workers were exposed to dioxins as a result of industrial accidents or poor housekeeping practices, many of the workers and, in a few cases, members of their families developed chloracne. Chloracne was also diagnosed in 187 people, mostly children, living in the section of Seveso that was most heavily contaminated with TCDD as a result of the ICMESA accident in 1976. Two laboratory workers who were exposed during the synthesis of TCDD developed serious cases of chloracne.

There are no authoritative reports in the literature that document an association between exposure to Agent Orange or similar herbicides and chloracne. The Air Force study of Ranch Hand personnel showed no excess of acne in those individuals when compared to unexposed controls and no cases of chloracne were found. Most of the epidemiologic studies of occupational groups involved in the spraying of herbicides like Agent Orange do not report the presence of chloracne among the workers who were studied. A research effort looking for cancer among herbicide sprayers in Finland turned up a few cases of possible chloracne, one of which was diagnosed by a dermatologist. It would appear, therefore, that chloracne is not a sensitive indicator of exposure to herbicides like Agent Orange.

Animal studies are of little use in measuring the potential of Agent Orange for causing chloracne in humans. The ingredients 2,4-D and 2,4,5-T have not been extensively tested, but it appears that they do not cause chloracne or similar skin conditions in experimental animals. Different kinds of animals react differently to TCDD, but it causes skin conditions very similar to chloracne when applied to the ears of rabbits and to the skin of certain kinds of mice. Scientists disagree, however, as to whether these skin effects are identical to human chloracne. Some types of experimental animals fail to show any acne-like condition when treated with TCDD. It seems that only monkeys exposed to TCDD develop a skin condition that appears identical to human chloracne.

One conclusion that is gaining support on the basis of both animal and human studies is that susceptibility to chloracne may be genetically controlled. Two individuals equally exposed to TCDD may respond differently because of variations in inherited susceptibility. This would explain why some of the workers exposed to dioxins in each of the seven industrial incidents did not develop chloracne, even though there is no reason to believe that they were less

exposed than workers who did develop chloracne. Thus, whereas chloracne may be a sensitive indicator of exposure to dioxins in some people, it may not be in others. Therefore, the absence of chloracne is not necessarily a reliable basis for concluding that a person has not been exposed to a chemical which is known to cause chloracne.

Neurobehavioral effects

It has been known for some time that exposure to relatively large amounts of 2,4-D, such as might occur when it is being mixed or sprayed, can cause adverse effects on the nervous system. Workmen who splashed 2,4-D on their skin or who stood for a long time in 2,4-D spray mist developed a variety of symptoms including tingling or decreased feeling in the hands and feet and tightening of muscles in the arms and legs. Examination of these workmen showed the loss of the knee-jerk reflex and an increase in the time for nerve impulses to travel from the hands or feet to the spinal cord and back. Studies in experimental animals give results similar to those seen in humans. These studies suggest that 2,4-D interferes with the transmission of nerve impulses to muscles. If the exposure is minimal the nervous system recovers. However, sustained exposure of experimental animals to relatively large quantities of 2,4-D may cause long-lasting changes in the brain and spinal cord itself.

A few studies of humans and experimental animals exposed to 2,4,5-T have failed to show any nervous system effects such as those caused by 2,4-D. There is some evidence, however, that humans exposed to dioxins as a result of industrial exposures or accidents may suffer impaired nervous system function. A wide range of signs and symptoms have been reported in these people including pain in the arms and legs, numbness in the hands and feet, muscular weakness particularly in the legs, headache, loss of memory and concentration, sleep disturbances, nervousness, and emotional and behavioral abnormalities. The speed of nerve impulses was slowed in two groups of workers who were probably exposed to dioxins.

There have been very few studies of the effects of TCDD or other dioxins on the nervous system in animals. It is not clear why this knowledge gap exists, but one possible explanation is that the doses of TCDD needed to cause detectable signs of nervous system damage in experimental animals are higher than those that cause other serious toxic effects. Scientists have therefore tended to concentrate on the other effects.

Whether nervous system and psychologic effects have occurred in individuals exposed to Agent Orange as a result of the Vietnam experience is unclear and controversial. It has been suggested that Vietnam veterans experience a high rate of psychologic problems, with certain symptoms appearing quite frequently. These symptoms include nervousness, disturbed sleep, irritability and short temper, depression, and suicidal thoughts. Many psychiatrists consider that some of these comprise a distinct collection of symptoms or a syndrome known as post-traumatic stress disorder and that this syndrome is unrelated to any chemical exposure. Evidence in support of this conclusion is that individuals such as prisoners of war and hostages who have undergone sustained stress display similar symptoms.

Unfortunately, there are almost no systematic studies of nervous system function or psychological problems among individuals exposed to Agent Orange. The recent Air Force

study of Ranch Hand personnel showed no difference between the exposed group and unexposed controls in several measurements of nervous system function including the speed of nerve impulse transmissions. On the other hand, when Ranch Hand personnel were evaluated by analyzing answers to questions on some of the tests designed to detect emotional disorders or personality disturbances, psychiatrists concluded that they were different from the comparison group and showed tendencies toward traits defined as "hypochondria, depression, hysteria, and schizophrenia." Ranch Hand personnel were also said to feel more isolated and to have a higher degree of nervousness and anxiety, to be more easily startled, and to experience more psychosomatic illness than did the comparison group. These differences were minor and are difficult to interpret. The methods used in this study would not show whether the differences between groups were due to post-traumatic stress, Agent Orange exposure, or both.

The fact that self-perception of psychologic problems is an important component of such an analysis was shown in a study of 100 veterans who were asked about their exposure to Agent Orange and their current mental and emotional well-being. Their potential exposure to Agent Orange was independently assessed by comparing their service records with records of the time and location of herbicide spraying missions in Vietnam. The frequency and seriousness of psychologic and emotional problems correlated very closely with how much herbicide the veterans *believed* they were exposed to, whereas the correlation was much weaker when the comparison was based on how much herbicide exposure the records showed.

The issue of the effects of Agent Orange on nervous system and psychologic performance is probably the most difficult health issue to resolve. There is a great deal of human and animal evidence that both 2,4-D and TCDD can adversely affect the nervous system. All of this evidence suggests that these effects are the result of short-term high level exposure rather than sustained exposure to lesser amounts.

Other toxic effects

Studies of people exposed to Agent Orange or similar herbicide mixtures have failed to reveal any significant toxic effects other than those discussed above. Other effects have been attributed to TCDD, however. As was mentioned briefly in the section on enzyme effects, there is suggestive evidence of a higher incidence of heart attacks among workmen exposed to dioxins in industrial accidents. This evidence is far from conclusive, but it is sufficient justification for continuing to observe the health of people exposed to dioxin, especially since it may take many years after exposure for adverse effects on the heart to show up.

The most dramatic sign of fatal dioxin poisoning in experimental animals is an apparent loss of appetite which leads to general body wasting. The animals eventually die of a condition very similar to starvation. This effect is observed following a large single dose of TCDD. No similar effect has been described in humans, so it may be of little relevance to human health. The mechanism by which TCDD causes this apparent loss of appetite is unknown and is the object of much current research. Some results suggest that TCDD may interfere with an appetite regulating system in the brain or thyroid.

Animal studies have suggested another aspect of the toxicity of TCDD which may have implications for human health. It has become increasingly clear that some animals are relatively resistant to some of the toxic effects of TCDD compared to others. Recent research has shown that this difference in susceptibility is genetically influenced and that mice with just one parent in common can show large differences in susceptibility to the toxic effects of TCDD. The effects for which susceptibility appears to be genetically controlled include the appearance of birth defects in the offspring of female mice exposed to TCDD, the increased activity of several enzymes including AHH and uroporphyrinogen decarboxylase, depression of immune function, chloracne, and the lethal effects of TCDD. This suggests the possibility that humans as a group who are known to be genetically very diverse, may have a wide variation in susceptibility.

7. Summary and Conclusions

What can we say about the health effects of Agent Orange? From the evidence now available we can arrive at almost no definitive conclusions. The limited evidence available suggests that 2,4-D and 2,4,5-T by themselves are not highly toxic to humans. 2,4-D appears to be capable of causing nervous system toxicity but only in situations where there is very high-level exposure. 2,4,5-T may contribute to birth defects when pregnant females are exposed. There is no evidence that purified 2,4-D or 2,4,5-T cause cancer, change the activity of enzymes, affect the immune system, or cause chloracne or porphyria cutanea tarda in humans.

There is very little direct evidence that Agent Orange causes adverse health effects in humans, but this may be the result of our limited ability or inability to identify different groups of people or large numbers of people with well-defined exposure and exposure to a known amount of the substances of concern. If adverse human health effects are found as a result of present or future research efforts, it is highly likely that these will be the result of the effects of toxic impurities such as dioxins, especially TCDD. The limited evidence of TCDD toxicity in humans comes from studies of humans exposed to dioxins, and indirectly from studies of dioxin toxicity in experimental animals. These studies provide some support for the possibility, but do not prove, that exposure to dioxin-contaminated herbicides may cause adverse health effects in humans.

These adverse effects may include chloracne, cancer at several different sites, spontaneous abortion and birth defects in the offspring of exposed females, altered enzyme activity, altered porphyrin metabolism, and altered immune function. Effects for which the available evidence is very inconclusive but which should be the subject of further study are neurobehavioral effects, including psychologic effects and heart disease. Chloracne does not seem to be of significant importance since it has not been commonly observed even among individuals heavily exposed to herbicides. Therefore chloracne does not appear to be a sensitive indicator of exposure to dioxin-contaminated herbicides.

What will future studies tell us about the health effects of exposure to Agent Orange? Studies that are planned or in progress have the potential to reduce much of the uncertainty about the health effects of exposure to Agent Orange. However, because of very serious problems in determining the exact amount and nature of exposure and in choosing appropriate

exposed and unexposed groups to examine, these studies will never be able to demonstrate conclusively the *absence* of a toxic effect. The areas in which future studies may be able to provide the most information are the delayed effects such as cancer.

Studies in experimental animals can still be helpful in suggesting possible adverse health effects of Agent Orange. Particularly helpful would be studies of the purified components of Agent Orange separately and in known combinations. Other important areas of investigation include effects on immune function and the genetic control of susceptibility to the toxic effects of dioxin.

In the meantime, exposed individuals can get some degree of reassurance from the fact that despite their inadequacies, the studies which have been completed to date have revealed no widespread or major adverse health effects among the people who were exposed. There is no evidence that the psychologic disturbances seen in Vietnam veterans are the result of exposure to Agent Orange.

For many of the potential health effects, there is little probability that they will first appear years after exposure. These include reproductive and enzyme effects, chloracne, and neurobehavioral problems. It is possible that cancer may first appear years after exposure. Persons exposed to Agent Orange should take no exceptional precautions beyond those that are prudent for everyone, i.e., consume a balanced diet, exercise regularly, have regular medical checkups, be alert for tell-tale signs of cancer, abstain from smoking, and use alcohol moderately, if at all.