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Journal/Book Title	
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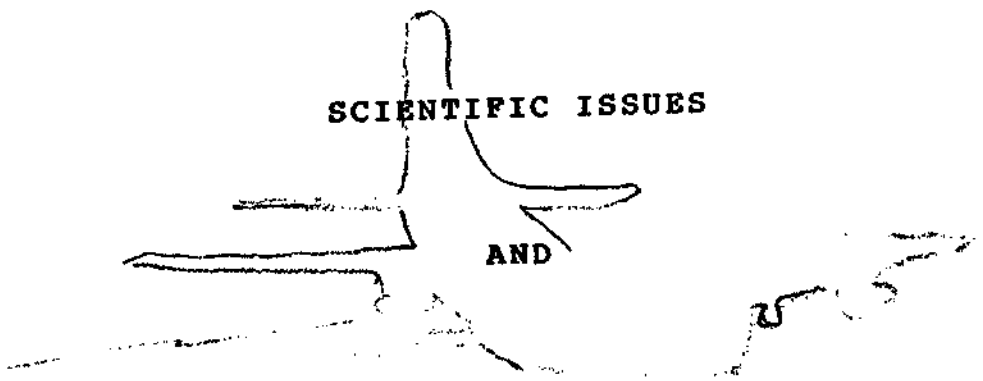
Description Notes	Items were filed together under the above heading.



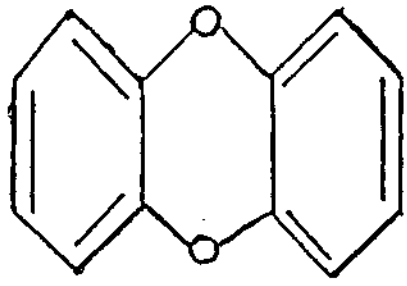
SCIENTIFIC ISSUES

AND

AGENT ORANGE EXPOSURE

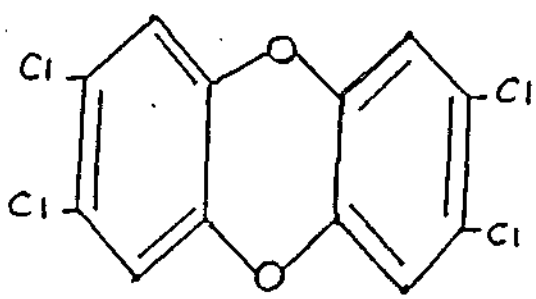
Slides for Q-T-AO presentation

"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?

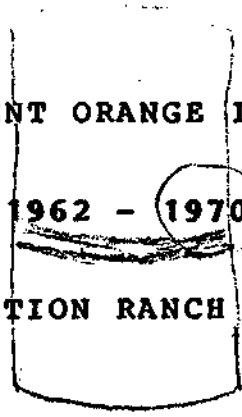
SOURCES OF HUMAN EXPOSURE

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

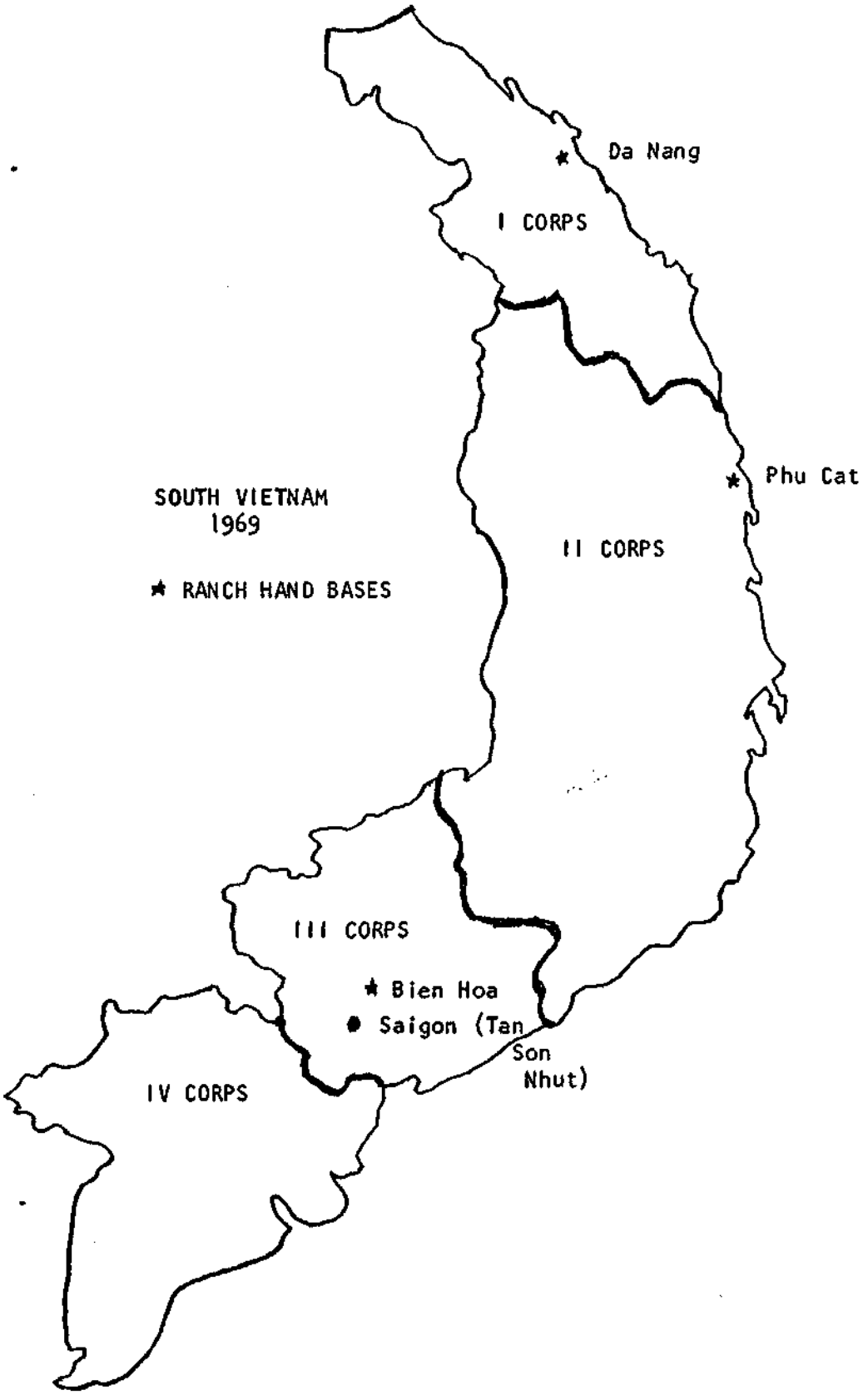
USE OF AGENT ORANGE IN VIETNAM

1962 - 1970 ~~1977~~

"OPERATION RANCH HAND"



More specific time frame 67-69 heaviest


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

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

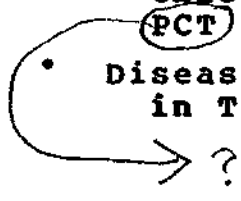
Chemical	Pounds
2,4-D	55,940,150
2,4,5-T	44,232,600
TCDD	368

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
- Abnormal liver function
- Sexual dysfunction
- Loss of appetite and weight
- Sleep disturbances
- Decreased memory and learning ability

HOW IS THE FEDERAL GOVERNMENT ADDRESSING VETERAN CONCERNS?

WHITE HOUSE	**AGENT ORANGE WORKING GROUP**	**CAPITOL**

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-JAN 1984

AIR FORCE HEALTH STUDY-JAN 1984

CONCERN - DYING IN INCREASED NUMBERS,
AT EARLIER AGES OR FROM UNEXPECTED CAUSES?

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 (JAN 1984)

VA MORTALITY STUDY (DEC 1984)

CONCERN - CONNECTIVE TISSUE CANCER
(SOFT TISSUE SARCOMA)

COMPLETED: SWEDISH SOFT TISSUE SARCOMA (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: NO PROVEN CASES in Vietnam veterans

ON-GOING STUDIES: AIR FORCE HEALTH STUDY-JAN 1984

CONCERN - OTHER HEALTH PROBLEMS? Why (?) be considered

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
  and Patient Treatment File
- Health Care
  Public Law 97-72

SEP 2 8 1983

USE OF HERBICIDES IN VIETNAM

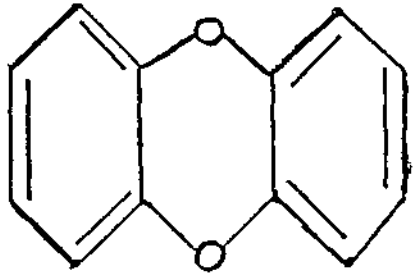
1961–1971

(1) Dioxin is contaminant (368#/10^6 + gals)

(2) Stress need for sci. study vs. post hoc argument

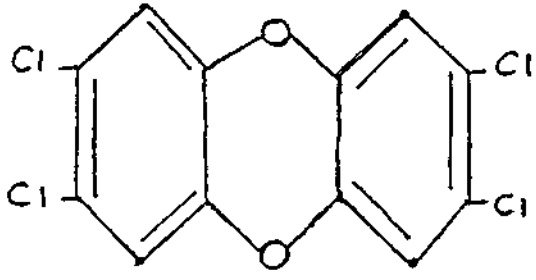
(3)

A dioxin is any of a family of compounds known chemically as dibenzo-para-dioxins.



There are 75 different chlorinated dioxins.
There are 22 different tetra isomers

Dioxin of Concern = 2,3,7,8-TCDD



SOURCES OF HUMAN EXPOSURE

- o Industrial Accidents (Trichlorophenol Production)
- o Occupational Exposure (NIOSH Dioxin Registry)
- o Contaminated Industrial Wastes (Missouri Episode)
- → o Herbicide Applications (Vietnam Episode)
- o Transportation Accidents
- o Food - Contaminated Fish (Great Lakes)
- o Low Temperature Combustion
- o Hexachlorophene Exposures

Significance: VA Adipose Study

TOXICITY OF 2,3,7,8-TCDD

Acute Toxicity:	Single Dose LD_{50} (µg/kg)
Guinea Pig	0.6
Rat	40
Rabbit	115
Monkey	70
Dog	150
Mouse	200
Hamster	3500
Bullfrog	Over 1000
Man	No deaths reported in literature
Teratogenic (Birth Defects)	
Mouse	Cleft palate, kidney abnormality
Other species	Embryo-and Fetotoxic
Mutagenic (Mutation)	Probably not a mutagen in higher animals
Carcinogenic (Cancer)	Liver, lung and oropharynx cancer noted in rats

Significance: Bioavailability on Environmental matrices

EXPOSURE TO AGENT ORANGE CAN

NEVER BE QUANTIFIED!

HOWEVER

AN INDEX FOR LIKELIHOOD OF EXPOSURE

HAS BEEN DEVELOPED

EPIDEMIOLOGY IS THE STUDY OF THE FREQUENCY AND CAUSE OF DISEASE IN HUMAN POPULATIONS.

- CASE-CONTROL STUDY - SUBJECTS (CASES) ARE SELECTED FOR HAVING A PARTICULAR DISEASE AND CONTROL SUBJECTS ARE SELECTED ON BASIS OR ABSENSE OF DISEASE. THE EXPERIENCES OF THE TWO GROUPS ARE COMPARED.

- COHORT STUDY - STUDY POPULATION IS SELECTED ON THE BASIS OF KNOWN EXPOSURE AND KNOWN NON-EXPOSURE AND IS EXAMINED FOR THE PRESENCE OF DISEASE.

HOW DO WE REACH A SCIENTIFIC CONSENSUS?

CONSENSUS WILL BE ACHIEVED WHEN:

- EPIDEMIOLOGICAL DATA ARE STATISTICALLY SIGNIFICANT
- RESEARCH FINDINGS CAN WITHSTAND THE SCRUTINY OF PEER REVIEW
- AND RESEARCH RESULTS CAN BE DUPLICATED BY OTHER INVESTIGATORS.

ARE THERE ANY DISEASES ON WHICH THE MEDICAL COMMUNITY HAS REACHED CONSENSUS AS BEING ASSOCIATED WITH DIOXIN EXPOSURE?

YES!

- Chloracne
- Temporary Health Effects

CHLORACNE - SKIN CONDITION, RESEMBLING COMMON ACNE, WHICH APPEARS WITHIN A FEW WEEKS OF EXPOSURE TO DIOXIN AS WELL AS SOME OTHER CHLORINATED CHEMICAL COMPOUNDS.

OTHER CONDITIONS REPORTED IMMEDIATELY AFTER DIOXIN EXPOSURE AND THAT ARE TEMPORARY

ABNORMAL LIVER FUNCTIONS

HEADACHE

APATHY

FATIGUE

MUSCLE PAIN

JOINT PAIN

SEXUAL DYSFUNCTION

LOSS OF APPETITE

WEIGHT LOSS

SLEEP DISTURBANCES

DECREASED LEARNING ABILITY

DECREASED MEMORY

TINGLING IN EXTREMITIES

WHAT ARE THE LONG-TERM HEALTH ISSUES WHICH HAVE BEEN ATTRIBUTED TO THE USE OF AGENT ORANGE IN VIETNAM?

- Skin disorders including chloracne and PCT
- Birth Defects and Miscarriages
- Increased Death Rate
- Development of unusual or rare cancers
- Dioxin in human tissue as a cause of future disease

HAS CHLORACNE BEEN DOCUMENTED
IN VIETNAM VETERANS?

PRESENT STATUS: INITIAL REVIEW OF OVER 3,000
VIETNAM VETERAN CLAIMS REVEALED
NO DEFINITE CASES OF CHLORACNE.

ON-GOING STUDIES: AIR FORCE HEALTH STUDY-JAN 1984

ARE VIETNAM VETERANS MORE LIKELY TO HAVE CHILDREN WITH BIRTH DEFECTS?

PRESENT STATUS: EPA ARKANSAS STUDY-1979

NIOSH NEW YORK STATE STUDY 1979

NEW ZEALAND HERBICIDE APPLICATORS-1982

AUSTRALIAN BIRTH DEFECTS STUDY-1983

PRESENT CONCLUSION: MEN AND WOMEN ARE AT NO INCREASED RISK

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

AIR FORCE HEALTH STUDY-JAN 1984

ARE VIETNAM VETERANS DYING IN INCREASED NUMBERS, AT EARLIER AGES OR FROM UNEXPECTED CAUSES?

STUDIES COMPLETED: FOUR INDUSTRIAL HEALTH STUDIES-1980-1983

FINLAND MORTALITY STUDY OF HERBICIDE APPLICATORS-1982

AIR FORCE HEALTH STUDY-BASELINE MORTALITY-1983

PRESENT CONCLUSION: NO EVIDENCE OF INCREASED DEATH RATE

ON-GOING STUDIES: NEW YORK STATE MORTALITY STUDY (JAN 1984)

VA MORTALITY STUDY (DEC 1984)

ARE VIETNAM VETERANS MORE LIKELY TO DEVELOP CONNECTIVE TISSUE CANCER (SOFT TISSUE SARCOMA)?

COMPLETED STUDIES: SWEDISH SOFT TISSUE SARCOMA (STS) STUDIES-1978-1983

NEW ZEALAND STS STUDY-1982

FINLAND CANCER STUDY-1982

INDUSTRIAL STUDIES-1980-1983

PRESENT CONCLUSION: NO CONSENSUS

ON-GOING STUDIES: NCI STUDIES IN KANSAS, WASHINGTON, MINNESOTA-1984/85

VA/ARMED FORCES INSTITUTE OF PATHOLOGY (VIETNAM VETERAN STUDY)-1985

CENTERS FOR DISEASE CONTROL STUDY-1985

NIOSH INVESTIGATION-1985

NEW YORK STATE DEPARTMENT OF HEALTH-1984

ARE VIETNAM VETERANS MORE LIKELY
TO DEVELOP OTHER FORMS OF CANCER?

COMPLETED STUDIES: FINLAND CANCER STUDY-1982

SWEDISH RISK EVALUATION OF PESTICIDES-1982

NCI FLORIDA PESTICIDE APPLICATOR STUDY-1983

INDUSTRIAL STUDIES-1980-1983

PRESENT CONCLUSION: NO CONSENSUS

ON-GOING STUDIES: AIR FORCE HEALTH STUDY-1984

NIOSH DIOXIN REGISTRY-1985

CDC AGENT ORANGE EPIDEMIOLOGIC STUDY-1987

DO VIETNAM VETERANS WHO WERE EXPOSED TO AGENT ORANGE HAVE RESIDUAL LEVELS OF DIOXIN IN THEIR BODY TISSUE? IF SO, IS IT LIKELY TO CAUSE ANY HEALTH PROBLEMS?

STUDIES COMPLETED: VA FEASIBILITY STUDY

PRESENT CONCLUSIONS: SMALL AMOUNTS OF DIOXIN CAN BE DETECTED

NO CORRELATION BETWEEN DIOXIN LEVEL, EXPOSURE OR HEALTH

ON-GOING STUDIES: VA/EPA DIOXIN AND FURAN STUDIES OF HUMAN ADIPOSE TISSUE

ARE THERE OTHER HEALTH PROBLEMS
PECULIAR TO VIETNAM VETERANS?

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

OTHER RELATED EFFORTS: VA AGENT ORANGE REGISTRY
VA PATIENT TREATMENT FILE

Data?

COMPONENTS OF THE FEDERAL STUDIES

ON-GOING HEALTH SURVEILLANCE

MORTALITY

MORBIDITY

SOFT TISSUE SARCOMAS/LYMPHOMAS

REPRODUCTIVE PROBLEMS

TCDD IN HUMAN ADIPOSE

INFORMATION DISSEMINATION

EPIDEMIOLOGICAL STUDY - CHRONOLOGY

December 1979	- Congress passes the "Veterans Health Programs Extension and Improvement Act of 1979." PL 96-151, Section 307 of the Act directs the Administrator to design a protocol for and conduct an epidemiological study of Vietnam veterans who were exposed to dioxins contained in herbicides (Agent Orange).
December 20, 1979	- President signs the Act into law.
January 8, 1980	- Decision made to use the competitive procurement method to obtain the required services for the design of the protocol.
January 10, 1980	- President directs the Administrator to forward protocol to Director, Office of Technology Assessment (OTA) for information purposes only.
February 4, 1980	- Announcement of intent to let contract for the design of the protocol published in Commerce Business Daily.
February 6, 1980	- Administrator advises OTA of President's directive and offers to cooperate to the extent that the Constitution permits.
February 21, 1980	- Chairman, Senate Veterans Affairs Committee, advised by Administrator of President's directive and assures him that VA would not proceed with a protocol to which OTA had serious objection.
March 19, 1980	Request for proposals issued.
April 11, 1980	- Pre-bid conference conducted by VA at VACO.

May 6, 1980	- National Veterans Law Center initiates legal action attempting to obtain a temporary restraining order to preclude VA from opening any proposals received for the contract for the design of the study.
May 7, 1980	- Court denies motion for temporary restraining order but retains jurisdiction.
May 8, 1980	- Last day for receipt of bids.
May 1980	- A selection panel of government epidemiologists (including one from OTA) reviews bids received and makes tentative ranking. On advice of U.S. attorney no further action is taken because of litigation and pending referral of bid protest to GAO.
June 13, 1980	At the request of the National Veterans Law Center, Judge Green refers matter to GAO to rule on bid protest.
June 1980	- VA General Counsel, with concurrence of Department of Justice, advises against award of contract prior to resolution of pre-award protest.
February 2, 1981	- GAO rules entirely in favor of VA.
February/March 1981	- VA contacts bidders and allows updating of submission if still interested in and capable of designing study protocol.
April 1981	- Panel of experts reconvened to review revised bids.
May 1, 1981	- School of Public Health, U.C.L.A., selected to design study protocol.
May 1, 1981	- U.C.L.A. receives notice of award. (contracted for $114,288). Has 60 days to submit draft of study protocol.
June 1981	- U.C.L.A. granted 30 day extension for submission due to difficulty experienced in working with DoD records.

August 6, 1981	- Preliminary design submitted by U.C.L.A.
August 1981	- VA submits design to Agent Orange Working Group, VA's Advisory Committee and OTA for review and comment.
October 8, 1981	- Response received from OTA and provided to U.C.L.A.
October 21, 1981	- Response from Science Panel, Agent Orange Working Group received.
November 3, 1981	- PL 97-72 signed, allowing Administrator to expand study to include other factors in Vietnam experience.
November 6, 1981	- Response received from VA's Advisory Committee.
November 9, 1981	- Responses from review groups sent to UCLA.
November 18, 1981	- Senate Committee on Veterans Affairs hearing on Agent Orange.
November 25, 1981	- VA notified UCLA that submission, as received and reviewed, was inadequate and allowed UCLA 35 days to resubmit.
December 14, 1981	- UCLA requested additional 35 days (to January 25, 1982) because of Principal Investigator's illness.
January 22, 1982	- Revised protocol for epidemiological study submitted to VA by UCLA with recommendation for two cohort effort.
February 1982	- Revised protocol provided to Agent Orange Working Group (AOWG), VA's Advisory Committee, and OTA.

March 24, 1982	- AOWG completed review of protocol and endorsed the design with certain recommendations.
March 1982	- OTA completed review with findings similar to those of the AOWG. VA's Advisory Committee members submit views. Comments sent to UCLA.
April 29, 1982	- Third and final protocol submission received from UCLA.
May 1982	- Revised protocol provided to Agent Orange Working Group and OTA.
May 13, 1982	- During special closed session, VA's Advisory Committee reviewed third submission.
May 20, 1982	- Contract signed with National Academy of Sciences (NAS) for review of proposed protocol.
June 10, 1982	- VA requested AOWG views on a number of issues, including selection and use of cohorts.
July 2, 1982	- Letter from DoD to AOWG argued for three cohort study.
July 6-8, 1982	- NAS review began.
July 15, 1982	- Science Panel of AOWG discussed cohort selection and established subcommittee to recommend how cohorts should be identified.
August 23, 1982	- NAS requests extension of time until October 31 to complete review of protocol.
September 3, 1982	- Cohort selection sub-committee sent status report to AOWG suggesting method of cohort identification to be tried in pilot test.
September 7, 1982	- VA requests additional justification from NAS to substantiate time extension.

September 15, 1982	- Subcommittee on Oversight and Investigations of House Committee on Veterans' Affairs held hearings on Federal Agent Orange activities. Witness from Centers for Disease Control (CDC) suggested that CDC could have designed and initiated the study more expeditiously than VA.
September 27, 1982	- Letter fron Congressman G.V. (Sonny) Montgomery (Chairman, House Committee on Veterans' Affairs), John Paul Hammerschmidt (Ranking Minority Member, House Committee on Veterans' Affairs and Ranking Minority Member, Subcommittee on Hospitals and Health Care), and Ronald M. Mohl (Chairman, Subcommittee on Hospitals and Health Care) recommended that VA contract with CDC to "conduct all phases of the Agent Orange Study."
September 30, 1982	- Letter from Administrator to Secretary of Health and Human Services (HHS) concerning possibility of transfer of study to CDC.
	- Letter from Office of Technology Assessment concerning progress on the study and the need to make decisions about the basic design of the study.
October 6, 1982	- Letter from Congressman Tom Daschle and 99 other members of Congress proposed that CDC "assume responsibility over the remaining segments" of the study.
October 14, 1982	- Letter from Administrator to Secretary of HHS requesting information on CDC's interest in performing the study.
	- Letter from Administrator to Chairman Montgomery stating "that it would be prudent to enter into an agreement with a non-VA scientific body" to perform study. Letter noted contact with HHS in effort to transfer study to CDC.

October 22, 1982	- Letter from Secretary of HHS to Administrator acknowledging letters of September 30 and October 14. He agrees in principle to the transfer of the study to CDC provided adequate resources are made available and requests that copies of all pertinent documents be forwarded to CDC.
	- Meeting between Chief Medical Director, VA, and Assistant Secretary for Health, Human Services (HHS). Agreement in principle to transfer study to CDC.
October 28, 1982	- NAS comments on proposed protocol received by VA.
November 23, 1982	- VA draft of interagency agency agreement submitted to CDC for review and comment.
November 31, 1982	- Chief Medical Director (CMD) discussed transfer of study at open meeting of VA Advisory Committee on Health-Related Effects of Herbicides. CMD indicated desire for expeditious finalization of interagency agreement.
December 6, 1982	- Letter from Assistant Secretary for Health, HHS, concerning transfer of study enclosed CDC's version of proposed interagency agreement and CDC's proposed protocol outline and tentative timetable for conduct of the study.
December 23, 1982	- Letter from CDC outlining requirements for conduct of epidemiology study

January 13, 1983 - Letter from CMD to Dr. Brandt, Assistant Secretary for Health, DHHS, transmitting interagency agreement signed by VA for review and signature by CDC.

January 14, 1983 - Interagency agreement between VA and HHS signed transferring epidemiology study to CDC.

February 2, 1983 - OTA receives copy of CDC's proposed study protocol. Copies forwarded to members of OTA Agent Orange Advisory Panel.

March 3, 1983 - Letter from John Gibbons, OTA, to Administrator commenting on CDC's "Outline" (protocol). Advised in letter that CDC expects to complete drafting of protocol into April or early May. Protocol outline and tentative timetable for study transmitted by letter.

March 4, 1983 - Letter from Assistant Secretary for Health, DHHS, to CMD briefly outlining CDC's FY 1983 resource requirements and suggested FTEE requirements for FY 1984. Request made by DHHS that VA take expeditious action to obtain OMB approval for transfer of resources. Draft letter from DHHS to OMB outlining resource justification provided to CMD.

March 11, 1983 - Meeting at VACO between Dr. David Erickson, CDC, Agent Orange Projects Staff, Comptroller's Office and Supply Service to discuss CDC's justification package for 28 FTEE requested by CDC in FY 1983. Participants advised by Dr. Barclay M. Shepard that a stronger justification is required. A conference call at this time with Annette Rooney, OMB, resulted in CDC agreement to prepare a stronger justification package and to participate in a March 18 meeting at OMB on CDC's request for FTEE.

- Dr. Barclay M. Shepard advised by Mr. Claud Picklesheimer, Finance Office, CDC, that CDC was under impression that $3 million was FY 83/84 money. Advised by Dr. Shepard that resources would be lost at close of fiscal year. Dr. Shepard urged that CDC request funds as soon as staff are on board for study and funds can be obligated.

March 15, 1983	- Administrator directs DM&S to continue to provide all necessary support and to expedite the transfer of resources to CDC in order to assist CDC in initiating the epidemiology study in the immediate future.
	- Contact made with Dr. David Erickson, CDC, requesting CDC participation in March 18 meeting at OMB to justify to OMB the resources requested by CDC.
March 17, 1983	- Letter transmitted from Assistant Deputy Administrator, Budget and Finance to OMB forwarding proposed study outline and request for personnel resources as submitted to VA by CDC.
March 18, 1983	- Meeting between VA/CDC/OMB at OMB on justification of resources requested by CDC.
March 25, 1983	- Letter from Administrator to Sam Clarkson, OMB, requesting 28 positions (14.0 FTEE) and notification that CDC is to provide VA with complete budget estimates and justification for FY 84 and beyond.
April 15, 1983	- Meeting with OMB representative and VA staff on need to request further justification for CDC's FY 1984 budget requirements.
May 27, 1983	- CDC FTEE justification for FYs 1984-1988 transmitted to VA
May 30, 1983	- Justification forwarded to OMB after internal review by VA
June 9, 1983	- CDC resource (dollars) justification to support FY 1984 epidemiology activities transmitted to OMB
	- Conference call between VA, CDC & OMB to further clarify CDC's justification for requested resources to support epidemiology study.

JUNE 9, 1983 - VA advised by CDC of projected information Collection Budget hours essential to conduct of study in FY 1984

JULY 1, 1983 - VA advised by CDC that CDC will require entire $2.1 million identified in FY 82/83 resources for necessary personnel services and ADP support.

JULY 21, 1983 - Projected FY 1983 obligation schedule for the $2,144,000 provided by CDC to VA including cumulative obligations through June, 1983, July-August to be estimated obligations

Recent Publications on the Dioxins

Tucker, R. E., A. L. Young, and A. P. Gray (Editors). 1983. Human and Environmental Risks of Chlorinated Dioxins and Related Compounds. Plenum Press, New York. 823 pages.
"Proceedings of the Second International Symposuim on Chlorinated Dioxins and Related Compounds", October 25-29, 1981, Arlington, Virginia.

Hutzinger, O., A. W. Frei, E. Merian and G. Reggiani (Editors). 1983. Chlorinated Dioxins and Related Compounds. 1982. Chemosphere 12(4/5):425-790.
"Proceedings of the Third International Symposuim on Chlorinated Dioxins and Related Compounds", October 12-14, 1982, Salzburg, Austria.

Coulston, F. and F. Pocchiari (Editors). 1983. Accidential Exposure to Dioxins - Human Health Aspects. Ecotoxicology and Environmental Quality Series. Academic Press, New York. 294 pages.
"Proceedings of an International Forum on Human Aspects of Accidential Chemical Exposure to Dioxins - Strategy for Environmental Reclamation and Community Protection", October 4-7, 1981, Bethesda, Maryland.

Choudhary, G., L. H. Keith, and C. Rappe. 1983. Chlorinated Dioxins and Dibenzofurans in the Total Environment. Butterworth Publishers, 10 Tower Office Park, Worburn, MS 01801. 512 pages
"Proceedings of the 1982 American Chemical Society's Symposium on Chlorinated Dioxins and Dibenzofurans in the Total Environment - I, September 1982, Kansas City, Missouri.

Extended Abstracts of the Division of Environmental Chemistry, American Chemical Socity's 186th National Meeting, Washington, D.C., August 28-September 2, 1983. Volume 23 No. 2. 1983. Available from Division of Environmental Chemistry, Attn: Gordon Bellen, c/o National Sanitation Foundation, P.O. Box 1468, Ann Arbor, MI 48106. 520 pages.
"Extended Abstracts of the ACS Symposium on Chlorinated Dioxins and Dibensofurans in the Total Environment - II" August 29-31, 1983, Washington, D.C.

9/9/83
MTL

BACKGROUND ON AGENT ORANGE AND DIOXIN

1. Nature of Agent Orange

- Is a defoliant, 50-50 mixture of n-butyl esters of 2,4,5-T and 2,4-D.
- Is contaminated by herbicide 2,4,5-T (2,4,5 trichlorophenoxyacetic acid), made from TCP (2,4,5 trichlorophenol)
- The toxic component of 2,4,5-T is 2,3,7,8-tetracholorodibenzo-p-dioxin (shortened as dioxin or TCDD).

2. Toxicity, Teratogenicity, Carcinogenicity of Dioxin

- Claim that dioxin is the "deadliest man-made substance" is based on its extreme toxicity in guinea pigs (.6mg per kg of body weight will kill half of the male guinea pigs receiving the dose).
- However, toxicity varies among animal species: less toxic in rabbits, mice and monkeys, least toxic in hamsters.
- Some toxicologists classify dioxin as a weak teratogen in animals. It is also shown to be fetotoxic in animals. Strong carcinogenicity in rats and mice. Some researchers speculate that dioxin may be a promoter, rather than an initiator of carcinogenicity; this theory is being studied.
- Diseases claimed to be linked to dioxin (and addressed by some currently proposed legislation) are:

  chloracne: skin lesion
  soft-tissue sarcoma: a rare form of cancer affecting muscle, nerve and fat tissue
  porphyria cutanea tarda: tumors in liver

- Studies of industrial accidents to determine the acute effects of dioxin on humans show that they are less sensitive to the toxic effects of dioxin than are guinea pigs (no clear case of human death caused by dioxin). Other acute symptoms, e.g., chloracne, generally disappear after a few years.
- Chronic effects of dioxin are much less well understood:
  - A Swedish study linked soft-tissue sarcoma to use of phenoxy herbicides. Method of study has been criticized, particularly because this disease is rare and pathologists have little experience in identifying it.

- Other studies link dioxin to miscarriage and birth defects, but design flaws in these studies cause scientists to question their validity.

- Other studies do not show this association: study in state of Washington shows high incidence among marine engineers and bankers, who are not exposed; New Zealand study shows no cases among herbicide applicators.

- Many on-going studies. The major ones are:

  1. Ranch Hand study (by the Air Force) of AF personnel who applied Agent Orange. Mortality data released on July 1 showed no significant difference between them and control groups. Morbidity data expected in October. This study will go on for 2,3 years.

  2. Birth defect studies (by CDC) examine children born in Atlanta from VN veterans and from non-VN veterans. Results expected next year.

  3. Ground Troops Epidemiology study (by CDC) to determine the effects of Agent Orange. Currently under review by Science Panel of Cabinet Council Working Group on Agent Orange.

3. Legislative Activity

- Five bills have been introduced and referred to the Committee in the House, four in the Senate. Of those, the ones most likely to move ahead are H.R.1961 sponsored by Thomas Daschle, and S.786 (companion bill) sponsored by Larry Pressler. Both establish presumption of service connection. Pressler's bill include "phenoxy herbicides as well as other environmental factors."

- OMB is concerned about S.1651, Cranston's bill. A similar bill was defeated in the House, but Cranston is attempting to introduce an amendment to VA compensations bill, which cannot be vetoed.

- Cranston's bill provides for presumption of service connection for diseases associated with Agent Orange (soft-tissue sarcoma, porphyria cutanea tardea and chloracne, with specific timeline) and radiation (malignancy, polycythemia vera or hypothyroidism). Requires regulations setting standards for compensation, giving veterans benefit of any doubt.

  (Jonathan Weinberg, staff to Cranston, very knowledgeable and very mean)

4. Dioxin and Agent Orange History

1948: 2-4-5 T first registered in the U.S. as a pesticide on March 2.

1949: First industrial accident at Monsanto plant in West Virginia exposing 250 workers.

1955: 2,3,7,8-TCDD first diagnosed as the cause of chloracne.

1962 to 1970: Spraying in Viet Nam. Stopped due to health and ecological concerns. Seven or so varieties of herbicides were used (of which agent orange has far less 2,3,7,8-TCDD: 1.98 ppm compared to as high as 65.6 ppm in agents pink and green).

1970: Dioxin's teratogenicity, fetotoxicity first reported in animals. USDA suspends some uses of 2,4,5-T.

1971: EPA cancels 2,4,5-T use on most food crops.

1972: FDA bans use of hexachlorophene in nonprescription soaps and deodorants.

1973: Vietnamese study links higher incidences of liver cancer, abortions and birth defects to agent orange spraying in that country.

1976: Industrial accident in Seveso, Italy releases several pounds of dioxin in densely populated area.

1978: EPA issues rebuttable presumption against registration for remaining uses of 2,4,5-T based on evidence of cancer, birth defects and fetal deaths in animals.

1979: EPA issues emergency suspension order to ban remaining 2,4,5-T uses except on rangeland and ricefields.

Class action suit on behalf of Viet Nam veterans against five manufacturers of agent orange. These manufacturers filed a third party action against the U.S. government for negligent misuse of the chemicals.

1981: Class action suit on behalf of Vietnam veterans filed against VA and DOD.

1982: Discovery of dioxin contamination in eastern Missouri.

1983: EPA offers to buy Times Beach, Missouri. As of May 1, 1983, VA has received 17,068 claims for disability payments because of agent orange exposure, and VA has treated 369,000 outpatients and 9600 veterans who claim

their medical problems are related to dioxin exposure. VA has resisted compensation due to insufficient evidence of connection between the illnesses claimed and exposure.

9/23/83

Q & A's on Agent Orange

QUESTION: The most often heard reason for not taking actions is that we don't know enough, first with acid rain, now with agent orange. Would the scientific questions regarding agent orange ever be resolved to satisfaction?

ANSWER: Science may never give us answers with perfect certainty. But then we must make decisions based on partial information most of the time. However, partial information is different from no information or misleading information, which is what we have now with agent orange.

QUESTION: How long would it take to develop sufficiently good information upon which to base decision? Can we afford to wait that long?

ANSWER: Knowledge can always be improved, but we can afford to wait for the major studies now ongoing to yield at least the first results. These first results won't answer all the scientific questions, but they provide a better basis for decision because, unlike previous studies they have been designed to answer the questions relevant to compensation decisions. The CDC studies, for example, cover a very large sample.
Also, by acting precipitously, we would be sending signals to the public that they have cause for alarm, and we would create for ourselves a situation where we cannot afford to wait for an adequate scientific basis.

QUESTION: If PCT is a rare disease, why should OMB be concerned about runaway costs, even under presumption of causation?

ANSWER: PCT caused by agent orange manifests itself within a short time period, ~~and also disppears within a short time.~~ However, PCT can have other causes, including genetic causes and alcohol and drug abuse. For these latter causes, the condition can last a long time. Presumption of causation would lead to compensating individuals not exposed to agent orange.

QUESTION: Agent orange is only one specific case. Health problems could have arisen from exposure to other herbicides used in Viet Nam, e.g., agent purple. Is the connection between other herbicides or other dioxins and health problems better established scientifically?

ANSWER: As far as we know, The other dioxins are much less ~~harmful~~ potent than 2,3,7,8-TCDD in Agent Orange.

QUESTION: The Congress always acts under pressure from its constituents. In this case, the public, and among them the veterans in particular, is not necessarily familiar with scientific data and are justifiably concerned. What are you doing to improve the public's knowledge?

The results of studies are published as they come out. Obviously, we are not as effective as the media because scientific data, particularly those showing no correlation with illnesses, are not as striking and sensational. We will continue to open our activities to public scrutiny and respond to any questions. Any assistance we can get from the Congress in communicating with your constituents would further serve to calm ~~unfounded~~ fears based on misinformation.

2. AGENT ORANGE

A. Briefings of Senators

Republican: 10/20/83 9:30 a.m. to 11:30 a.m. Room 450
Democratic: 10/27/83 10:00 a.m. to 12:00 a.m. Room 450

Background:

Our office has the lead, and the Veterans Administration assists us. The briefings were requested by Tom Harvey (Chief Counsel to Senator Simpson, Chairman of the Veterans Affairs Committee) to John Cogan of OMB. Cogan in turn asked JK to host these briefings. This is a favor from OSTP to OMB.

To be done:

- Finalize JK's speech and Q and A's.
- Review and comment on Al Young's briefing.
- Send out letters to Democratic Senators no later than 10/15/83.
- 10/15/83 and 10/22 Make sure we still have Room 450 (Raise .... if we don't)
- 10/15/83 or some time before briefing date, visit Room 450 to find out how projector would be set up for slide presentation.
- Revise JK's speech and Q and A's for Democratic Senators based on reaction from earlier briefing.

Contacts:

- Alvin L. Young, Air Force, Lt. Colonel, detailed to VA
- John Murphy, VA General Counsel (the key point of contact if we have something to request of VA)
- John Gronvall, VA Deputy Medical Director
- Tom Harvey, Chief Counsel to Senator Simpson
- John Merck, OMB (Branch Chief under John Cogan)
- Robert Willmore, OMB (Staff to Mike Horowitz, OMB General Counsel)

(Phone numbers on Minh-Triet's Rolodex)

AGENT ORANGE FACT SHEET

U.S. Research Efforts Underway

• 64 Federally sponsored research efforts costing more than $150 million are currently underway.

• More than 10 studies are specific only to Vietnam veterans.

Some Study Results to Date

• Agent Orange Registry. Extensive information on all Vietnam veterans who have received an Agent Orange Exam. VA analysis of exam results of 85,000 persons indicate no unusual incidence of disease.

• Air Force Ranch Hand study. No statistically significant differences have been found in the death rates of the Air Force personnel involved in Agent Orange spraying in Vietnam compared to a non-Ranch Hand comparison group.

• Australian Birth Defects Study. Determined that Australian vets who served in and may have been exposed to Agent Orange in Vietnam were not at increased risk of fathering a malformed child.

Government Bodies Involved in Agent Orange Research

• Studies are conducted and funded by five Federal agencies, coordinated by a Cabinet level White House Agent Orange Working Group.

• 18 State Agent Orange Commissions conduct research and outreach programs about the possible health effects of Agent Orange exposure.

• Scientific oversight of Federal activities is conducted by Office of Technology Assessment, the General Accounting Office, the National Academy of Sciences, the Advisory Committee on Special Studies Related to the Long-Term Health Effects of Phenoxy Herbicides and Contaminants, and the VA Advisory Committee on Health Related Effects of Herbicides.

Congressional Efforts

• P.L. 96-151. Directed the VA to conduct an epidemiological study of persons who served in the U.S. Armed Forces during the Vietnam conflict to determine if they have suffered long-term adverse health effects resulting from exposure to the dioxin in Agent Orange.

• P.L. 97-72. Authorized priority medical care in VA medical facilities, pending results of P.L. 96-151 study, for Vietnam veterans who suffer from health effects they believe to be related to Agent Orange exposure.

• 8 Congressional hearings held by the Senate and House Veterans' Affairs Committees on Agent Orange/Dioxin to date during the 98th Congress.

• Pending legislation: S. 374, S. 786, S. 991, S. 1651; H.R. 1961

VA Health Care For Vietnam Veterans

• Agent Orange Physical Exams. Some 120,000 Vietnam veterans have received initial exams and some 28,000 have received follow-up exams.

United States of America

Congressional Record

PROCEEDINGS AND DEBATES OF THE 98th CONGRESS, FIRST SESSION

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Senate

Mr. SIMPSON. Mr. President, my colleagues may know, that I am not much in the habit of submitting for publication in the CONGRESSIONAL RECORD any newspaper article that I may come across that strikes my fancy or serves only to support a securely held position of mine. But recently I came upon an article in the Baltimore Evening Sun by Pulitzer prizewinning reporter Jon Franklin, which presented to me a very interesting and compelling new perspective on an extraordinarily tough, hard, complex, and emotional issue.

The issue is agent orange, and the emotion bubbles along at an all-time high. There is major legislation pending in both Houses which would respond to that heavy charge of emotional pressure by establishing various new schemes for payment of VA compensation to veterans who were allegedly exposed to agent orange. I do feel that before we become overwhelmed by the simple emotional appeal of this form of bill, that we should examine the issue with some very real care and without the present impatience, frustration and emotional bias.

I feel it is most important to recognize that the inclination to trivialize or oversimplify the issue of agent orange is evident on both sides of the issue. It is my view that both attitudes border on the irresponsible—whether the attitude be that the Government or the VA has coldheartedly and wantonly trampled upon and poisoned the health of Vietnam veterans, all cleverly compounded by a contrived delay in action—or—that this is all a hysterical witch hunt where many factions in the media and the public are out to get the chemical companies, and to lay the blame on a wholly harmless substance known as dioxin.

For these reasons, I found it most refreshing to read this article by Mr. Franklin. It is a thoughtful, objective, and well researched article which tackles and grapples head on with the emotional aspects of the issue. But I think the most significant thing about the article is the author's unusual perspective. He was first assigned to cover agent orange in the late 1970's, at which time he was apparently much favorably inclined and compelled by the arguments and the charges that had been leveled against Dow Chemical and the military. This article is a discussion of how several years of careful research produced in him a more informed and moderate position. The article condenses into a relatively short space, and the inquiry-and-learning process described is one that might be appropriate for all of us to undertake, if but only we had the time in this fascinating arena. I highly commend this fine journalistic effort to the attention of my colleagues. It seems quite honest and up front to me.

I ask unanimous consent that the article be printed in the RECORD.

There being no objection, the article was ordered to be printed in the RECORD, as follows:

[From the Evening Sun, June 24, 1983]

DIOXIN CHARGES ARE FLAWED

(By Jon Franklin)

Times Beach . . . Love Canal . . . and a million Vietnam soldiers and Marines who were sprayed with dioxin-containing Agent Orange. In Washington, bureaucrats maneuver to cover up The Truth. Citizens march in opposition to chemical waste dumps. Angry victims parade their crippled children before congressional committees. There is terror in the land.

Fred Wilcox's latest book, "Waiting for an Army to Die," lies on the table beside me, open at random to page 53. "Vietnam veterans," Wilcox is saying, "have fathered hundreds and perhaps even thousands of seriously deformed children."

The book should sell well. Chemical terror is at least as marketable today as was the Red Menance in the '50s.

I haven't always felt that way. In the 1960s, while I was still in college and Dow Chemical was manufacturing napalm to incinerate Vietnamese women and children, I marched against the company—and the war that fed its corporate balance sheet.

So in the late 1970s, when I was assigned to cover the then-emerging Agent Orange issue, I was ecstatic. It would be, I thought, the story of my science-writing career. I gathered about me that righteous fervor that is the armor of the crusading reporter, and I went to work.

The first step was obvious. Veterans groups were leveling all sorts of charges against Dow Chemical and the military. My first step was to verify that those charges were legitimate.

I wasn't looking for, or expecting, proof. In matters environmental, truth is so complex that proof of anything can rarely be established. But I was, in good journalistic conscience, obligated to investigate accusations before legitimizing them in The Evening Sun.

One of the first charges I set out to verify involved the matter of birth defects among children of Vietnam veterans.

So began, for me, an odyssey into the strange world of Agent Orange and dioxin where, to borrow the reasoning of Cyrano de Bergerac, "a lie is a sort of a myth, and a myth is a sort of a truth."

And yes, Fred Wilcox, Vietnam veterans probably have fathered "hundreds and even thousands of seriously deformed children."

The normal rate of birth defects is 2.1 percent of all live births. If a million men served in Vietnam, and if each had one child upon returning, they would be EXPECTED to father a lot of deformed children. More than 20,000.

And I remember sitting in a rowhouse in northern Baltimore, listening at length to a veteran who was participating in the massive lawsuit against the government. He was "too nervous to work," he told me, a situation he blamed on Agent Orange. He clearly remembered being sprayed with an orange powder.

Unfortunately for his case, "Agent Orange" was a clear liquid, named for the color of the drums it arrived in.

A few days later I sat in another house while another veteran blamed Agent Orange for his wife-beating, child abuse and heavy use of alcohol.

As the months passed I talked to many more "victims" like those.

In making their charges, they frequently quoted scientific studies—studies which, somehow, never seemed to be anywhere at hand. But, they assured me, I could always look the papers up. Or I could do what other reporters were doing, which was taking veterans' word for it.

Fortunately, my editors had told me to take all the time I needed (a luxury many of my fellow reporters, working on the same story, didn't have), so I wasn't forced to take their word for it.

I spent more than a week at the University of Maryland medical library, tracking down citations and conducting a computer search of the National Library of Medicine archives. When I was finished, I had a stack of technical papers about two feet high.

Reading those reports was a tedious but enlightening process.

The scientists I talked to said dioxin had been around for a long time, and existed in such small quantities that its discovery, in the fat of some veterans for instance, was more a tribute to the sophistication of scientific instruments than to the dangers of dioxin.

"Give me enough money," one scientist boasted, "and I'll find anything in anything. We're getting that good!"

Many of the scientists asked to speak off the record. Thus protected, they complained bitterly about the way their work was being distorted by veterans and by grandstanding politicians. The ruckus being raised, the scientists said, simply did not reflect reality.

Why wouldn't they say so on the record? The explanations were various. Some just didn't want to get involved. Others were afraid that, if they spoke out, they'd be harassed by members of the growing Agent Orange movement. Several admitted that, with the federal grant program dying, they hoped to get money to study dioxin. And further studies, they pointed out, would be necessary in any case. So why jeopardise their chances?

One feeling seemed to be almost universal. The scientists, while rejecting the veterans' interpretations of their scientific work, nevertheless sympathized with the cause. Everywhere, I encountered the sentiment that the veterans had been sorely used then forgotten. They deserved help and, facts aside, perhaps Agent Orange was a workable pretext.

Through all this I was haunted by a hunch that the veterans were correct in one sense. Somehow, each in his own way, the men I talked to were in trouble.

I wondered . . . perhaps, if Agent Orange wasn't the culprit, perhaps something else was. I began boning up on tropical diseases endemic to Southeast, Asia, and to which the soldiers might have been exposed. I inquired about malaria-preventing drugs they were given.

And then I ran across a paper about "soldier's heart."

It was an old paper, published after the Spanish-American War, and on my first trip through the stack I had skipped it. There seemed to me, after all, to be little connection between that remote war and the agony of Vietnam.

But, on contemplation, there were some critical similarities. The soldiers of both wars had been wrested from civilian life, hassled by junior officers, made to wear ill-fitting uniforms, shipped overseas, hassled some more . . . and then been thrown up against an army of people who were trying to shoot them or blow them to bits.

As I read the ancient report, the symptoms of soldier's heart practically leaped off the page at me. The Spanish-American War veterans had experienced a range of heart symptoms that were practically identical to many of the complaints I'd heard from Vietnam veterans.

True, the Spanish-American War veterans didn't exhibit excess incidence of cancer or birth defects but, as the scientific literature was making clear to me, there was no evidence that the Vietnam veterans did, either. The difference was that cancer and birth defects were fears of the modern era; Spanish-American War veterans worried far more about tuberculosis.

Thus primed, I began researching studies completed after other, later wars. Each war, I found, had left a legacy of not just soldier's heart but also alcoholism, intestinal ailments, myterious skin reactions, and a variety of ailments that, today, easily fall in the category of "stress reactions."

By this time I was writing stories, but they were tentative things, anemic by journalistic standards, background pieces about soldier's heart and standard birth defect rates—the sort of thing guaranteed to make a wire editor yawn.

Other reporters were faring better. As I grew increasingly skeptical and puzzled, the Agent Orange story exploded around me. Charge after unsubstantiated charge moved on the wires and appeared on front pages across the country.

And the fear spread. Dioxin had contaminated not only Agent Orange but domestic herbicides as well. Every American, it seemed, was a potential victim.

In Pennsylvania there was a cluster of deadly brain tumors. Agent Orange, obviously, was the culprit. None of the stories mentioned the fact that brain tumors, along with leukemias, lymphomas and Hodgkin's disease, had been known for years to occur in clusters.

Now and then I thought I had a shred of evidence, but it always vanished somehow before I could get my hands on it. I particularly remember the scientist who, the veterans said, had showed that tiny quantities of dioxin caused a suspicious range of diseases in monkeys. So I called his laboratory. He was no longer with the university, I was told.

As it turned out, he had left under inauspicious circumstances, in the midst of an investigation into unusual disbursements of his grant money. I had no idea whether he was guilty or whether, as the "Agent Orange victims" charged, he had been framed. The only thing I knew for certain was that, once again, I had come up empty-handed.

Perhaps it was those charges of frame-up and "conspiracy of silence" that led me, in the end, to an unbidden suspicion. I had approached the Agent Orange story from the point of view of medical science. But perhaps it wasn't that kind of a story at all. Perhaps it was, instead, a modern witch-hunt.

It was an uncomfortable idea and one which I, as a science writer, was not well equipped to tackle. And yet . . . with that view, the evidence coalesced into something that was, at least, coherent.

The veterans I talked to represented the range of human personalities and capabilities, but they had one thing in common. They has been ill-used by their government, and they had as a result incurred an abiding suspicion of it. They were perfectly willing to believe that the politicians who sent them to Vietnam were capable of poisoning them while they were there and denying it when they returned.

They also saw scientists as a monolithic force, a force capable of large-scale conspiracy, a group of faceless intellectuals who would, naturally, share the government's interest in obscuring the facts.

The civilians who joined the Agent Orange movement came from many backgrounds but they too, from housewives to maturing hippies in Oregon, shared that fierce distrust of government . . . and of chemicals, pernicious chemicals that could not be seen, touched or tasted, that were poisoning us all and causing an epidemic of cancer.

I looked up that last charge, of course. The statistics verified no such epidemic, save in one category: lung cancer. And that correlated not with Agent Orange or exotic chemicals, but rather with the everyday poisons in cigarette smoke.

At that juncture, for me, other priorities intervened and I took a two-year leave of absence to write a book. But I watched, in my evening newspaper and on the television news, as the story grew, and grew, and grew. By the time I returned to reporting, the fear of dioxin had grown to alarming proportions. It was, it seemed to many, the key threat to the nation's health.

I thought a lot about the problem, and my mind returned again and again to the explanation that nagged at me.

There had been a war, and a loss of confidence in government, and in the industries that had profited by the useless killing. Soldiers had returned, forever scarred by their experience. Leaders of the new left, like the officials of the March of Dimes, had been unwilling to relinquish their power after their cause had been won.

And on the part of the general population, there was anger, undirected anger that turned to fear, fear that, without an obvious enemy, focused instead on the unseen, almost mystical, poisons. Paranoia . . . and the need for a scapegoat.

Fred Wilcox isn't a newcomer to this game. His first work, a primer and source book for anti-nuclear activists, dealt with another form of invisible terror. Now his second, subtitled "The Tragedy of Agent Orange," lies open in front of me.

As Wilcox reminds us, there *is* profit in poisons. Certainly Dow Chemical, in manufacturing such products as napalm and Agent Orange, profited handsomely.

But there is also profit in terror. Wilcox's book, paperbound, cost Vintage Books (a division of Random House) perhaps 75 cents to print. It is offered, for youf reading pleasure, at the bargain price of $6.95.

It contains some 200 pages chock full of mostly unprovable charges, terrifying in their implications, throwing gasoline on a fire that rages in our minds, unmatched since the paranoid era of Joe McCarthy, pointing a bony finger at the men and women who captain our government and industry.

We are all leery of the subtle chemicals of the new technology, and I suspect we should be. But "Waiting for an Army to Die" reminds me that the mind, as well as the body, is susceptible to poisons.

Dow, at least, is required to list its ingredients on the can. With books your only protection is the ancient warning *caveat emptor*.

Let the reader beware.

Agent Orange Projects Office
August 1983

Veterans Administration
Agent Orange Activities

Since the issue of Agent Orange first surfaced as a matter of concern to Vietnam veterans in 1978, the Veterans Administration (VA) has been intensively involved in various activities, including significant research, to resolve the health care issues raised by the use of that defoliant in Vietnam. Through participation in key federal committees including the White House established Agent Orange Working Group and its Science Panel, the VA Advisory Committee on Health-Related Effects of Herbicides and the VA Agent Orange Policy Coordinating Committee, the agency is making a concerted attempt to review and coordinate agency and interagency efforts to secure creditable scientific answers.

As of June 30, 1983, over 120,000 Vietnam veterans had participated in the VA's computerized Agent Orange Registry which serves to identify concerned Vietnam veterans, establish permanent medical records, detect significant health trends in the Vietnam veteran population and, finally, provide a mechanism to support follow-up efforts with Registry participants.

The passage on November 3, 1981, of Public Law 97-72, the "Veterans Health Care, Training and Small Business Loan Act of 1981," gave the VA legislative authority to provide medical care to Vietnam veterans, subject to guidelines established by the Chief Medical Director, for health conditions possibly related to their exposure to Agent Orange without proof that it was the cause. During the period of February 1, 1982 to February 1, 1983, over 9400 inpatient admissions and 369,000 outpatient visits were experienced at VA health care facilities.

Significant VA research efforts now underway or planned include the following:

- VA Mortality Study of Vietnam veterans
- Vietnam Experience Twin Study
- Retrospective Study of Dioxins and Furans
- Soft-Tissue Sarcoma Study
- 10 specially solicited animal research projects
- Financial support of CDC Birth Defects Study in Atlanta, Georgia

As of January 14, 1983, responsibility for conduct of the epidemiology study mandated by Public Law 96-151, the "Veterans Health Programs Extension and Improvement Act of 1979," enacted December 20, 1979, was transferred from the VA to CDC. The interagency agreement stipulates that the VA will provide the necessary resources to enable CDC to conduct the study. It is currently projected by CDC that the epidemiology study will be completed in December 1988.

Other non-research efforts undertaken by the VA include:

- Ongoing review of chloracne skin claims
- Review of Patient Treatment File (PTF)
- Preparation of Agent Orange Monographs
- Agent Orange Literature Update

The VA has reviewed and commented on the intent and scope of legislation introduced relative to the compensation of Vietnam veterans for health conditions possibly related to their exposure to Agent Orange. In particular, the VA has commented and/or testified on the following bills:

- S. 374 - a bill that would provide presumption of service connection for the occurrence of certain diseases in veterans exposed to phenoxy herbicides while in Vietnam;
- S. 786 - a bill that would establish a service connection presumption for certain diseases caused by exposure to herbicides or other environmental hazards or conditions in veterans who served in Southeast Asia during the Vietnam era;
- S. 991 - a bill that would require regulations providing for the resolution of Veterans Administration benefit claims based on certain exposures to herbicides containing dioxin, to ionizing radiation from detonations of nuclear devices and to certain other hazardous substances;

- H.R. 1961 - a bill that would provide a presumption of service connection for the occurrence of certain diseases (i.e., soft-tissue sarcomas, porphyria cutanea tarda, active and residual chloracne and chloracne-form lesions).

The premise for H.R. 1961 is that each of the specified disorders, no matter how long after military service symptoms appear, can be attributed to exposure to a phenoxy herbicide. The Veterans Administration is prepared to resolve compensation claims in a manner favorable to veterans. Unless there is affirmative evidence to the contrary, the VA, for purposes of providing health care, is prepared to presume exposure if a veteran served in Vietnam during the relevant period. This approach is consistent with the agency's longstanding policy of giving veterans the benefit of the doubt. However, there are some cases in which affirmative evidence refutes even the possibility of exposure, and, therefore, the agency's policy is necessarily qualified. An example of this is affording presump-

tion to veterans who served in Southeast Asia, a far broader region than Vietnam, embracing areas where no phenoxy herbicides were used. This approach inappropriately expands the category of veterans intended to be benefited.

A principal concern relates to the concept of an open-ended presumption that would be established by H.R. 1961 and to the conclusions it embodies as to the specific disorders of chloracne, porphyria cutanea tarda (PCT), and the several malignancies grouped as soft-tissue sarcoma. Other presumptive service connections for additional disorders that "medical research" has shown "may be" attributible to chemical exposure or environmental hazards is also provided for by the bill. Such requirements are vague. Rules creating such presumptions should be based only on well-accepted, scientifically valid findings. Such requirements are also unnecessary in view of the Administrator's current authority to issue regulations.

The agency concedes, in the case of chloracne, that such a condition is directly attributable to exposure to dioxin if the symptoms of exposure manifest themselves within a relatively short time following such exposure. There is no basis, however, for the award of compensation for "chloracneform lesions" as outlined in the proposed legislation as this term is vague and broad and is not found in either medical or scientific literature.

There is no evidence to suggest that porphyria cutanea tarda (PCT) is a latent effect of exposure. Various other chemicals, including alcohol, can trigger such a liver disorder. Also, there is no evidence that an attack of PCT induced by Agent Orange or exposure to any other chemical during service in Vietnam years ago would impair a veteran's health today. The proper application of section 313 of Title 38, United States Code, making section 312 presumptions rebuttable if there is evidence of an intercurrent cause, would reduce the likelihood of awards of service connection based on the PCT presumption, if enacted.

The issue of "soft-tissue sarcomas" (STS) is a more complex problem than chloracne or PCT. Such malignancies are rare and encompass a broad spectrum of malignant tumors or cancers but not those arising from "hard tissues" such as bone or cartilage. There is no evidence that all soft-tissue sarcomas have a common etiology or cause. Such malignancies also differ from one another as to how rapidly they grow and spread, how they are treated, and the results that treatment achieves. Because such malignancies are rare, it is difficult to devise adequate techniques to investigate their causes. Various studies including those conducted in Finland, New Zealand, Great Britain, the Netherlands and Italy have not confirmed Swedish studies on soft-tissue sarcomas which suggest a

relationship between herbicide exposure and soft-tissue sarcomas. In fact, a separate investigation of Swedish forestry workers casts some doubt on the results of the Swedish studies.

The comprehensive epidemiology study mandated by Public Law 96-151, together with other agency studies including some devoted specifically to the soft-tissue sarcoma issue, may resolve many of the controversial questions raised by the use of Agent Orange in Vietnam. There is no evidence, however, supporting any conclusion that chloracne or PCT is a delayed effect of exposure, nor has it been satisfactorily demonstrated that exposure can cause soft-tissue sarcoma.

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Agent Orange Information for Veterans Who Served in Vietnam. Question and Answers.

PORPHYRIA CUTANEA TARDA

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PORPHYRIA CUTANEA TARDA

Definition: Porphyria cutanea tarda (PCT) is the most frequent of a group of uncommon diseases, the porphyrias, that comprise disturbances in the body's formation of hemoglobin, the red chemical in blood. A specific pattern of chemicals called porphyrins, excreted in the urine and stool, characterizes PCT and reflects a deficiency of one of the liver's enzymes involved in hemoglobin formation. The disease manifests itself in the skin where small and large blisters form on the exposed parts of the body, probably as a slow response to sunlight. The skin becomes very fragile and easily rubs off to produce sores that scab over and sometimes leave scars. PCT appears to be inherited, at least in some cases, but exposure to some chemical or other external factor is required before it becomes manifest. (1-4)

Clinical Manifestations: PCT is usually first noticed when small or large blisters appear on the face, the back of the hands, and the arms usually following exposure to sunlight many hours or days earlier. This contrasts with the prompt reaction to sunlight in other porphyrias. The skin slowly becomes so fragile that even slight rubbing strips off the top layer leaving an open shallow sore that scabs over and heals slowly. The thin skin that forms in the area gradually returns to normal over months. It may instead scar permanently or, in severe cases, may progressively stiffen and thicken until it resembles another skin disease, scleroderma. (5, 6) In a few very severe cases, the skin changes have resulted in the loss of parts of the nose, ears or fingers. (2)

Hair, especially around the temples and upper cheeks, may grow dark and prominent. (7) The skin may darken or may lighten abnormally in the affected areas. (8) Small "white heads" sometimes appear before or after blistering.

The porphyrins in the urine often give it a pink, dark red or brown color. They fluoresce red in ultra-violet light, a phenomenon that assists in diagnosing PCT. (3)

Several methods of treating PCT are available, the most frequently used being repeated bleeding, and the disease is more successfully treated than are other porphyrias. The most important measure, however, is the avoidance of any chemical or other factor that precipitated the attack. (1, 2)

The time it takes the patient to recover seems to depend upon how severely the body was damaged. The skin changes disappear first, usually within 6 months when even severe cases are treated. (9, 10) The disturbance of the body's chemistry clears up in

about a year. In less severe cases, simply avoiding contact with the causative chemical or other external factor is followed by complete recovery within a year. (11) Children who developed PCT after prolonged and intensive exposure when they ate seed grain treated with a chemical were very ill and had scarring, hairiness, arthritis and stunted growth even 20 years later. (12)

PCT is usually accompanied by some liver damage and in 4 percent or more of the patients a particular form of liver cancer develops. (1) It is difficult to determine whether the liver is damaged by PCT or by alcoholism which often precipitates the porphyria.

Causes: At present, PCT is thought to have two causes: heredity and external factors. There is little agreement on the relative role of these two or on exactly how they interact.

Heredity: There is good evidence that some cases of PCT have a hereditary basis. This has been demonstrated by finding, in healthy blood relatives, the same chemical defects as appear in patients although the changes are less severe in the well relatives. (13 - 16) The few available studies (16, 17) indicate that 6 to 10 percent of the general population have the hereditary defect; most never develop obvious PCT.

The various family studies show that PCT is inherited as what geneticists call an "autosomal dominant gene." (13 - 16) This gene decreases the liver's ability to produce an enzyme called "uroporphyrinogen decarboxylase" that is essential for the normal production of hemoglobin. A deficiency of this enzyme can result in the appearance in the urine of unusually large amounts of substances called "uroporphyrins" as well as related changes in the body's chemistry. (1 - 4)

The situation is more complicated, however, than this suggests. Not all persons who have the hereditary defect develop PCT and not all persons with PCT have evidence of the hereditary defect. It apparently requires exposure to some other factor, generally an environmental one, to produce the disease prophyria cutanea tarda even in the presence of the hereditary defect.

External Factors: A wide variety of chemicals, diseases, and even bodily states can disturb the liver's ability to bring about normal chemical reactions in the formation of hemoglobin and so produce one or another type of prophyria. (18) Some of these changes are relatively slight and transient; others are more serious and longer lasting.

The chemicals that produce PCT have been divided by some investigators into two catagories: those that trigger attacks in

people with the hereditary enzyme defect and those that produce the disease in people without the defect. The chemical hexachlorobenzene is most often given as an example of a substance that produces PCT in anyone. This is largely because 4000 people in rural Turkey who ate, over several winters, seed grain treated with the chemical developed attacks of PCT that were often severe and protracted. (12) Relatively large doses of the female hormone estrogen is said to produce PCT only when the hereditary defect is present. (2) The interaction of hereditary and external factors is still not understood but it is important in several situations, two of which are alcoholism and exposure to TCDD or dioxin.

Chronic alcoholism is unquestionably the most common precipitating factor producing PCT among the populations of North America and Europe where about 68 percent of PCT patients are alcoholic. (19) The alcoholic patients who develop PCT, however, have often not been so impaired by their drinking that they could not hold jobs.

Alcohol abuse has many deleterious effects, of course. Among them are the storage of an excessive amount of iron in the liver and the production of various liver changes culminating in hepatic cirrhosis. Both of these changes are associated with PCT but exactly how they are related to it is not clear. (1) While alcoholism is common among PCT patients only about 2 percent of alcoholic patients with cirrhosis develop uroporphyrinogen decarboxylase deficiency and PCT. (20) This suggests that a hereditary defect probably plays a part in the appearance of PCT in alcoholics.

TCDD or dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin) has been implicated as the cause of PCT in only two industrial episodes, both involving prolonged contact with large amounts of the chemical. In both instances, the workers were exposed to other chemicals as well.

At the Diamond Chemical plant in New Jersey that manufactured chemicals containing TCDD, 55 men were examined in 1963 when 3 workers were found to have had the skin and hair changes of PCT and to pass urine containing uroporphyrin. When no longer in contact with TCDD, one man recovered completely within a year and another had recovered during a two-year period. The third had only some scars a year after being removed from contact with TCDD. Another 11 men had uroporphyrin in their urine without skin changes. Of the 55 men, 17 had the other skin disease, chloracne, indicating exposure to TCDD or a related chemical but there was no relationship between the occurrence of PCT and of chloracne. (21)

Six years after the initial examination, a second group of doctors examined 73 men working at the same New Jersey plant which

had taken steps to protect its employees from exposure to TCDD after the earlier episode. No PCT was found and only one worker continued to pass uroporphyrin. Some men still had slight to moderate chloracne, however, (22)

The second industrial episode involved intense exposure to similar chemicals, including TCDD, between 1965 and 1968 in a manufacturing plant in Czechoslovakia. In all, 80 of 400 workers became ill. (23) A total of 78 developed chloracne as evidence of contact with TCDD or pentachlorophenol both of which were present. Twelve workers, more than half of them over 40 years of age, were diagnosed as having PCT. One man is said to have been exposed to the chemicals for only two and a half weeks before he developed PCT and in one patient porphyria is reported to have progressed rapidly into hardening of his brain's arteries. (24) Neither the rapid onset nor the progression to arterial hardening is known to occur in PCT.

Among 55 workers examined repeatedly, 11 persistently had large amounts of uroporphyrin in the urine; 12 others intermittently passed large amounts. These values gradually decreased during a four-year period. Of the 11 workers with a heavy output of porphyrin, 10 had the usual skin changes of PCT. (25)

The patients knew of no porphyria in members of their families and the researchers were unable to determine whether any of the men drank excessively. (26) In 1974, the doctors reported that the amount of uroporphyrin in the urine had been greatest in 1969 but had returned to normal as the skin changes improved. After 9 years of observation excessive excretion of uroporphyrin and skin manifestations were "exceptional" occurrences. (27) A year later such abnormalities were said to be "very rare." (23)

In addition to these two incidents of PCT as a consequence of exposure to high concentrations of TCDD, other researchers have described a less severe and completely non-symptomatic change in the liver's enzyme performance following the industrial accident at Seveso, Italy in 1976. Two years after the accident the amount of porphyrins in the urine was normal but the types excreted showed minimal changes in 84% of the people examined. This may indicate that TCDD has an effect but it did not indicate that the people had any disease. (28)

To make matters more complicated two related persons who lived near Seveso were found to have PCT. Examination of 66 family members demonstrated, however, that the two were suffering from the hereditary form of PCT. (29) It raises the possibility that TCDD as an environmental factor may have enabled the hereditary enzyme defect to exert its adverse effect.

Treatment: The most important therapeutic and preventive measure for PCT patients is the avoidance so far as possible of further contact with the external factor or factors that precipitate the attacks. This is critical whether alcohol, estrogen, polychlorinated biphenyls (PCBs), hexachlorobenzene, certain drugs, TCDD, or other factors are involved.

The usual active treatment is repeated bleeding. In most patients with severe PCT there are excessive iron stores, especially in the liver. Judicious bleedings, as in blood donations, remove this iron and improve the patient's condition. There are medications that can be used to reduce the body's iron stores although generally they are not as safe as bleeding.

Untreated, the disease grows worse year by year if the external factors are not removed. Eventually the liver becomes seriously damaged. Removal of the external cause, however, expecially after a single or a few relatively brief contacts, is followed by slow but progressive improvement with apparent recovery. (30)

Agent Orange as External Factor: Since one component of Agent Orange contained small amounts of TCDD, it has been suggested that the herbicide acted as an external factor to cause porphyria cutanea tarda, with persistence of the condition to produce continuing trouble at the present time. This seems unlikely for several reasons.

PCT is a skin problem with a dramatic appearance and under conditions of combat in Vietnam would probably have been incapacitating, unlike chloracne which would have been relatively inconspicuous in most cases. In New Jersey and Czechoslovakia, the only two episodes where TCDD is known to have produced PCT, the skin changes were readily noticed.

The industrial exposures to TCDD causing PCT were intense and prolonged, lasting several years for most of the workers. Troops in Vietnam were exposed to much less TCDD.

Recovery from PCT usually follows removal from contact with the external cause within five years. The last contact with Agent Orange in Vietnam was ten years ago.

There are current external factors much more likely than Agent Orange exposure a decade or more ago to cause attacks of PCT at present. Among them are various medications, PCBs and alcoholism, none of them rare in America today. They should be eliminated from consideration as the precipitating factor before Agent Orange is accepted as a cause of PCT in any individual.

L. B. Hobson April 11, 1983

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EPIDEMIOLOGY OF SOFT-TISSUE SARCOMA AND RELATED HUMAN RESEARCH

(as related to herbicide exposure)

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EPIDEMIOLOGY OF SOFT-TISSUE SARCOMA AND RELATED HUMAN RESEARCH

Initiation of Swedish Studies of Herbicides and Cancer

In 1972 Swedish newspapers published rumors that railroad workers were dying from lung cancer as a result of exposure to herbicides used in their work. The National Board of Occupational Safety, as a result, requested Professor Olav Axelson, a specialist in occupational medicine, to undertake an epidemiological investigation of the matter.

The results of this investigation have been reported in a series of four papers, 1-4. Another series, 5-7, was prompted by criticism of the epidemiological and statistical methods employed in this and related studies. Attention in the United States has focussed on the pre-publication manuscript of the 1980 paper by Axelson, Sundell, Andersson, Edling, Hogstedt, and Kling, 4.

This paper dealt with two aspects of the study of railroad workers. The initial phase was a cohort study of 348 men who had been exposed, individually rather than as a group, to herbicides for more than 45 days during 1957 to 1972 and who were followed through October 1978. Exposure information was incomplete but the workers were divided into subcohorts with exposure to phenoxy acids (which include the ingredients of Agent Orange), amitrol, or to both herbicides. The mortality rates for these exposed subcohorts were compared to the age-specific national death rates for Swedish men, the latter serving as the control cohort.

Overall 49 deaths were expected in the exposed cohort; 45 occurred, a result attributed to the "healthy worker effect." There were, however, 17 tumors found where 11.85 were expected. Among the deaths occurring at least ten years after the first exposure, 6 cancers were found although only 1.78 were expected. Dr. Axelson, 8, later increased this to 7 tumor cases. Each subcohort had an excessive number of tumor deaths, the greatest being in the group exposed to both phenoxy herbicides and amitrol.

Although initially, 2, amitrol was associated with an increased tumor mortality, somewhat different results were found in a second phase of the examination, described as a case-referent study (identical to a case-control study). The data indicated a "statistical association" of phenoxy herbicides and excess tumor mortality, 3. Suspicion was increased by finding that workers exposed to phenoxy acids

alone had a "statistically significant excess of stomach cancer", specifically 2 cases compared to 0.33 expected when this type of herbicide was used alone and 3 cases as compared to 5.1 expected (increased from 4.1, 8) for all workers exposed to phenoxy herbicides, alone or with amitrol.

The series of papers on railroad workers has been criticized on several methodological grounds, 9, and Axelson has replied to these criticisms, 6. Richard D. Remington, Dean of the School of Public Health, University of Michigan, reviewed this and other Swedish studies for the Office of Technology Assessment. His evaluation, 10, was that the Axelson investigations had been "carefully conducted" and "well reported." He pointed out the limitations of the statistical methods used and found that "the numbers available ... are inadequate to permit definite conclusions" although "the results ... are suggestive."

Of interest in connection with the question of soft-tissue sarcomas and phenoxy herbicides is the type of tumors found by Axelson's group, 4. One case of Hodgkin's lymphoma occurred among the eight tumors in men exposed to phenoxy herbicides alone and no soft-tissue sarcomas or non-Hodgkin's lymphomas was diagnosed among the eight tumors appearing in workers exposed to both amitrol and phenoxy herbicides. In other words, no sarcomas were reported for the total of 207 men exposed to phenoxy compounds, 2. A reticulum cell sarcoma and a Hodgkin's lymphoma were found among the 7 tumors of workers exposed to amitrol alone. Thus, there was one soft-tissue sarcoma reported for 152 men exposed to amitrol, 2. Another 28 persons described as exposed to "other herbicides and combinations" cannot be identified as to exposure to specific herbicides but apparently none developed a tumor.

Axelson's work is directly related to the later work on soft-tissue sarcomas and lymphomas by Lennart Hardell. Indeed, Axelson suggested to Hardell in 1976, that he conduct a case-control study of soft-tissue sarcomas and has actively assisted in Hardell's work since then.

Swedish Investigation of Soft-Tissue Sarcoma

That work began when Hardell admitted for treatment 3 patients in the autumn of 1976, each with a soft-tissue sarcoma, and a history of exposure to phenoxy herbicides. He then found a total of 7 patients with "malignant mesenchymal tumors" (soft-tissue sarcomas) who gave a history of having worked with phenoxy herbicides 10 to 20 years earlier. The cases were among 87 patients with soft-tissue sarcomas, 55 of

whom were men. Of these men, 9 were forestry workers, 6 worked in forestry and on farms, and 6 were employed in saw mills or pulp plants. Another two tumors appeared in men whose connection with forestry was less direct. The malignancies found were two leiomyosarcomas, two rhabdomyosarcomas, two neurofibrosarcomas, with one each of fibroid liposarcoma, myxofibrosarcoma, and polymorphocellular sarcoma, 12.

Following Axelson's advice, Hardell began a case-control study that was published in two journals, 13, 14, a common practice of reporting in Swedish with an almost identical paper in English. The second paper in English aroused much interest in the United States.

Hardell and Sandstrom found 21 living and 31 dead men who were diagnosed as having soft-tissue sarcomas in Hardell's oncology department in northern Sweden. They were matched for age and place of residence, as well as date of death for the deceased, with other men selected from the Swedish National Population Registry or from the National Registry for Causes of Death. Each living patient had 4 living controls; each dead man had 4 deceased controls. Exposure information was sought by the use of a mailed questionnaire that has never been published. It contained 130 questions, including 16 about the use of organic solvents, 4 about plastics, 3 about glues, 4 about drugs, "several" about smoking habits and an unstated number about exposure to phenoxy herbicides and chlorophenol as used in the lumber and paper mills. This questionnaire was mailed to the patient or to his next of kin if he were dead, 15.

When the answers to the questionnaire were less than clear, a supplementary interview was obtained, usually by telephone, with the interviewer unaware of the health status of the person in question. Employers, neighbors, and others were consulted "if necessary to verify and monitor the accuracy of the exposure information," 15.

Using the criteria for exposure established for the study, 36.5% of the 52 patients and 9.2% of the 208 controls had been exposed to phenoxy herbicides and/or chlorophenols. The "relative risk" of developing soft-tissue sarcomas was calculated as 5.7, i.e. men exposed to the chemicals had almost six times as great a change of developing a sarcoma as did those who were not exposed. The relative risk was 5.3 for the 46 men exposed to phenoxy herbicides alone, and 6.6 for the 40 men exposed only to chlorophenols. It was thought that confounding factors had an insignificant effect.

The authors concluded that "the investigation showed an increased risk for soft-tissue sarcomas" but "a specific evaluation of the effect of separate chemical substances was not possible," 14.

The study's methods have been criticized and doubts have been expressed about the 100% response rate to the questionnaire approach, 9. (Actually, 2 of 208 controls did not answer, 14.) The statistical approach was described as slightly misrepresented and a major criticism was leveled because of the possibility of "selective recall," the greater tendency for an ill person to remember a supposed "cause" for the illness than a well person would have to remember the same "causal" event.

The criticisms evoked several replies. Axelson defended the case-control design, the objectivity of obtaining exposure data retrospectively, and the statistical techniques, 6. He concluded that the use of interviews for determining exposure is justified, 7, and defended in principle the treatment of confounding factors, 16. Hardell recalculated the 1979 results and his subsequent papers to substantiate his earlier findings and performed a separate investigation in support of his confidence that "no substantial observational bias could exist in the studies," 15.

Remington, 10, expressed the view that "the findings of this particular investigation are suggestive" and that "a relative risk of 5.3 for exposure to phenoxyacetic acids must be taken seriously." However, "case-control studies are uniquely susceptible to hidden sources of bias" even when the investigators are "unusually careful" as they are in this "excellent investigation."

Hardell's group also undertook a second case-control study of identical design in southern Sweden which is more devoted to agriculture than to forestry, 17, 18. In this investigation each of 72 living and 38 dead patients was matched with two controls. Among the 110 cases, 22.7% reported exposure to phenoxy herbicides or chlorophenols and, among the 219 controls, 5.9% were so exposed. This gave a relative risk of 5.1 with matching and 4.7 when the matching was dissolved, i.e. when sorting by age was ignored during statistical calculations. The relative risk from exposure to phenoxy herbicides was calculated to be 6.8, and that from chlorophenols to be 3.3. Exposure to more than a dozen other noxious materials, e.g. asbestos, smoking, DDT, and lindane, were considered as possible confounding factors although none was found to be clearly associated with an increased risk by itself.

The reports list the diagnoses of all 110 cases of soft-tissue sarcoma as: leiomyosarcoma, 33; malignant fibrous histiocytoma, 19; liposarcoma, 15; neurogenic sarcoma, 11; angiosarcoma, 9; myxofibrosarcoma, 7; fibrosarcoma, 5; dermatofibrosarcoma, 3; atypical fibroxanthoma, synovial sarcoma, sarcoma NOS, 2 each; Ewings's sarcoma (extraskeletal) and rhabdomyosarcoma, 1 each. No statement is made as to which of these tumors was found in the 25 cases with identified exposures and no histological diagnoses are reported for the northern Swedish series, 13, 14.

The authors of the southern Swedish study conclude that "exposure to phenoxy acids and chlorophenols might constitute a risk factor in the development of soft tissue sarcomas," 18. The investigation has been the subject of the same criticisms and refutations as the earlier study.

Remington concludes that "the results are consistent with the hypothesis that phenoxy acid exposure increases the risk of tumors of this type" but adds that "case-control methodology is intrinsically susceptible to subtle and unmeasurable biases."

Swedish Investigation of Lymphoma

In May, 1978, Hardell was prompted to a new study by a patient with a malignant histiocytic lymphoma and a history of "massive exposure to phenoxyacetic acids." All men admitted to the oncology department with this type of tumor during the first nine months of 1978 were asked about their occupation and possible chemical exposure. Of 17 patients, 14 reported an occupation consistent with exposure and 11 of them had had contact with phenoxy herbicides or chlorophenols ten or more years earlier, 19.

These observations led to a case-control study, the report of which in 1981, 21, differs considerably from that in 1980, 20. The earlier report was commented upon in manuscript form by various experts but the later version will be used here.

The investigation, in collaboration with Axelson, 20, included both Hodgkin's disease and non-Hodgkin lymphomas. The 169 cases consisted of 60 Hodgkin's disease patients (lymphocyte predominance, 20; nodular sclerosis, 3; mixed cellularity, 27; lymphocyte depletion, 10), 105 men with non-Hodgkin's lymphomas (follicular center cell (FCC) type, 53; non-FCC type, 52), and 4 individuals with unclassifiable lymphomas. Each case had two matched controls, 338 in all. Of the cases, 62 had died as had 124 of the controls.

Questionnaires and interviews were used to determine exposure to phenoxy herbicides, chlorophenols, organic solvents, or medicines and to characterize jobs, hobbies, and smoking as they were determined in the soft-tissue sarcoma investigations, 20. All cases and controls were from northern Sweden.

Cases in which exposure was reported to chlorophenol, or to "mutagenic" solvents (benzene, trichloroethylene, perchloroethylene and styrene) were divided into high-grade and low-grade exposure groups. Continuous exposure for a week or less or repeated exposures totaling less than a month were considered low-grade. Analyses also divided cases into two groups depending on whether 5 years had elapsed as a latency period between the first exposure to the chemical and the tumor diagnosis.

Of the cases, 36.1% had been exposed to phenoxy herbicides or chlorophenols; 9.6% of the controls had been so exposed. The relative risk for these exposures was 6.0 with matching and 5.3 without it. Phenoxy herbicides gave a relative risk of 4.8 although it was greater if exposure was for 90 days or more. Chlorophenols gave relative risks of 8.4 for high-grade exposure, 2.9 for low-grade. High- and low-grade exposure to organic solvents gave relative risks of 2.8 and 1.2 respectively. On the other hand the few cases with both phenoxy herbicide and high-grade organic solvent exposure was calculated to have a relative risk of 11.2 and some other combinations also gave large relative risks. The length of the latency period, however, seemed to have no effect.

The authors conclude that "this investigation suggests that exposure to organic solvents, chlorophenols, and/or phenoxy acids constitutes a risk factor for malignant lymphoma," 21. Dr. Remington commented that "a substantial and statistically significant relative risk is found for this group of tumors. And again, pnenoxy acid exposure is specifically incriminated." He continues, however, that the limitations of case-control methods have to be considered as well.

Swedish Investigation of Carcinoma of the Colon

Hardell undertook to answer doubts that his questionnaire and interview methods allowed observational bias in assessing exposure by conducting a case-control study of "colon cancer." The condition is not suspected of having any association with phenoxy herbicides or chlorophenols. In consequence, if the previously used exposure determination

resulted in a relative risk of 1.0 or near it, there had been no observational bias in the questionnaire-interview procedure used in the earlier studies of soft-tissue sarcomas and lymphomas.

Of the 157 men with colon cancer all but 3 answered the questionnaire. The controls consisted of the control groups from the soft-tissue sarcoma study (206 men) and the malignant lymphoma study (335 men). In all, 41% of the cases and 45% of the controls were dead. Of the cases and controls, 11.0 and 10.4% respectively had been exposed to phenoxy herbicides or chlorophenols. For phenoxy herbicides, the relative risk was calculated to be 1.3 and for chlorophenol it was 1.8. Neither was significantly above 1.0. The conclusion was that "the previously reported associations between exposure to phenoxy acids or chlorophenols and soft-tissue sarcoma and malignant lymphoma cannot to any essential degree be explained by observational bias," 15.

Later Criticism of Swedish Studies

There remain, however, doubts about the practical significance of the Swedish epidemiological studies stemming from several of their characteristics. The main criticism is the reliance on recall of the men or their relatives, employers and associates for undramatic events years earlier as well as the possibility of unconscious bias on the part of the interviewer, the "observational bias" discussed above. Coggan and Acheson point out that the positive association between exposure to phenoxy herbicides and the development of several or many soft-tissue sarcomas, Hodgkin's disease and non-Hodgkin's lymphoma may indicate "a serious undetected bias" even though the explanation has been offered that all these tumors are embryologically related, 22. These authors conclude that "it is as yet impossible to estimate with any precision the risk of soft-tissue sarcoma due to phenoxy herbicides" but add that "there is suggestive evidence of a biological association between phenoxy herbicides (or their contaminants) and soft-tissue sarcomas." They feel that there is weaker evidence for an association between herbicides and lymphomas.

Hardell and Axelson reject the idea of observational bias, citing the colon cancer study as evidence, 23. They also defend the aggregation of tumors because of the "so-called addition theorum for chi-square and Poisson distributions" as well as the embryological relationship of the neoplastic tissues.

American Support for Swedish Conclusions

Support for the connection between soft-tissue sarcomas and exposure to phenoxy compounds has been reported in several papers from outside Sweden. The data most often cited as favoring the relationship are derived from observations in the American chemical industry.* The first was a note by Honchar and Halperin in which they pointed out that of 105 deaths in four exposed industrial "cohorts" 3 (2.9%) were due to soft-tissue sarcoma, whereas only 0.07% of deaths among adult American men are so caused. The three cases were malignant fibrous histiocytoma, fibrosarcoma, and liposarcoma. The authors felt that these "suggest a common pattern," 24. Cook added a fourth case, another malignant fibrous histiocytoma and noted that all four were smokers and two had chloracne, 25.

Moses and Selikoff reported a fifth case, a non-smoker, with neurogenic sarcoma (malignant schwannoma). They give the total annual incidence of soft-tissue sarcomas as 4500 (less than 1% of newly diagnosed cancers) in the U.S. and quote 4.9% of soft-tissue sarcomas as malignant schwannoma, 26.

Johnson and his co-workers briefly described a young man who died of fibrosarcomatous mesothelioma some four years after first being exposed to phenol. His father had a liposarcoma after "prolonged exposure" in a plant manufacturing chlorinated phenols among other chemicals, 27.

Hardell and Ericksson accepted the two additional cases to total 7 deaths from soft-tissue sarcoma among 105 deaths among American industrial workers, the expected number being 0.07%. This would "fit in with" the Swedish investigations, they believe, 28.

To date no critical review has been made of the cases and the industrial population in which they were detected. The reports have been brief "Letters to the Editor" and each discusses one to three cases. The total of 105 deaths used as the number of dead workers has not been kept current as new soft-tissue sarcoma cases were added and the total number

*Data given by Honchar and Halperin, Cook, Moses and Selikoff, and Johnson et al pertain to workers at Monsanto Company and Dow Chmical Company. For details of studies of these workers see 24a and 25a.

of exposed workers has not been given. No use has been made of controls, even in the form of a retrospective cohort comparison.

A case report without statistical data briefly described three soft-tissue sarcomas among Vietnam veterans who reported exposure to phenoxy herbicides in that country. One man had an inflammatory histiocytoma, another suffered from a fibrosarcoma, and the third had a leiomyosarcoma, 29.

European Support for Swedish Conclusions

Barthel determined the frequency of malignant neoplasms among 1791 pesticide sprayers and agricultural technicians in East Germany during 1976 to 1979. He states the retrospective cohort study used police as controls but gives no data for them. After eliminating "on statistical grounds" 133 cases who died before 1970, he compared the mortality rate and cancer incidence with corresponding figures from the death statistics and the cancer registry of the Health and Social Welfare. The "case" group had multiple exposures over the years to fungicides, insecticides, and herbicides including phenocyacetic acids. Among 169 malignant neoplasms in 1658 exposed men were 1 lymphosarcoma, 3 plasmacytomas, 1 described as a malignancy of lymphoid tissue, and 1 of soft-tissue, not otherwise characterized. Bronchogenic carcinoma was the most common malignancy with 59 cases, double the expected occurrence, although the cases had smoking habits like those of the general population, 30. A brief report describes a case of non-Hodgkin's lymphoma and a second of malignant lymphoma among 158 workers with pentachlorophenol. This type of neoplasm would have an expected occurance of 0.28, 31.

Studies Not Supporting Swedish Conclusions

In contrast to the reports of an association between phenoxy herbicides or related compounds and soft-tissue sarcomas and malignant lymphomas, some investigators have found no association. Some of these investigated a possible relation, others were "follow-up" studies of industrial workers in whom no sarcomas or lymphomas were found.

Dr. Riikimaki and his collaborators have completed nine years of mortality study following 1,926 persons who worked with phenoxy herbicides in Finland during the 1955-1971 period. All had at least two weeks of exposure and a quarter of the men totalled eight weeks or more as of 1971. The mortality rates among the workers were compared with the national death rates. As of 1980, there had been 82 deaths

of exposed men as compared to 91 expected and, of these, 17 were cancer deaths with 18.4 expected. There were no cases of soft-tissue sarcoma nor of lymphomas although 0.1 and 0.8 would have been expected. The authors believe that "the investigation cannot be regarded as a conclusive negative study" but point out that the "results do not confirm the ... association between mixed herbicide exposures" and cancer risk, 32.

Hogstedt and Westerlund compared the mortality rate of Swedish supervisors and workers in forestry. The supervisors were fewer in number (142) than the workers (244) but the former were judged to have been more heavily exposed. The relative risk of death was about the expected but, after a 10-year latent period, the relative risk for cancer was about 4 for the supervisors and only about 0.4 for the workers. The fatal tumors were of various types but there was no soft-tissue sarcoma or lymphoma, 33.

Two case-control studies in New Zealand have been initiated by Smith et al to examine the association suggested by Swedish studies of phenoxy herbicides with soft-tissue sarcomas and malignant lymphomas. In the first investigation, 102 cases of soft-tissue sarcoma have been identified in men from the New Zealand Cancer Registry between 1976 anmd 1980. An equal number of matched controls with other forms of cancer were selected for comparison. The sarcomas are fibrosarcomas, 25; liposarcomas, 20; rhabdomyosarcomas, 9; leiomyosarcomas, 7; malignant histiocytomas, 6; other types, 22; and unspecified, 13. The preliminary report compares cases and controls as to the occupation shown on the Registry enrollment. There was no significant difference betwen the groups as to the number of men working in agriculture, forestry, and fishing, the occupations with the greatest likelihood of exposure to phenoxy herbicides and chlorophenols. The only occupations associated with soft-tissue sarcomas exclusively are blacksmiths, machine tool operators, electrical fitters, and electrical workers. The investigators are now obtaining work histories for cases and controls by telephone interviews and warn that later results may change their conclusions. The data at present "do not give evidence for a relationship (of soft-tissue sarcoma) with occupational exposure to phenoxy herbicides and chlorophenols" but "should not be taken as substantive evidence against the hypothesis", 34.

A second report by Smith et al includes the results of the telephone interviews regarding 80 cases and 92 controls already completed. Probable or definite exposure to phenoxy herbicides for more than one day earlier than five years before cancer registration was found in 17 cases and 13 con-

trols, giving an odds ratio of 1.6. This would be expected to increase when the exposure criteria were more stringent but, when exposure was at least five days and more than ten years before registration, there were 13 cases and 12 controls included reducing odds ratio of 1.3. Neither ratio is statistically significant and there have been no soft-tissue sarcomas reported among the most highly exposed group of 2000 aerial and ground sprayers. The results, the authors believe, "do not generally support the hypothesis that exposure to phenoxy acid herbicides cause soft-tissue sarcoma," 35.

A brief initial report by Edling and Granstam compared the causes of death for 375 Swedish forestry workers, aged 25 to 69 years, who died during 1968 to 1977, with the mortality figures from the Swedish national statistics. There were 75 deaths from all malignant tumors, as compared to 86 expected. Renal tumors killed 8 with 3.84 expected and "tumors of lymphatic and hematopoetic systems" were responsible for 14 deaths with 7.5 expected. No deaths were attributed to soft-tissue sarcoma, 36.

In addition to these studies, several small industrial groups have been followed well into the latent period for solid tumors. None has been reported to include cases of soft-tissue sarcoma or malignant lymphoma. May examined 41 of 79 workers who developed chloracne following accidental exposure to trichlorophenol in 1968 at the Coalite Company in Great Britain. Another 54 employees were possibly exposed. None of the workers had significant changes ten years after the accident and neither death from nor evidence of neoplasm was found, 37. Jirasek's group has closely followed 55 men who were intensely exposed during the manufacture of 2,4,5-trichlorophenoxyacetate from 1965 to 1968 in Spolana, Czechoslovakia, and who developed evidence of acute intoxication. Two workers died of bronchogenic carcinoma 5 to 5.5 years after the first exposure. There was no other evidence of malignant neoplasms during a ten-year follow-up, 38.

In 1963 an explosion at Philips-Duphar, Amsterdam, exposed 106 workers involved in manufacturing 2,4,5-tetrachlorophenyoxy acewtate. Among the 93 workers followed to 1977, only one death 14 months after the accident was due to cancer and the pancreatic carcinoma involved was apparently symtomatic before the explosion. No case of soft-tissue sarcoma or malignant lymphoma was reported, 39.

One study is often cited with the Swedish studies although it did not deal with soft-tissue sarcomas and malignant lymphomas, 40. A more recent review by Thiess et al reports that all 74 exposed persons are still being followed

after 26 years. There have been 21 deaths, about equal to the 18 to 20 deaths expected from major comparative populations and 18 and 19 deaths expected among matched unexposed controls. Cancer was responsible for 7 deaths as compared to 4.1 expected from the comparative populations and 5 in each internal control group. Gastric carcinoma in 3 exposed persons exceeds the expected 0.61 to 0.70 expected cases. There were, however, no soft-tissue sarcomas or malignant lymphomas among these chemical workers at BASF, 41.

A number of other industrial exposures to phenoxy herbicides, their precursors or contaminants were reported before 1973, 42. The populations were small but generally heavily exposed. Unfortunately it has not been possible to locate late reports on the exposed populations although ten years or more have elapsed since exposure.

The accident at the ICMESA factory in Seveso, Italy, in July 1976 exposed many people to trichlorphenol; more than 5400 adults and children of both sexes are known to have been in contact with the chemicals for several days, 43. Although only about six years have elapsed since the exposure, the population has been under surveillance and the rate and causes of death are being followed. To date no soft-tissue sarcomas or malignant lymphomas have been reported.

Another less systematic observation bears on the situation. The phenoxy herbicides have been used frequently and extensively in agriculture and forestry in the United States since the late 1940's. They were used on lawns in cities, as well, for most of that period. If the relative risk of developing so distinctive a group of tumors as the soft-tissue sarcomas and the malignant lymphomas had increased by 5 of 6 fold over that before 1945 as the Swedish studies would predict, it almost certainly would have been evident to clinicians and pathologists, especially in the rural areas, even without systematic studies. No such increase was noted.

Critical Evaluations

The Swedish investigators have been cautious in interpreting their results. In his medical dissertation based on his epidemiological studies, Hardell judges that the similar results in the two case-control investigations (12, 13, 14, 16) "seem to increase the confidence that the observed association of exposure to phenoxy acids and soft-tissue sarcoma was not spurious" and did not believe that confounding factors "could account for the observed relation." In summary, he concluded that "it is suggested that exposure to phenoxy

acids should be looked upon as an occupational cancer hazard," 44.

Other reviewers have been more skeptical as to the significance of the work. Remington's overall opinion was that "in toto, the Swedish work is credible if not fully conclusive. Certainly this work would seem to justify further investigation," 10. Coggan and Acheson, after reviewing other work as well as the Swedish studies, state that "on the present evidence it seems possible that soft-tissue sarcomas have arisen in association with exposure to phenoxy herbicides" but continue that "it is as yet impossible to estimate with any precision the risk of soft-tissue sarcoma due to phenoxy herbicides." They conclude that "there is suggestive evidence of a biological association between phenoxy herbicides (or their contaminants) and soft-tissue sarcoma. The evidence relating these products to the occurance of lymphoma is weaker," 22. An unsigned editorial in Lancet commenting on the opinions of Coggan and Acheson seems to agree with their conclusions with regard to soft-tissue sarcomas, 45.

Hardell and Axelson disagreed with both the Coggan and Acheson's opinions and the Lancet editorial, 23. They have been at some pains to counter charges of "observational bias," 15, but have not convinced everyone that faulty memories do not result in significant errors in evaluating exposure, 45.

The causal connection between phenoxy herbicides and soft-tissue sarcomas would be much more likely if there were a unique preponderance of one type or even of a few types in the exposed men. The Swedish reports never compare the morphological types or location of the malignant tumors in cases with those in controls, 45. Their only justification for aggregating the types, and presumably for omitting the data from their reports is "the uncertainty of relations between the various histological groups in terms of causal mechanisms" and "the so-called addition theorem for chi-square and Poisson distribution," 23. The uncertainty of causal relations is precisely the reason for reporting the groups and the addition theorem cannot justify the aggregation of unlike

*2,3,7,8-tetrachlorodibenzo-p-dioxin has been suggested as the principal carcinogen in the phenoxy herbicide 2,4,5-T and trichlorophenols but this has been disputed. See 22, 23, 45, 46. The controversy is not considered in this discussion.

entities unless significant common factors have been demonstrated.

Scientific results are strengthened greatly when independent investigators substantiate them. The Swedish studies have been said to be independent and confirmatory. The two soft-tissue sarcoma investigations do support one another (12, 13, 14, 16) but they are the work of the same group of investigators. The investigation of malignant histiocytic lymphoma was also conducted by the same group but was a case-control study of a separate entity, (19-21). Axelson's work on herbicide exposure and cancer (1-4) was not truly independent from Hardell's efforts since Hardell has recognized his indebtedness to Axelson for his assistance in the first case-control study, (13, 14). More important Axelson did not associate phenoxy herbicides or chlorophenolic compounds with soft-tissue sarcomas nor with malignant lymphomas among railroad workers, 1-4.

The reports of soft-tissue sarcomas among chlorphenol workers in the United States (24-27) have been cited as supporting Hardell's conclusions, 24, 28, 44, 46. The data have been reported piecemeal without a clearly enumerated total population from which they were drawn. The comparison was made to mortality data for the general population of the appropriate age and sex. The type of soft-tissue sarcoma is known for each case; among the 7 men were 2 malignant fibrous histiocytomas, 2 liposarcomas, as well as one each of fibrosarcoma, malignant schwannoma, and fibrosarcomatous mesothelioma. As before, the tumors are not of a uniform type.

Coggan and Acheson comment that the Swedish studies and the American reports taken separately do not "provide convincing evidence that the incidence of soft-tissue sarcomas is increased after exposure to phenoxy acids and chlorophenols, -- Considered together the whole becomes more persuasive." They add that "it is surprising that the association should apply to tumors of such a variety of tissues," 22. The Lancet editorial finds only that "the number of deaths due to soft-tissue sarcomas [in the American data] is disturbing," 45.

In addition to the American experience, the British (37), European (30, 32, 33, 36, 38-41) and New Zealand (34, 35) medical and scientific writers have studied populations five years or longer after exposure to phenoxy herbicides and/or chlorophenols in a variety of situations, some intense and acute, others prolonged. Only one observer (30) reported a case described as a soft-tissue malignant neoplasm without

further characterization. The same report included a lymphosarcoma, a malignant neoplasm of lymphoid tissue and 3 plasmocytomas. No other study found a soft-tissue tumor.

In summary, the Swedish studies of soft-tissue sarcomas cannot be considered to have proved that exposure to phenoxy herbicides is the cause of one or more types of this varied group of malignant tumors. There are no fully reported systematic studies to confirm what the Swedish investigators describe as an association. There are an epidemiological study (32) and observations of exposed populations that do not support the finding as opposed to uncorrelated American observations and an East German study (30) that do strengthen the case for such an association.

At best, the Scottish verdict of "Not proven" seems most realistic at this time. The Advisory Panel on Toxic Substances of the American Medical Association says that "while 2,4,5-T and 2,4-D pesticides (phenoxy herbicides in Agent Orange) have been used in agriculture, forest management and residential landscaping for over 30 years, there is still no conclusive evidence that they and/or TCDD (a contaminant of Agent Orange) are mutagenic, carcinogenic, or teratogenic in man, nor that they have caused reproductive difficulties in the human," 47.

L. B. HOBSON 3/5/83

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The Analysis of 2,3,7,8-Tetrachlorodibenzodioxin in Fat Biopsy Specimens

On the basis of conversations with the analysts named on the appended list, a conclusion has been reached concerning the feasibility of analysis of 2,3,7,8-tetrachlorodibenzodioxin (TCDD) in fat biopsy samples. Using existing methods, analysis of 5-10 g samples at the low (10) part per trillion level with an accuracy of 20-40% is feasible. Several respondents consider that this same sample size can yield results of the same reliability even at the 1 part per trillion level. Cost per sample estimates ranged from $600-1200 per sample, based on a project involving 100 samples.

It is important to note that these estimates do not imply that everyone queried was either willing or able to carry out these analyses. In fact, some respondents consider that only 2-4 laboratories in the United States are currently capable of performing such analyses reliably. All analytical schemes now in use involve time-consuming and tedious procedures that require inordinate attention to the most minute detail. All respondents agree that a large number of blanks must be distributed among the unknowns to provide assurance that contamination by TCDD or other substances has not occurred. These blanks are partly responsible for the above cost estimates although it seems reasonable that their number might be reduced as a given laboratory gains experience with a large number of samples. On the other hand, the use of several independent laboratories provides cross-checking that is considered essential at the present stage of development of this analysis.

Regarding analytical methods, there is general agreement that gas chromatography-mass spectrometry has sufficient selectivity and sensitivity to do the job. Commercially available capillary columns have demonstrated resolution of 2,3,7,8-TCDD from all other isomers but access to isomers eluting near 2,3,7,8-TCDD is still needed in checking g.c. resolution. Several respondents consider that electron capture gas chromatography is itself sufficiently sensitive to provide reliable quantitation provided the sample has undergone a careful cleanup procedure. However, confirmation that the eluted peaks are actually TCDD is best done by mass spectrometry and any laboratory heavily involved in this work should have access to both high and low resolution spectrometers. Internal standards of 2,3,7,8-TCDD (^{13}C and ^{37}Cl) are available.

One respondent, in a preliminary investigation, has shown that needle biopsy samples (0.25-1 g) may be practicable, at least at the 20 ppt level. Further evaluation of this technique is desirable since the usual 5-10 g biopsy involves considerable trauma. Such a study might be carried out in parallel with the limited project recommended below.

Most respondents feel that it would be very unwise (perhaps even impossible) at this time to initiate a large scale project involving thousands of samples using one rigid analytical protocol. There has been insufficient experience on this particular type of sample (human fat biopsy) and, as mentioned, the surgery

involved is not trivial. More appropriate is a second series of analyses involving a limited number of samples, perhaps 100-200, from the population at risk which would be compared to a like number from the general population. If values from individuals in the two populations are found to be grossly different, certain economies might be effected in larger scale efforts. If the two populations turn out to be statistically similar, even more rigid protocols will be necessary. It is even possible that new methods will have to be developed to provide the necessary accuracy. The precise number of samples and overall design of the experiment should be conducted with advice from experienced epidemiologists so that this necessarily expensive and laborious experiment will yield statistically significant results.

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Status of Federally Sponsored Human Studies Related to Agent Orange - April 25, 1983

Department of Health and Human Services

Centers for Disease Control

Epidemiologic Study of Ground Troops Exposed to Agent Orange during the Vietnam Conflict.

The protocol for this study is currently in preparation and is scheduled for review at the end of May, 1983. Presently identified reviewers include the Congressional Office of Technology Assessment and the Science Panel of the Cabinet Council Agent Orange Working Group. CDC has proposed to conduct two separate but related investigations: One to evaluate the possible long-term health effects of exposure of U.S. ground troops to Agent Orange; the other to make an assessment of the possible health effects of service in Vietnam. 30,000 veterans are expected to participate. CDC has also proposed an additional study of the risk of contracting certain cancers, particularly soft tissue sarcoma, and its relationship, if any, to service in Vietnam. The conduct of the epidemiology study was transferred by interagency agreement to CDC from the Veterans Administration January 14, 1983. The study will be monitored by an advisory committee of scientists drawn from the private sector. The completion date of this study is September, 1987.

Centers for Disease Control

Birth Defects and Military Service in Vietnam Study.

This study of the possible association between military service in Vietnam and subsequent fathering of congenitally malformed children is based on the Birth Defects Registry in the metropolitan Atlanta area. The case-control epidemiologic study is designed to include the families of about 5,400 case babies and 3,000 control babies. Data collection is scheduled to be completed by the end of this year, with preliminary analysis to be accomplished soon after.

National Institute of Occupational Safety and Health

Soft Tissue Sarcoma Investigation

This is a comparative pathology study of tissue from 7 cases of soft tissue sarcoma in the United States. Among these cases, 4 are known to have been occupationally exposed to dioxin and the other three may have been. This study is not designed to test the possible association between exposure to dioxin and soft tissue sarcoma, but rather to identify any particular pattern of cancer subsites which might be unique among cases who have been exposed to dioxins. It is possible that other cases may be added to this series.

Investigation of Leukemia in Madison County, Kentucky allegedly associated with pentachlorophenol treated ammunition boxes.

This study of the possible association between exposure to pentachlorophenol treated wood (containing hexadioxins but no

Tumor Registry and data collection will be completed by October 1983. A report of findings from this study is expected in the spring of 1984. The study is being conducted in Kansas because of the agricultural practices among wheat growers in which phenoxy herbicides are applied to large acreages without siumultaneous application of insecticides.

Additional studies are being conducted in the States of Minnesota and Iowa where insecticides are generally applied simultaneously with herbicides to corn and other corps. A similar case control design is being employed in these areas to compare pesticide exposures in general among cases of leukemia and lymphoma and suitable controls. Although information will be obtained on herbicide use, it is anticipated that it may not be possible to separate possible associations between exposure to insecticides and herbicides. Results of these studies may be available in late 1984.

Study of Mortality Among Pesticide Applicators from Florida.

This study compared cause specific mortality rates among pesticide applicators licensed in Florida in 1965-66 to those for the State of Florida and the U.S. of appropriate age, sex, and racial characteristics. Findings included a significant increase in lung cancer among pesticide applicators, but it was not possible to compare groups according to whether they had used herbicides or not. There was no increase in soft tissue sarcoma or lymphoma deaths among applicators. Results are included in a manuscript currently in press for publication by the Journal of the National Cancer Institute.

Department of Defense

Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicide Orange (Air Force Health Study "Ranch Hand").

This study will compare mortality and morbidity of Air Force personnel involved in defoliant operations in Vietnam (Operation Ranch Hand) with that of a suitable group of Air Force personnel not exposed to herbicides. Health status will be based on clinical and laboratory examination, which has been completed. Data will be available following review by the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants, which was established for this purpose. It is anticipated that data will be made available to the public in June, 1983 for the mortality and in October, 1983 for the morbidity aspects of this study.

Armed Forces Institute of Pathology (AFIP) Agent Orange Registry of Vietnam Veterans Biopsy Tissues.

This is a pathology study of tissues from Vietnam Veterans identified within the AFIP archives. Approximately 1200 specimens have been identified to data, and no unusual patterns, especially of cancer, have been found. The study will continue indefinitely and will include new specimens as they are entered into the registry.

Since the pathological diagnosis offered by this group is uniformly of high quality, tissues from any sources are often

submitted for verfication of diagnosis. The accession list for the AFIP provides a good source of case identification for rare tumors, and a case-control study of soft tissue sarcoma initiated by the Veterans Administration is currently being considered.

Veterans Administration

Vietnam Veteran Mortality Study

This study is a major research effort to assess mortality patterns of U.S. servicemen of the Vietnam era. The researchers will examine the information contained in the records of 60,000 deceased veterans who served during the Vietnam era (1964-1975). The study will compare mortality patterns and specific causes of death between those who served in Vietnam and those who did not. Contracts for the work have been let and the work has begun with expected completion by the end of 1984.

Vietnam Veteran Identical Twin Study

This study will be designed to compare mental and physical health status of identical twins, one of whom did and the other did not serve in Vietnam. The protocol for this study will become available for review by mid-June, 1983.

Survey of Patient Treatment File for Vietnam Veteran In-Patient Care.

This survey will identify Vietnam veterans among in-patients' files in the various Veterans Administration facilities in order to identify morbidity patterns specific to this group of veterans. The initial survey is scheduled for completion in 1983.

Agent Orange Registry Examinations

Approximately 107,000 Vietnam veterans have been examined to date and are entered into an Agent Orange Registry. Since this is an entirely voluntary procedure and exposure to agent orange is self-reported, there can be no scientific basis for measuring any association between particular health outcomes and exposure to agent orange while in Vietnam. These data may be useful in determining morbidity patterns which are of concern to Vietnam veterans. The Registry is currently being examined for diagnoses of cancer and is intended to be continued indefinitely.

TCDD in Body Fat of Vietnam Veterans and Other Men

A preliminary study to determine 2,3,7,8-TCDD in body fat of U.S. males, including some Vietnam veterans has been completed. The study found low parts-per-trillion levels of TCDD in adipose tissues of some Vietnam veterans and some non-Vietnam veterans. The accurate laboratory determinations of very low levels had not been verified, nor have any health implications of such levels been assessed. Results of this study, however, are suggestive of additional work to be done in this area, and are currently in preparation for publication.

Retrospective Study of Dioxins and Furans in Adipose Tissue of Vietnam-Era Veterans.

This study is a follow-up of the TCDD in Body Fat Study and is based on archived body fat samples in the EPA Survey of Human Adipose Tissue. The study will select a reliable analytical method for determining very low levels of dioxins and furans in human adipose tissue, identify a cohort of persons in the age

range for having been a Vietnam-Era veteran among archived tissue samples, identify Vietnam veterans among those and complete the analytical work. A protocol for this study will be available in June, 1983 and the study is expected to be completed in 1985. Since the analytical chemistry to be utilized in this study is so highly technical, the Committee to Coordinate Environmental and Related Programs (CCERP) has agreed to follow the progress of this study and to offer technical advice when and if needed.

Environmental Protection Agency

Report of Assessment of a Field Investigation of Six-Year Spontaneous Abortion Rates in Three Oregon Areas in Relation to Forest 2,4,5-T Spray Practices.

The study, also known as the "Alsea Report", which examined the rate of hospitalized spontaneous abortions in both spray and non-spray areas, was completed in 1979. Because of serious methodolical problems the conclusions which can be drawn from the study are unclear.

National Pesticide Monitoring Project of Human Adipose Tissue.

This survey has been going on for a number of years, and includes quantitative and qualitative determination of 14 pesticides plus PCB in a broad U.S. sample of human fat tissues obtained at biopsy or autopsy. The survey is scheduled to continue indefinitely, and annual reports are published in the Pesticide Monitoring Journal. Of particular interest to Agent Orange concerns is that tissues contained in the archives of this project will be the source of

adipose tissue to be analyzed for dioxins and furans in the retrospective study of Vietnam-Era veterans currently being conducted jointly with the Veterans Administration.

Department of Agriculture

A Case-Control Study of the Relationship Between Exposure to 2,4,-D and Spontaneous Abortions in Humans.

This study of agriculture and forest workers and residents in Oregon and Washington has been completed and is published in a monograph. Extensive review of this report indicated that conclusions derived from this study could not be supported.

Exposure Measurements of Mixers, Loaders and Applicators of 2,4-D on Wheat.

This study was reported in ACS Symposium Series, No. 182 Pesticide Residues and Exposure in 1982. Results of this study indicated that the amount of 2,4-D excreted in the urine of occupationally exposed workers who were spraying wheat was proportional to the number and length of exposure to the herbicide. No health status indicators were measured, but mixers and loaders had the highest levels in urine (compared to applicators and one-time workers).

Exposure of Forest Workers to Ground Applications of 2,4-D.

Findings from this study are in final preparation for publication, and results essentially similar to that for mixers, loaders and applicators on wheat reported earlier.

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TESTIMONY BY DR. VERNON N. HOUK

DIRECTOR

CENTER FOR ENVIRONMENTAL HEALTH

CENTERS FOR DISEASE CONTROL

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON VETERANS' AFFAIRS

of the

UNITED STATES SENATE

JUNE 15, 1983

Mr. Chairman and members of the Committee:

I am Dr. Vernon N. Houk, Director, Center for Environmental Health (CEH), Centers for Disease Control (CDC), Atlanta, Georgia. I am accompanied by Dr. Paul W. Wiesner, Assistant Director for Medical Affairs, CEH, and Dr. Marilyn A. Fingerhut of the Industrywide Studies Branch, the Division of Surveillance, Hazard Evaluation and Field Studies, of CDC's National Institute for Occupational Safety and Health (NIOSH).

I am pleased to be here this morning in response to your request for testimony regarding the plans for the Centers for Disease Control's conduct of the epidemiological study mandated by Public Law 96-151 as amended, regarding Agent Orange and the work CDC's NIOSH has done in evaluating the health of workers who may have been exposed to dioxin, the major toxic contaminant of Agent Orange.

On September 15 of last year I appeared before the Subcommittee on Oversight and Investigations of the House Committee on Veterans' Affairs, testifying as Chair of the Science Panel, Agent Orange Working Group. The matter of CDC's involvement in the epidemiology study was mentioned at those hearings. As a result, CDC began consideration of the issue well before the Administrator of Veterans Affairs asked HHS to consider this possibility. CDC had determined as early as the first week of October that, if called upon and provided with appropriate resources, it could design and conduct a scientifically sound study. On October 22, the HHS Assistant Secretary for Health, Dr. Edward N. Brandt, Jr., met with the VA's Medical Director, Dr. Custis, to begin discussions about transferring responsibility for the study to CDC.

On October 27 I asked Dr. Wiesner to assign staff and resources to start work on development of a scientifically acceptable protocol outline along the lines of other epidemiological investigations conducted over the years at CDC. Dr. J. David Erickson, Chief of the Cancer Branch of CEH's Chronic Diseases Division, agreed to chair a task group of experienced medical epidemiologists and biostatisticians from among CDC staff. They were aided by a VA senior staff person loaned to us to give the CDC group first hand information about the VA's previous work in this area. The task group held its first meeting on November 1, 1982. During the first few days of November its members traveled to several cities to meet on the subject with the Army, Air Force, and National Institutes of Health personnel, and with developers of the UCLA proposed protocol which had previously been submitted to the VA.

I must say that I am proud of the energetic manner in which our scientific team attacked the task of developing a protocol outline. By November 8, the CDC task group was meeting daily working to complete the protocol outline, which was submitted by Dr. Brandt to the Veterans Administration on December 6. The outline we proposed included two separate but related investigations: one to evaluate the possible long-term health effects of exposure of U.S. ground forces to Agent Orange; the other to make an assessment of the possible health effects of service in Vietnam. The protocol outline calls for the participation of 30,000 veterans, comprising five cohorts--or groups--of 6,000 each. Three of these five cohorts will provide data for the Agent Orange exposure portion of the CDC study, and will be made up as follows: one cohort of veterans who served in areas of Vietnam where herbicides were used and who were likely exposed; a second cohort of veterans who, though serving in areas of Vietnam where herbicides were used, were unlikely to have been exposed; and a third cohort of veterans who served in

areas of Vietnam where herbicides were not used. Data from the fourth and fifth cohorts will be used in the other investigation of the possible health effects of the "Vietnam Experience". Of the two cohorts in this related study one will comprise Vietnam-era veterans who served in Vietnam; the other will be made up of veterans who served during the same years, but in other parts of the world.

Each of the two concurrent studies will have three major components. First, a mortality assessment to determine which veterans may have died since being discharged and the cause of the death; second, a health interview and; third, a comprehensive medical examination and laboratory assessment. This third component--the examination and laboratory work--will be provided to 2000 men from each of the five cohorts. Although both of the concurrent studies will have several other features in common, the sampling plan, timetables, and some of the health outcomes measured in the interview and medical examinations will differ between the two studies. They are designed to answer related but different questions of importance to Vietnam veterans and their families.

Because of the concern that Vietnam veterans may be at increased risk for contracting certain cancers, particularly soft tissue sarcomas and lymphomas, we have since proposed an additional study of this problem and its relationship if any, to service in Vietnam. The soft tissue sarcoma and lymphoma case control study has been approved by the Assistant Secretary for Health as a third element of the CDC Agent Orange Epidemiology Study and has been recommended by PHS to the VA for funding.

The choice of veterans for inclusion in the various study cohorts will derive from review of military records from the Vietnam era. Considerable work with

records from Vietnam has already been done in consultation and cooperation with the Department of Defense (primarily staff of the Army Agent Orange Task Force) and the White House Agent Orange Working Group. CDC has assigned a staff member to work full time with the Army Agent Orange Task Force. We continue to be pleased with the energetic and dedicated work of the Army Agent Orange Task Force under the able leadership of Mr. Dick Christian.

In approving the Interagency Agreement with the Public Health Service on January 13, the VA accepted CDC's concept of a Vietnam Experience Study in addition to the original Agent Orange exposure investigation, and committed to provide $3 million to CDC and has obtained OMB approval for 28 full time staff positions during FY 1983 for the beginning phases of the studies, including the development of a complete research protocol. Since early November a small Agent Orange Projects staff within the Center for Environmental Health has been preparing for the planned studies. We are now in the process of recruiting the appropriately qualified professional and support staffs for the continuing formative and implementation phases of the studies.

In late January and early February, 1983, Drs. Wiesner and Erickson called on several of the largest veterans' organizations to seek their advice and to describe the investigations we intend to pursue. During this same time, they also met with staff members of the House and Senate Committees on Veterans' Affairs. In addition, on May 2 Drs. Wiesner and Erickson held an update briefing for representatives of about 15 veterans' organizations.

As required by Public Law 96-151, the CDC protocol outline has been reviewed by the Office of Technology Assessment of the Congress. During the first week

of March, Mr. Chairman, you and other Congressional leaders should have received OTA's favorable report on the protocol outline. OTA Director John Gibbons' covering letter notes the concurrence of the OTA Agent Orange Review Advisory Panel with the proposed studies as outlined by CDC and states that, "The two studies together address the questions of greatest concern to veterans and their families: What, if any, are the health effects of 1) exposure to Agent Orange, and 2) service in Vietnam, which may have included exposure to Agent Orange, other chemicals, drugs, and other factors in an exotic environment?" OTA has only one serious reservation with CDC's plan. OTA feels that our proposed timetable, which calls for completion of our studies at the end of 1987 is rather optimistic. While our estimate may be optimistic, we believe we can meet that timetable and certainly will make every effort to do so.

On April 19, the HHS Assistant Secretary for Health, Dr. Edward N. Brandt, Jr., at the request of VA and OMB, submitted to the VA a budget estimate and justification for the CDC Agent Orange Epidemiology Study which now has three components: Agent Orange exposure, Vietnam Experience, and soft tissue sarcoma and lymphoma. Resources for the activity will be appropriately sought through the Veterans Administration appropriation. This budget proposal estimates expenditures and staffing needs during Fiscal Years 1984-87. The VA has submitted our budget proposal to the Office of Management and Budget requesting an amendment to the FY 1984 budget to include specific funding for the studies. Additional justification material has been requested by OMB and is being supplied.

On May 27, CDC completed the full protocol for these investigations and submitted it for review by the Office of Technology Assessment. The Science

Panel of the Agent Orange Working Group and the HHS Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants have been asked to formally review the protocol. Copies have been sent to others, including 15 veterans' organizations, for their information. We will accept individual comments from these other groups.

In addition to these proposed studies to be carried out under PL 96-151 as amended, CDC is currently conducting, with support from the Veterans Administration and the Department of Defense, a case-control epidemiologic study to determine whether Vietnam veterans may have a higher risk of fathering children with birth defects. The study "cases" are the families of babies born with major birth defects during the years 1968-1980 in metropolitan Atlanta and who have been registered by CDC's Metropolitan Atlanta Congenital Defects Program. Study "controls" are families of babies without defects who were born in the Atlanta area during the same time period and identified through State of Georgia birth certificates. This study is designed to include the families of about 5400 case babies and 3000 control babies.

The major objective of this study is to determine whether an unusually high proportion of fathers of babies born with defects served in Vietnam. This comparison will yield an estimate of the risk of fathering a child with a defect for Vietnam veterans relative to that risk for non-veterans. Because information about other potential risk factors for birth defects will be gathered, this study will permit an evaluation of their contribution, both in Vietnam veterans and in the population at large. Data collection is scheduled to be completed by the end of this year, with preliminary analysis to be accomplished shortly afterward.

In addition to these studies either proposed or under way in CEH, NIOSH is conducting studies of the health effects of exposure to dioxin. Since 1979, NIOSH has been investigating the possible link between dioxin exposure and health effects in workers occupationally exposed to dioxin-contaminated products. In 1979, NIOSH began work on a registry of United States production workers who were potentially exposed to dioxin during the synthesis or formulation of substances contaminated with dioxin. These substances include such commonly used products as trichlorophenol; 2,4,5-trichlorophenoxy acetic acid (2,4,5-T), the herbicide which was one component of Agent Orange; and pentachlorophenol, a wood preservative.

After completion of the NIOSH registry, our first research task will be to compare the causes of death in these workers to the causes of death in the U.S. population. We expect to include about 6000 workers in this study. As of May 1, 4000 have been included in the registry. Enrollment will be completed by December of this year. We plan to have all information relating to the status of these workers collected and analyzed by March 1985, well before the final results of CDC's Agent Orange Epidemiology Study will be available.

NIOSH is exploring other uses of the worker registry, including studies of certain illness and problems with reproduction among persons exposed. A decision to proceed with these kinds of studies depends on scientific feasibility and availability of resources.

Since most of the workers included in the NIOSH registry were exposed during the period 1940-1970, to the extent that there may be diseases with long

periods of latency, we will be able to find them. However, we propose to continue to evaluate the health status of these persons at 5 year intervals into the future.

There are also workers exposed to dioxin in other countries. The production workers in these facilities constitute a valuable study group. A contract was awarded to the International Agency for Research on Cancer (IARC) by the National Institute for Environmental Health Sciences (NIEHS) to establish and maintain an international register of persons exposed to phenoxy acid herbicides and contaminants, parallel to the NIOSH registry. In December 1982, Dr. Patricia Honchar, on detail from NIOSH to IARC, completed the feasibility assessment for this project. Cohorts from more than 20 production facilities throughout Europe and in Australia and New Zealand were evaluated to determine their suitability for epidemiologic study.

In addition to the above studies, NIOSH continues to examine reported association between dioxins and disease in occupationally exposed workers. In 1977, cases of soft tissue sarcoma were reported among Swedish lumberjacks who had previous exposure to phenoxy acid herbicides. This clinical observation led researchers in Sweden to conduct two separate epidemiologic case control studies which showed increased risk of soft tissue sarcoma. Subsequently, four independent small studies in the U.S. were reported to show no association between soft tissue sarcoma and work exposure to dioxin. However, when data from the 4 U.S. studies (which include three deaths with soft tissue sarcoma) were combined, the same association noted in the Swedish studies was found. Later, four additional persons who worked at 2,4,5-T production facilities in the U.S. were reported to have soft tissue sarcomas. At NIOSH, work is currently underway to gather pathologic specimens and the work histories for all seven cases. NIOSH will evaluate the histories of exposure,

The goal is to gain an understanding of any common characteristics which may exist among the sarcoma cases and to focus medical expertise on the question of the legitimacy of grouping different types of sarcomas.

We feel that information suggesting an association of soft tissue sarcoma in humans and exposure to dioxin-contaminated products is accumulating. While this may be true, one must also be aware of the fact that international studies as conducted and reported fail to confirm any existence of an association between soft tissue sarcoma in humans and exposure to dioxin contaminated products. The controversy over this association is ongoing within the scientific community. For these reasons, careful epidemiologic analyses are needed. The question of an association of sarcomas and exposure to phenoxy acids and chlorophenols is being addressed in the NIOSH Dioxin Registry mortality study, and would be addressed by the IARC study. In addition other studies, such as case control, are now being proposed and being conducted. Epidemiologic studies like these will further delineate the association.

In summary, we are proceeding with all deliberate speed on the Agent Orange Epidemiology Study. The Birth Defects Study, studies of dioxin exposed workers in the U.S. and other countries, continued study of the soft tissue sarcoma issue, combined with the results of other studies, some of which you are hearing about today, should help provide answers to the questions we all seek. All these studies need to be approached with objectivity and thoroughness, if we expect to achieve a scientifically valid finding. For these reasons, the Administration believes that any legislation in this area at this time would be unnecessary and unwarranted.

Mr. Chairman, that concludes my formal remarks. My colleagues and I will be happy to answer any questions you or other members may have.

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STATEMENT OF

WILLIAM J. JACOBY, M.D.

DEPUTY CHIEF MEDICAL DIRECTOR

VETERANS ADMINISTRATION

BEFORE THE

COMMITTEE ON VETERANS' AFFAIRS

UNITED STATES SENATE

JUNE 15, 1983

Mr. Chairman and Members of the Committee:

Good morning. We are pleased to have the opportunity to appear before this Committee to discuss VA research on the health effects of exposure to Agent Orange, the current state of knowledge concerning such exposure and associated health effects, and the VA's provision of health care benefits to Vietnam veterans under Public Law 97-72.

The VA is keenly aware of the depth of veterans' concerns over this subject and is engaged in a multi-faceted scientific research effort to resolve the issue. The VA, and others, are engaged in this research to assure that we find answers to the scientific and medical questions surrounding such exposure. Research studies here and abroad have begun to provide pertinent information. We foresee that these and other well-planned, carefully executed studies will enable us to

provide scientifically acceptable answers to whether or not exposure to Agent Orange plays a significant role in the development of disease or other disorders.

We would stress that we are approaching these questions with dedication, objectivity, and a commitment to achieving scientific validity. The scientific process on which these studies must be based is necessarily exacting and time consuming. Understandably, this lengthy process tries the patience of concerned veterans and their families. As we proceed painstakingly on the research front, we are deeply aware of the need to exercise compassion, respect, and understanding in responding to these veterans.

Let me stress that while we pursue the resolution of these concerns through many significant research efforts, we are providing medical examinations and care to Vietnam veterans under Public Law 97-72 without regard to whether medical science can demonstrate that a condition may be caused by exposure in Vietnam to an herbicide or defoliant.

RESEARCH

As you know, Mr. Chairman, the VA has undertaken or supported several major studies as part of a coordinated federal effort. Permit me to outline the current status of those studies.

Vietnam Veteran Mortality Study:

In the conduct of any large scale health survey which examines the effects of chemical or other environmental agents, an essential element is an examination of mortality data.

A carefully designed and well-executed mortality analysis of Vietnam veterans would provide answers to many questions raised by the Agent Orange exposure issue, in particular, and the possible health effects of service in Vietnam, in general. Accordingly, VA developed the Vietnam Veteran Mortality Study to analyze and compare mortality patterns and specific causes of death of veterans who served in Vietnam and comparable veterans who did not. Researchers are examining information contained in the records of 60,000 deceased veterans who served during the Vietnam era.

The data-gathering phase of this important study is well underway and we anticipate that data collection will be completed by March 1984. Data analysis, final review, and publication of results should occur by December 1984.

Vietnam Veteran Twin Study:

The Vietnam Veteran Identical Twin Study involves a study of identical twin veterans, where one twin served in Vietnam during the period of Agent Orange spraying, and the twin sibling did not serve in Southeast Asia. This study, which will examine up to 500 pairs of twins, will use a battery of psychological, physiological, and biochemical tests to measure the psychological and physical impact, if any, of service in Vietnam.

Any differences in results within the twin pairs will be examined as a function of both service in Vietnam and herbicide exposure. The study will include a pilot phase to validate the proposed physical and psychological tests and measures on a series of identical and fraternal twins who will not be a part of the main study. This study has been incorporated into the agency's Cooperative Studies Program, and the project team has been assigned to our Cooperative Studies Center in Chicago. This step should assure the project full support from the research management group most experienced in conducting large scale epidemiological studies.

We anticipate the development of a final protocol for the study within the next four to five months. Projecting dates for completing the examination phase and the final study itself

depend upon the degree of success we have in locating and recruiting participants quickly. The results of the study should not be expected for two to three years. We would stress, however, that this study will provide the most sensitive means we can devise for detecting any subtle effects of Vietnam service.

Dioxin/Furan Adipose Tissue Study:

In a limited study conducted in 1979-1980, the VA found that dioxin, or TCDD, could be detected and quantified in adipose tissue removed from Vietnam-era veterans. Although no clear relationship was found between levels of TCDD and Vietnam service, exposure to Agent Orange, or current health status, the study indicated the need for further investigation.

Since 1970, the Environmental Protection Agency has been collecting human adipose tissue from a statistically representative segment of the general population to be analyzed for residues of selected pesticide-related chemicals and polychlorinated biphenyls (PCB's). Within the bank of approximately 4,000 tissue specimens available for further chemical analysis, there are specimens from 555 males born between 1937 and 1952. Many of these individuals will have served in the military during the Vietnam-era, and some will have served in Vietnam during the period of Agent Orange use.

Under an interagency agreement between VA and EPA, we will conduct a study of these tissue samples which will provide a basis for assessing whether service in the military, and especially in Vietnam, has had an effect on the TCDD levels. The analysis involved in this study is both exacting and lengthy. Accordingly, we do not expect final results until 1985.

The study itself has three phases. In the first phase, researchers will contact hospital pathologists to identify tissue donors and determine their service status from their military records. The second phase involves developing analytic methods of determining selected dioxins and furans in human adipose tissue and subjecting that methodology to rigorous independent validation. The last phase is the tissue analysis itself and preparation of a final report.

At this time, we have begun to obtain details about the 555 men, including their military service and other occupational history, and are also in the process of designing a uniform method of analyzing TCDD levels in the tissue specimens.

Epidemiological Study of Agent Orange:

Public Law 96-151 directed the VA to design and conduct an epidemiological study of veterans who, while serving in

Vietnam, were exposed to dioxins contained in herbicides, including Agent Orange. The VA entered into a contract with the University of California at Los Angeles (UCLA) to design the study and, subsequently, four reviews of the resulting protocol were accomplished, three of them by groups outside the VA.

The efforts to develop a protocol led us to conclude that it would be difficult and time consuming to determine who had been exposed to Agent Orange in Vietnam, and who had not. Initially, it was believed that such a determination would be virtually impossible, and consequently there was considerable doubt among scientists that such a study could be accomplished. Accordingly, in an amendment in Public Law 97-72, Congress authorized the Agency to enlarge the scope of the study from Agent Orange alone to focus broadly on adverse health effects of Vietnam service including exposure to other chemicals and environmental conditions. Diligent efforts by the Army Agent Orange Task Force, under the able leadership of Mr. Richard Christian, have now made it likely that groups or cohorts of exposed and unexposed Vietnam veterans can be identified.

As you know, subsequent developments culminated in the VA and the Public Health Service of the Department of Health and Human Services' executing an interagency agreement which provides

that the Centers for Disease Control would design and conduct this epidemiological study. CDC has agreed to complete the study as expeditiously as possible, but not later than September 30, 1987.

The CDC has been, and will remain, completely independent of the VA in designing and conducting the study. The CDC has just recently completed its proposed protocol which calls for two parallel studies, one to examine the effects of exposure to Agent Orange and the other, consistent with Public Law 97-72, to determine if there are any adverse health effects of Vietnam service, in general.

CDC Birth Defects Study:

In addition to the epidemiology study, the Centers for Disease Control is proceeding in its conduct of a birth defects study in the Atlanta, Georgia area. Subjects for this study are identified through the CDC's Metropolitan Congenital Defects Surveillance Program, and the study is continuing to be jointly funded by the VA, Department of Defense, and the Department of Health and Human Services. It is our understanding that CDC expects to complete the study by December 1983 or January 1984. We are continuing to monitor with great interest their progress in this significant research effort.

In this connection, two international studies reported within the past few months are noteworthy.

An Australian Birth Defects Study ("Case Control Study of Congential Anomalies and Vietnam Service Birth Defects Study") examined records from 34 hospitals and four cytogenetic laboratories to identify infants with birth defects. Matched healthy infants born in the same hospitals served as controls. In all, approximately 8,500 children were involved in the study. The fathers of the defective infants and the controls were identified and their service in the Army was determined as well as their duty in Vietnam. The study found no evidence that service in Vietnam increased the risk of fathering a child with a birth defect.

In New Zealand, the manufacture and spraying of phenoxy herbicides have exposed many workers to these chemicals. Both sprayers and their wives are exposed during field spraying and in the purchase and handling of chemicals. A survey of 981 professional sprayers and a control group of unexposed agricultural contractors determined the number of births, congenital defects, and miscarriages among these families. The analysis showed that there was no statistically significant difference between the number of birth defects and miscarriages in the two groups. In addition, exposure to the wives also had

no detectable reproductive effect. (The study is entitled "Congenital Defects and Miscarriages Among New Zealand 2,4,5-T Sprayers.")

VA Specially Solicited Research Projects:

In 1981, through a special solicitation letter, we urged VA scientists to submit research proposals on the biochemical, physiological, or toxicological aspects of herbicide and TCDD exposure. During fiscal year 1982, our Medical Research Service approved, and in fiscal year 1983 funded, 10 new research studies that investigate the impact of low levels of exposure to the ingredients of Agent Orange on basic biological processes. These studies will include an analysis of the effects of the components of Agent Orange on liver cell function, on neuro-behavioral functions, and the biochemistry of chloracne. We expect to fund another 10 studies in fiscal year 1984 dealing with the effects of exposure to phenoxy herbicides and related chemicals.

Chloracne Review:

As you know, a VA chloracne Task Force is charged with reviewing and evaluating skin conditions resembling chloracne, coordinating special examinations of veterans with questionable skin conditions, developing a chloracne examination protocol, and preparing a monograph on chloracne.

As part of its activities, that body conducted a special revie of cases of Vietnam veterans who had sought VA compensation fo conditions claimed to be due to exposure to Agent Orange. Fro a review of some 3,200 claims, some 300 cases were selected as having descriptions of conditions that might suggest chloracne.

A VA dermatologist then reviewed the medical records of the 300 claimants and identified 14 veterans who could have chloracne. Using the services of three prestigious non-VA clinics, 13 of these 14 men have received a complete medical examination, including a special dermatological evaluation. The remaining veteran, although located, has not yet been examined due to his remote job location. None of the 13 veterans examined was diagnosed as having chloracne although two men gave histories of exposure and a subsequent skin problem that is compatible with chloracne.

Soft-Tissue Sarcoma Studies:

The VA has initiated two efforts to investigate whether there is a relationship between service in Vietnam and the subsequent development of soft-tissue sarcomas. Several studies carried out in foreign countries, most notably studies conducted in Sweden, have indicated a possible association between exposure

to phenoxy herbicides and subsequent development of soft-tissue sarcomas. Other international studies failed to confirm the existence of this association.

The first VA effort in this area involves a review of the records of Vietnam-era veteran patients discharged from VA hospitals with a diagnosis of soft-tissue sarcoma. The military records of these individuals will be reviewed to determine whether they actually served in South Vietnam. The medical records of all of the individuals will also reveal the specific type and location of the sarcoma. This study should permit us to compare incidence and types of soft-tissue sarcomas in Vietnam veterans, as compared to similarly aged veterans who did not actually serve in South Vietnam. This review is ongoing.

The second VA effort in this area is a special soft-tissue sarcoma study which will be accomplished in cooperation with the Armed Forces Institute of Pathology. This study will use the AFIP register of soft-tissue sarcomas, one of the largest and most consistently accurate in the world, to provide cases among males of the Vietnam veteran age group. Their veteran status will be obtained from their military records. This study is designed to determine if veterans who served in Vietnam have a higher risk of developing this type of tumor than those who did not. We believe these two research efforts,

dealing as they do with Vietnam veterans, will go far to resolve many of the existing questions concerning any association between Agent Orange exposure and soft-tissue sarcomas.

HEALTH CARE

Clearly, science does not have ready answers to all the complex medical and scientific questions relating to veterans' exposure to herbicides and defoliants in Vietnam. Pursuant to the provisions of Public Law 97-72, we are providing medical care, as well as screening examinations, to Vietnam veterans without regard to the uncertainty as to whether that exposure produces adverse health effects. The eligibility provisions of that law are being implemented with liberality and compassion.

Under our guidelines, each veteran who served in the Republic of Vietnam, and who requests VA medical care, is provided a complete medical history, physical examination, and appropriate diagnostic studies. When it is determined that a condition exists requiring treatment, the responsible staff physician makes a determination as to whether the condition resulted from a cause other than the specified exposure to Agent Orange. With very limited and specific exceptions, the Chief Medical Director determined that almost all conditions will be considered as related to exposure for purposes of medical

care. That determination is not supported by present scientific knowledge, but believe it is consistent with the intent of the law. Even as to those conditions attributable to other more common causes, the treating physician is directed to exercise professional judgment and may allow eligibility for medical care under this provision if, in the physician's judgment, treatment is appropriate.

We have attempted to monitor the number of outpatient visits and hospital admissions resulting from the implementation of Public Law 97-72. Our review of these reports indicates that between February 1982 and February 1983, for example, we had approximately 9,400 admissions of Vietnam veterans for inpatient care for problems which they related to Agent Orange. During this same period, there were approximately 369,000 outpatient visits which could be related to the provisions of Public Law 97-72.

I might add that since establishment of the Agent Orange registry in 1978, over 114,000 veterans have received an initial examination. Some 27,000 followup exams have been provided. During the first quarter of fiscal year 1983, some 6,400 initial examinations were performed.

Let me note also that many Vietnam veterans are seen and assisted through counseling in our Vet Centers for readjustment problems which they relate to Agent Orange.

We will continue to provide these needed services.

CONCLUSION

Mr. Chairman, research and health care represent perhaps the most visible and far-reaching of our efforts to assist Vietnam veterans concerned about exposure to Agent Orange. In light of the focus of this hearing and, in the interest of brevity, I will limit any further remarks. Suffice it to say that VA's efforts to respond to this issue are multi-faceted and have continued to expand.

By way of illustration, we have recently initiated an update of the literature review prepared pursuant to Public Law 96-151, and anticipate the publication of an updated report in early 1984. We are also preparing a series of scientific monographs on subjects related to the use of herbicides in Vietnam for distribution to VA health care staff. Our Central Office staff in the Agent Orange Projects Office has expanded in number and in breadth of pertinent expertise.

We believe we are responsibly meeting the concerns that have been expressed: through the continuing delivery of health care to eligible Vietnam veterans, special Agent Orange-related examinations and maintenance of the Agent Orange Registry, significant research related to Agent Orange and other phenoxy herbicides, updating the review of worldwide scientific literature, and other activities.

That concludes my statement, Mr. Chairman. I will be pleased to answer any questions you or members of this Committee may have.

D E P A R T M E N T O F T H E A I R F O R C E

PRESENTATION TO THE SENATE VETERANS' AFFAIRS COMMITTEE

JUNE 15, 1983

SUBJECT: Veterans' Exposure to Agent Orange

STATEMENT OF: Major General Murphy A. Chesney
Deputy Surgeon General
United States Air Force

Not for Publication Until Released by the
Veterans' Affairs Committee, United States
Senate

MAJOR GENERAL (DR.) MURPHY A. CHESNEY

Major General (Dr.) Murphy A. Chesney is Deputy Surgeon General, Headquarters U.S. Air Force, Washington, D.C.

General Chesney was born November 29, 1927, in Knoxville, Tennessee, and graduated from Central High School near Knoxville in May 1945. He attended the University of Tennessee in Knoxville from September 1945 to March 1947 in an accelerated premedical program and graduated with a bachelor of science degree. He earned his doctor of medicine degree in June 1950 from the University of Tennessee's College of Medicine in Memphis.

In June 1951 he completed his internship at the Scott and White Hospital, Temple, Texas, and entered private practice as a surgeon and general practitioner at the Edgar Renegar Clinic in Levelland, Texas. A year later he moved to Rule, Texas, where he was associated with Dr. Robert E. Colbert in the Rule Clinic. While residing there he was elected president of the Chamber of Commerce.

General Chesney entered the U.S. Air Force in April 1955, attended the basic orientation course at Gunter Air Force Base, Alabama, and later the primary course in aviation medicine at Randolph Air Force Base, Texas. In July 1955 he was assigned to the dispensary at Portland International Airport, first as flight surgeon and then as commander. He continued to serve as commander when the dispensary became a hospital.

From July 1957 to June 1960, General Chesney was at the University of Tennessee in Memphis where he completed his Air Force-sponsored residency in internal medicine. During his last year of residency he was appointed chief resident and was involved in several research papers and projects. He also served as a university instructor from July 1959 to June 1960. For the next two years he was assigned as chief of hospital services and chief of the Department of Internal Medicine at Homestead Air Force Base, Florida.

In May 1962 he transferred to the dispensary at Ben Guerir Air Base, Morocco, as commander. He moved to the 401st Tactical Hospital, Torrejon Air Base, Spain, in June 1963 and became deputy commander and senior internist.

General Chesney returned to the United States in June 1966 and assumed command of the 852nd Medical Group at Castle Air Force Base, California. He became director of professional services in the Office of the Command Surgeon Pacific Air Forces, in August 1969 and deputy command surgeon in June 1972. While there his duties included supervision of the professional medical care of patients, including combat-injured personnel, intratheater aeromedical evacuation, flight medicine, preventive medicine and bioenvironmental engineering, medical aspects of the drug abuse program and the prisoner of war release program.

In April 1973 General Chesney transferred to Headquarters Tactical Air Command, Langley Air Force Base, Virginia, as command surgeon. He moved to Brooks Air Force Base, Texas, in August 1978 where he was commander of the Air Force Medical Service Center. General Chesney served as director of medical plans and resources, Office of the Surgeon General, Headquarters U.S. Air Force, from January 1980 until assuming his present position in April 1980.

General Chesney is a member of the Society of Air Force Physicians, Society of Air Force Flight Surgeons, International Congress of Medical Astronautics and Cosmonautics and Phi Rho Sigma Medical Fraternity. He is a fellow of the American College of Physicians, fellow of the American College of Preventive Medicine and diplomate of the American Board of Internal Medicine.

He holds the aeronautical rating of chief flight surgeon. His military decorations and awards include the Distinguished Service Medal, Legion of Merit, Meritorious Service Medal, Air Force Commendation Medal, Air Force Outstanding Unit Award ribbon, National Defense Service Medal and the Spanish Cross of the Aeromedical Order of Merit, 2nd Class.

He was promoted to major general February 8, 1979, with date of rank July 1, 1975.

General Chesney is married to the former Mary Ann Wilson. They have four children: Murphy A. III, Charles Allen, Carol Jean and John Lowell.

Mr. Chairman and Members of the Committee:

I am Major General Murphy A. Chesney, Air Force Deputy Surgeon General. I thank you for the opportunity to present an update on the progress of the Air Force Epidemiologic Study of Ranch Hand personnel exposed to herbicides in Vietnam from 1962-1971. Our previous presentations to this Committee included information on the use of the herbicides in Vietnam, the development and peer review process of the Air Force study design and protocol, the process of study implementation, compliance figures, program costs and preliminary mortality findings. The basic protocol and study were developed and conducted at the School of Aerospace Medicine, Headquarters Aerospace Medical Division, Brooks Air Force Base, Texas.

The information that I will present today includes final study participation figures, an update of the mortality study, a description of some of the types of morbidity data which will be analyzed and which will be of special interest to this Committee, and the dates on which we expect the reports to be available.

The Louis Harris and Associates contract for in-home questionnaire administration to the study participants was completed on November 15, 1982. Of the 2,878 subjects selected for the questionnaire and physical examination phases of the study, only two Ranch Handers and nine comparison subjects could not be located. Therefore, our location rate for the baseline data base is 99.6% (2867/2878), a substantial achievement.

A total of 1,172 or 97% of the Ranch Handers and 1,156 or 93% of the initial 1,241 comparison subjects participated in the questionnaire. All comparison subjects who declined the questionnaire and/or the physical examination were substituted with willing subjects who were equally well qualified for inclusion in the study. Three hundred seventy-two in-home questionnaires were completed on comparison group substitutions to maximize questionnaire

and physical examination participation. In addition to the study subject questionnaire, Louis Harris and Associates completed in-home interviews on 2,546 former or present spouses, and 84 next-of-kin of known dead study subjects. They also completed 84 telephone interviews on the population that refused to participate. Thirty-four Ranch Handers and 158 initial and/or control substitutes were classified as absolute questionnaire refusals in the study. Forty-five percent (87/192) of these refusals stated their reason for refusal as "having no time or interest"; 18% (35/192) were passive refusals (located but totally nonresponsive); and 14% (27/192) refused because they felt that participation could adversely affect their military or civilian careers. The remainder of the refusal population cited factors such as job commitment (25/192), dissatisfaction with the military (14/192) or fear of the physical examination (2/192). However, ill health was cited as a reason by only two individuals, both comparison subjects.

One thousand forty-five (87%) of the Ranch Hand population and 940 (76%) of the initial comparison population participated in the physical examination. Two hundred eighty-seven comparison substitutions also completed the physical examination prior to the contract completion date on December 15, 1982, for a total of 1,227 comparison participants. Reasons cited for refusal to participate in the physical examination included: no time/no interest (54 Ranch Handers, 159 comparisons); job commitment (29 Ranch Handers, 92 comparisons); passive refusals (9 Ranch Handers and 21 comparisons) confidentiality/active duty (11 Ranch Handers, 16 comparisons); travel/distance/family considerations (4 Ranch Handers, 19 comparisons); fear of the physical examination (5 Ranch Handers, 6 comparisons); health reasons (5 Ranch Handers, 5 comparisons) and dissatisfaction with the military (5 Ranch Handers, 0 comparisons). Overall, the average participation rate was 81.5%, (not including the comparison

substitutes) which is substantially higher than the 60% rate cited in the study protocol. These are very high compliance rates compared to most other major health studies and will enhance the statistical power of our effort.

The mortality data that I am presenting today includes deaths up to September 1, 1982. The mortality analysis is an ongoing process, and additional deaths will be included in subsequent reports.

As of September 1, 1982, there were 67 documented deaths in the Ranch Hand group: 22-killed in action; 18-accidental deaths; 3-suicides; 1-homicide; 3-malignant neoplasms, 1-endocrine, nutritional, metabolic and immunity disorder; 14-diseases of the circulatory system, and 5-diseases of the digestive system. For the same time period there were 235 deaths among the comparison subjects. The larger number of comparison subject deaths is a result of the 1:5 Ranch Hand to comparison subject mortality study design. The causes of death for this group includes: 91-accidental deaths; 12-suicides; 3-homicides; 34-malignant neoplasms; 2-neoplasms of uncertain behavior; 1-endocrine, nutritional, metabolic and immunity disorder; 68-diseases of the circulatory system; 11-diseases of the digestive system; 3-infectious and parasitic diseases; 1-nervous system and sense organ disorder; 4-respiratory system diseases; 2-genitourinary system conditions and 2 ill-defined conditions. No statistically significant differences in the crude death rates were found between the Ranch Hand and the comparison group.

The overall survival pattern of the Ranch Hand and the comparison group was contrasted to the 1978 U.S. white male population vital statistics. Both study groups continue to experience significantly less mortality than equivalently aged U.S. white males, an epidemiologic phenomenon called the

healthy worker effect. This effect is due in part to the selection of healthy individuals for entry into the Armed Forces as well as the availability of health care throughout their careers and retirement.

The refined analyses of more than four million pieces of information currently available will account for the effects of exposure patterns, social habits, other medical factors, family history or predisposition to specific diseases, and time spent in Southeast Asia. We are dealing with 2,272--two and one half day long executive physical examinations and 5,330 detailed subject, spouse, and next-of-kin interviews. Analysis of these interrelated factors will improve our ability to properly delineate any adverse health effects of herbicide exposure.

I would like to outline some of the data analyses we are going to accomplish which may give you a clearer understanding of how we will be assessing the overall health of the study population. Those described are major areas of concern expressed by numerous lay and scientific groups and focus on target organ systems identified in the scientific protocol. These include mortality (will be updated in all subsequent reports), assessments of general health (perceptions of both subject and physician); fertility/infertility (fertility index, live birth rates, sperm counts); reproductive abnormalities (birth defects, learning disabilities); cancer (organ specific rates, soft tissue sarcomas); dermatologic (chloracne, porphyria cutanea tarda); hepatic (liver functions); psychologic (depression, anxiety, fatigue, anger); neurologic (muscle weakness, coordination, reflexes); and cardiovascular (blood pressures, cholesterol levels, abnormal heart sounds, electrocardiogram abnormalities). There are many other parameters which will also be reported.

This initial round of questionnaires and physicals will form the basis for the remainder of the study. Follow-up examinations will be at 3, 5, 10, 15 and 20 years.

In summary, we have concluded our initial mortality study and have presented an update of that effort to you today. The mortality data will be submitted to the Advisory Committee for review and should be available for public release by 30 June 1983. The morbidity data (questionnaire and physical examination data) will be submitted for review and should be available for public release by early October 1983. We estimate that approximately two months of the interim period will be required to accomplish the necessary review and Federal Register notification for each of these reports.

I would like to reiterate to you at this time the importance and necessity for these data to be appropriately reviewed by the Advisory Committee before premature or public release.

The original Scientific Panel of the Interagency Work Group to Study the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants, later redesignated as the Agent Orange Working Group by President Reagan in 1981, recommended to the White House in August 1980, that the conduct of the Ranch Hand study be overseen by an independent peer review group.

That recommendation was accepted and the Secretary of Defense was so directed in September 1980. On 31 March 1981, an announcement was made in the Federal Register by the Department of Health and Human Services (HHS) on the formation of the Advisory Committee on Special Studies Related to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants.

The charter of the Advisory Committee is to advise the Secretary of the HHS and the chair of the Working Group of its oversight of the conduct of the Ranch Hand II Study, provide to the Air Force technical assistance and to provide oversight of other studies when directed to do so by the Working Group. It is chaired by Dr. John Moore, Deputy Director for the National Toxicology Program, Research Triangle Park, North Carolina.

The review of data presented to the Advisory Committee will be made after appropriate notice in the Federal Register. This independent, scientific review is the essence which lends technical validity as well as public confidence in the study.

The questionnaire and protocol were made available to the public upon completion of the physical examination phase. The following reports may be obtained from the National Technical Information Service:

1. USAF School of Aerospace Medicine; Technical Report SAM-TR-82-42, Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides: Baseline Questionnaires; NTIS ID No. ADA 121285.

2. USAF School of Aerospace Medicine; Technical Report SAM-TR-82-44, Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides: Study Protocol; NTIS ID No. A 122250.

We will continue to work closely with this Committee, the Veterans Administration, and other Federal agencies in the resolution of the herbicide issue.

I will be happy to answer questions at this time.

Testimony of
Michael Gough
Senior Associate
Office of Technology Assessment
United States Congress

before

Committee on Veterans' Affairs
United States Senate

June 15, 1983

Public Law 96-151 directed that an epidemiologic study be carried out to determine if veterans of the Vietnam conflict are suffering long term health effects from exposure to herbicides. The same Law mandated that the Office of Technology Assessment (OTA) review and approve the study protocol and subsequently monitor the conduct of the study. In carrying out its mandated responsibilities, OTA has kept abreast of the development of plans and techniques for executing the large and complex studies that are necessary to answer questions about possible health effects stemming from the Vietnam conflict.

We all know that three and a half years have passed since Congress directed that this study be done. Because the actual study has not been implemented, because it is still in the planning stage, there is a great temptation to look at the time that has passed as lost time. While an argument can be sustained that the past three and a half years could have been more productive, real progress has been made, and the study, when it begins, will benefit from work that has been done.

In February, the Centers for Disease Control (CDC) furnished OTA with copies of its "Protocol Outline and Tentative Timetable for Epidemiological

Studies of the Health of Vietnam-Era Veterans (Agent Orange)." As required by Public Law 96-151, OTA reviewed that outline and sent its comments to the appropriate Committees of Congress. The contents of the CDC outline provide solid evidence of the progress that has been made in approaching a difficult task.

A "cohort study," which is the accepted method for studying Agent Orange, seeks to compare the health experiences of two or more groups of people who have been exposed to different conditions. There are two critical factors in its design. One is the selection of individuals for inclusion in the cohorts. Members of different cohorts should be as comparable as possible and, in the case of Agent Orange, differ primarily in that one cohort is composed of individuals who were exposed to the herbicide, and another is composed of unexposed individuals. Differences in exposure must be carefully documented and well understood. The second critical factor is that the aspects of health and disease to be examined in members of all cohorts be those aspects which are most likely to have been affected by the exposure.

The Department of Defense, primarily through the hard work of the Army Agent Orange Task Force, has developed methods to determine the location of a veteran with respect to uses of Agent Orange. That effort, which has taken long months, has paid off in a classification scheme. That scheme, in turn, will be the basis for the assembling of cohorts of veterans for the Agent Orange study. The Army can tell the time and distance that separated a veteran from a use of Agent Orange, but the development of criteria for deciding whether a particular time and distance places a veteran in either an "exposed" or "non-exposed" cohort is the responsibility of the protocol designers at CDC.

CDC has decided on a three cohort study of Agent Orange. One cohort will consist of combat troops exposed to Agent Orange. The second cohort will consist of combat troops who served in the same areas of Vietnam at the same time, but who were less likely to have been exposed. If the separation in terms of exposure between the two cohorts is sharp, a comparison of the health of their members should reveal any effects of Agent Orange. CDC recognizes, however, that all combat troops in the same area might have been exposed to some degree and that there might be some misclassification of individuals who were actually exposed into the unexposed cohort. To compensate for that possibility, CDC will include a third cohort of veterans who served in different areas and were not exposed. The third cohort will be, with certainty, a group of non-exposed individuals.

We are less far along in knowing what health and disease endpoints to examine in the study. Associations have been suggested between exposure to Agent Orange and a large number of diseases. The CDC outline provides information about the broad range of health outcomes that will be examined. The approach entails questioning the 6,000 veterans in each cohort about their health and lifestyles and then examining 2,000 from each cohort to obtain medical information.

As an example of a small step that will save time and money, the CDC outline proposes using telephone interviews to administer the questionnaire. There has been some skepticism about the usefulness of telephone interviews. However, CDC has used telephone interviews in its study of birth defects, and a member of a veterans organization who serves on the OTA Agent Orange Advisory Panel, after seeing how those interviews worked, called to say that he was very impressed, and that in his opinion it would work well. This was a

turnaround for his earlier position that face-to-face interviews were necessary. Without the openness that has characterized CDC's approach, this advance would have been unlikely.

For more than a year after the Agent Orange study was mandated, there was great doubt that a system to classify veterans into exposed and not exposed cohorts was possible. Congress responded to that uncertainty, and in PL 97-72 authorized an expansion of the study to investigate possible health effects associated with service in Vietnam. After consensus was reached that an Agent Orange study could be carried out, the idea of studying the "Vietnam experience" remained attractive because of the possibility of exposures other than Agent Orange having caused adverse health effects.

The CDC outline responds to the desire to study the Vietnam experience by including a study parallel to the Agent Orange study. It is a two cohort study: one cohort of veterans who served in Vietnam, the other of veterans who served elsewhere.

Each cohort in both studies will consist of 6,000 individuals, which means that the two studies will include 30,000 participants. All will be invited to participate in the questionnaire; 10,000 will be invited to undergo a health examination. By any standards, this is a very large study. While the Agent Orange and Vietnam experience studies will be conducted separately, the efficiency of both will probably be improved by sharing of resources and information.

The Federal government has ongoing a number of other studies concerned with Agent Orange and the Vietnam experience. The soon-to-be available results from the Air Force Ranchhand Study and from the CDC Birth Defects

Study may turn out to be of great value in the final planning of the epidemiologic study of ground troops.

Finally, the CDC outline provides a description of pilot studies to test whether the protocol will work, and precise cutoff points for deciding that participation in the study is not good enough to justify its continuation. For instance, CDC expects 90 percent of the veterans in the study to agree to complete the questionnaire. If that percentage falls below 70 or 75 percent "careful consideration should be given to not proceeding with the main studies." OTA, in one of its several comments and suggestions about the outline, mentioned that close cooperation between the CDC and veterans organizations would contribute to a high rate of cooperation.

In summary, progress has been made. There is much more information about classifying exposure status; the sizes of the cohorts have been largely agreed upon; mechanisms of cooperation between the study designers and veterans are being put in place; whether to study Agent Orange, the Vietnam experience, or both has been resolved; and results now or soon-to-be available from other studies will further assist CDC.

OTA received a copy of CDC's complete protocol on May 31st. Copies were made and mailed to the advisory panel that participates in the OTA review, and a meeting of that panel will be held on June 24th to discuss the protocol. OTA will report the results of its review to this and other Committees of Congress soon after.

I will be happy to answer any questions you might have.

H

STATEMENT OF

RICHARD S. CHRISTIAN

CONCERNING

ARMY AGENT ORANGE TASK FORCE RESEARCH MISSION

IN SUPPORT OF THE CENTERS FOR DISEASE CONTROL

EPIDEMIOLOGICAL STUDY

BEFORE THE

COMMITTEE ON VETERANS' AFFAIRS

UNITED STATES SENATE

15 JUNE 1983

Not for publication until
released by the Committee on Veterans' Affairs
United States Senate

STATEMENT Record Version

Mr. Chairman and Members of the Committee:

I am Richard S. Christian, Chief of the Army Agent Orange Task Force (AAOTF), Office of the Adjutant General, Headquarters, Department of the Army. I am accompanied by Mr. Douglas Clark, Team Leader and Mr. Carlton Chapman, Section Chief. It is a pleasure to appear before the Committee in response to your request for testimony regarding the AAOTF's plans for the research mission in support of the epidemiological study as mandated by Public Law 96-151, as amended. Much progress has been made by the AAOTF since I appeared before this Committee on November 18,1981.

As you know, the Task Force was established to conduct research into the Vietnam War records. This effort continues to be a major undertaking since there are as yet, no computerized records which determine where an individual soldier was located at any precise time in Vietnam. Further, there were no documents created to record exposure to Agent Orange. There was no requirement to do so since the herbicides were not considered toxic.

On December 4, 1981, Dr. Jerome Bricker (Special Assistant for Legislative Affairs, Office of the Assistant Secretary for Health Affairs), working with the AAOTF developed and presented to the Science Panel of the White House Agent Orange Working Group an exposure index model. This model provides for the systematic selection of

study subjects after a series of research steps. The first step begins with the selection of units which were in the most heavily defoliated areas of Vietnam during the time frame when most of the "Ranch Hand" spraying took place. The model prescribes the identification of individuals serving in the units and computer matching to determine who was exposed during a precise time and distance to spray missions. From this information we can also determine which individuals were not likely to have been exposed.

A new tool for determining exposure has been developed by the AAOTF, and is known as the Services HERBS tape. Research is continuing on this automated listing which contains helicopter perimeter spraying of base camps/fire bases, back-pack spraying, truck-spraying, herbicide leakage at depots, aborts and other incidents used to determine exposure. In addition, this tape contains records of "Ranch Hand" spray missions not previously included in the original National Academy of Science HERBS tape. There are 1700 entries on this tape.

In April 1982 an alternative exposure index model was developed for the CDC Birth Defects Study. The model allows the AAOTF to determine possible exposure to Agent Orange by tracking soldiers in various defined areas by calendar quarter periods. In this case control study the AAOTF has completed research on over 300 study subjects. We expect to complete our portion of the research in December 1983.

The AAOTF has been alerted to prepare for other studies such as the Soft Tissue Sarcoma investigation by the Centers for

Disease Control, The National Institute of Occupational Safety and Health study of dioxin in workers occupationally exposed to dioxin contaminated projects, the Veterans Administration Twin Study and the Armed Forces Institute of Pathology Soft Tissue Sarcoma Study all requiring research of military personnel and organizational records.

Concurrently, the Department of the Army Declassification Branch has continued to purify the combat records of all the U.S. divisions and separate brigades that served in Vietnam. This activity will permit rapid identification of units who have chronologically complete records and also facilitate quick retrieval of unit records for research by the AAOTF.

Over 6700 Agent Orange and related organizational records have been entered into a computerized index to permit instant location and retrieval for use in the ground troop studies.

On April 26, 1982, Secretary Weinberger designated the Department of the Army to be the lead agency for the purpose of providing the V.A. with cohort selection lists and other data. The Navy, Marines, and Air Force were tasked to provide support to the Army Agent Orange Task Force.

In the very near future, because of the importance placed on the AAOTF, the Task Force will be assigned as a special activity directly under the Deputy Adjutant General of the Army. The AAOTF now has 15 researchers assigned. Recruiting of the remainder of the researchers is currently under way. The AAOTF has a Public Health Advisor

assigned from CDC. An Army Epidemiologist has been assigned to the AAOTF and is expected to report for duty the first of September 1983. Navy, Marine and Air Force representatives have been assigned to the AAOTF since July 1982. There are 6 Vietnam veterans and 4 Vietnam era veterans presently assigned to the AAOTF.

Funding for 27 researchers has been approved. Office and research space have been provided to the AAOTF. All Agent Orange activities are consolidated in one location, readily accessible to Health and Human Services and VA staffs. Up-to-date office equipment has either been provided or is on order. Equipment and automation requirements are being finalized.

The AAOTF participated in six sessions, held by a sub-committee of the Science Panel, of the White House Agent Orange Working Group, to document step-by-step procedures in the cohort formation selection of study subjects for the major Agent Orange study. The AAOTF has been meeting with CDC's principal investigators since October 1982 in connection with the records to be used in the major epidemiological study. We have provided the CDC principal investigator, Dr. J. David Erickson, and staff with detailed briefings on the Vietnam records collection. Our working relationship with Dr. Vernon Houk, Director of the Center for Environmental Health at CDC, and his associates is outstanding.

On April 12, 1983 the AAOTF completed work on the research of one thousand study subjects in connection with the CDC Protocol Planning Phase of the major epidemiological study.

During the past year the AAOTF has continued to provide briefings to Veteran's groups and Congressional staff members.

In 1983 alone, the AAOTF has responded to over 900 requests from concerned Veterans asking for information about Agent Orange exposure. Further, we have worked with several state Agent Orange organizations to assist them where possible. This past year AAOTF and DOD representatives briefed several state Agent Orange Commission members at the New York State Dioxin conference in New York City.

In summary, support to the major epidemiological study has received top-priority by the Army staff. The AAOTF has been researching the Vietnam War records collection in preparation for this study, the CDC Birth Defects Study and other research projects, as requested by the Science Panel of the White House Agent Orange Working Group. In addition, the AAOTF has been heavily committed to responding to subpoenas in connection with ongoing litigation. The AAOTF has the capability to conduct the research requested by CDC. We are ready to start pilot work on the research immediately and begin the full study on or about September 1, 1983 as directed by CDC. We have every confidence that we can respond to the needs of CDC.

I shall be most pleased to answer any questions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF EXECUTIVE SECRETARIAT

RECORD OF CLEARANCES

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EXECUTIVE ASST. TO SEC.	8/25/83		

Karen Deasy
Signature of Policy Coordinator
Executive Secretariat

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Date

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Extension

DRAFT
9/14/83
MTL

REMARKS OF DR. GEORGE A. KEYWORTH
TO MEMBERS OF THE SENATE

September 30, 1983 (Republican Members)
October 6, 1983 (Democratic Members)

"Caution about Dangers of Implied Causality"

It is not often that the Administration and the Congress have an opportunity for discussion before important legislation is passed, and I am pleased to be able to share with you this afternoon a status report on our current scientific knowledge about Agent Orange. I have asked Dr. Alvin Young to come today and to give us the benefit of his vast experience with this subject.

Before I turn the meeting over to him, I would like to say a few words of caution about the implied causality reflected in the legislation being considered.

None of us would argue against the moral obligation of the government to protect its citizens against dangers to their health and lives. It is this obligation that lead to food and drug safety laws, environmental laws, occupational safety and health laws, consumer product safety laws, and other laws.

In addition, the government also cannot deny its responsibility to provide adequate and fair remedies when the citizens suffer

adverse health consequences resulting from the government's actions. These are undoubtedly the goals sought by currently proposed legislation with respect to veterans exposed to Agent Orange.

However, the manner in which the government fulfills these goals is as important as the goals themselves. The question is "How can the government fulfill its obligation toward the Viet Nam veterans, as well as other groups, in a responsible manner? Because the rest of society cannot be placed in jeopardy by the care for one or several special groups.

More and more, legislation has recognized the artificiality of a no-risk society, and the potential disruptive effects of well-intentioned legislation. Thus, for example the Toxic Substances Control Act provides for "protection against unreasonable risk" and the Comprehensive Environmental Response, Compensation and Liability Act of 1980 or Superfund, limits the liability of the Federal government in order to avoid the indiscriminate and limitless burden to society as a whole.

The question of what constitutes a fair compensation system is a difficult one. The courts and the agencies have been struggling to find the legal and economic answers. Whatever solutions are adopted, however, the scientific evidence of cause and effect relationships cannot be ignored. Statutory presumptions

of such relationships can only create a grossly unfair and inefficient distribution of benefits and costs. Such presumptions, for example, has raised the costs, in terms of benefits paid, of the Black Lung program from $25 million in 1977 and $43 million in 1978 to $615 million/year. The result has been the necessity to reimpose stricter medical requirements for eligibility, as well as a mandated 100 percent increase in the coal tonnage tax to help pay for the Black Lung Trust Fund expenses until it becomes solvent. So, the burden is borne by industry for an ill-thought out legislative decision.

The potential for a similar mistake is great in the current rush to do something about Agent Orange. As Dr. Young's presentation will point out, scientific evidence of link does not exist for all illnesses that have been attributed to Agent Orange. There is reasonable evidence of link for chloracne and some acute illnesses, such as fatigue or malaise, or some disturbances in the peripheral nervous system. These illnesses manifest themselves in a relatively short time after exposure, and generally cease after a few years. On the other hand, the scientific evidence for chronic health effects in humans is far from established. Once again, we must remember that evidence of toxicity, carcinogenicity or teratogenicity in animal tests cannot be extrapolated to humans. Even among animal species, the response to exposure to dioxin varies greatly.

An additional complicating factor is the fact that there is insufficient knowledge to define the population with sufficient exposure to Agent Orange to have suffered adverse effects. Thus, presumption of causation leaves much room for intentional abuse or unjustified expenditures due to ignorance.

Statutory presumption of causality, by simply disregarding these scientific facts, establishes an extremely irresponsible and dangerous precedent. This precedent could be extended to other cases, such as radiation and asbestos. Already, asbestos-related cases are being used by analogy in other toxic substance contexts. The Rand Corporation estimated that 20,000 people have filed lawsuits claiming asbestos-related injury or death. At least three major corporations have filed Chapter 1 bankruptcy petition based on the projected costs of asbestos litigation.

Hasty action on Agent Orange that would create hysteria and establish dangerous precedent is unnecessary at this time. The Veterans Administration is already now authorized, through PL 97-72 to provide medical examination and care to veterans regardless of whether medical science can demonstrate that a condition may be caused by exposure to herbicide in Viet Nam. Also, major studies are being conducted that would give us a more solid and rational basis for decision, and it is well worth our waiting for the results so that we may act responsibly.

Let me stop here and let Dr. Alvin Young begin his presentation. Dr. Young has been involved with herbicides for as long as anyone I know. His Ph.D. was in Herbicide Physiology/Toxicology and he has 15 years of work experience, as a scientist with phenoxy herbicide. I am sure you will find his presentation informative.

STATEMENT

BY

BART KULL, SPECIAL ASSISTANT TO THE
ACTING DEPUTY UNDER SECRETARY FOR

INTERGOVERNMENTAL AFFAIRS
DEPARTMENT OF HEALTH AND HUMAN SERVICES
AND
ASSISTANT TO THE CHAIRMAN
AGENT ORANGE WORKING GROUP OF THE
CABINET COUNCIL ON HUMAN RESOURCES

BEFORE THE

COMMITTEE ON VETERANS AFFAIRS

UNITED STATES SENATE

JUNE 15, 1983

MR. CHAIRMAN AND MEMBERS OF THE COMMITTEE:

I AM BART KULL, SPECIAL ASSISTANT TO THE ACTING DEPUTY UNDER SECRETARY FOR INTERGOVERNMENTAL AFFAIRS, DEPARTMENT OF HEALTH AND HUMAN SERVICES. I AM ALSO ASSISTANT TO THE CHAIRMAN OF THE AGENT ORANGE WORKING GROUP OF THE CABINET COUNCIL ON HUMAN RESOURCES.

I AM PLEASED TO APPEAR BEFORE THIS COMMITTEE TO REPORT ON THE ACTIVITIES OF THE AGENT ORANGE WORKING GROUP.

WITH ME IS DR. CARL KELLER, SENIOR EPIDEMIOLOGIST WITH THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES OF THE NATIONAL INSTITUTES OF HEALTH; AND CHAIRMAN PRO-TEM OF THE AGENT ORANGE WORKING GROUP'S SCIENCE PANEL.

DR. KELLER, A LONG-TERM MEMBER OF THE WORKING GROUP'S SCIENCE PANEL IS SERVING AS CHAIRMAN PRO-TEM OF THE PANEL TO INSURE THE FLOW OF ACTIVITIES BY THE PANEL UNTIL A PERMANENT CHAIRPERSON IS DESIGNATED.

THE FORMER CHAIRMAN OF THE SCIENCE PANEL, DR. VERNON HOUK, DIRECTOR OF THE CENTER FOR ENVIRONMENTAL HEALTH OF THE CENTERS FOR DISEASE CONTROL, HAS STEPPED DOWN FROM THE CHAIRMANSHIP, BUT REMAINS AN IMPORTANT MEMBER OF THE SCIENCE PANEL.

REPRESENTATIVES OF THE VARIOUS AGENT ORANGE WORKING GROUP MEMBER AGENCIES INVOLVED IN THIS RESEARCH ARE PRESENT TO PROVIDE REPORTS ON STUDIES UNDER THEIR PURVIEW. I WILL LIMIT MY REMARKS TO AN OVERVIEW OF THOSE CONSIDERABLE RESEARCH EFFORTS.

I AM PLEASED TO ANNOUNCE THAT HEALTH AND HUMAN SERVICES SECRETARY MARGARET HECKLER, IN HER CAPACITY AS CHAIR PRO TEM OF THE CABINET COUNCIL ON HUMAN RESOURCES, HAS NAMED HHS UNDER SECRETARY, JOHN A. SVAHN, AS CHAIRMAN OF THE AGENT ORANGE WORKING GROUP. BY TAKING THIS ACTION AND NAMING THE SECOND HIGHEST OFFICIAL OF THE DEPARTMENT TO THIS KEY POSITION, MRS. HECKLER... IN HER WORDS...."REAFFIRMS THIS ADMINISTRATIONS'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." MR. SVAHN WAS UNABLE TO BE PRESENT TODAY, BUT ASKED ME TO CONVEY TO YOU HIS COMMITMENT TO ADDRESSING THE IMPORTANT ISSUES RELEVANT TO THE AGENT ORANGE WORKING GROUP.

THE VA AGREED BY INTERAGENCY AGREEMENT SIGNED JANUARY 13TH AND 14TH THAT CDC BE PROVIDED THE RESOURCES AND AUTHORITY FOR THE DESIGN, IMPLEMENTATION, ANALYSIS AND SCIENTIFIC INTERPRETATION OF THE EPIDEMIOLOGY STUDY MANDATED BY CONGRESS UNDER SECTION 307 OF PUBLIC LAW 96-151 AS AMENDED.

THE OFFICE OF MANAGEMENT AND BUDGET HAS APPROVED THE HIRING OF PERSONNEL BY CDC FOR FISCAL YEAR 1983 FOR THESE PURPOSES. THE PROPOSED PROTOCOL FOR THIS STUDY HAS BEEN COMPLETED BY CDC AND SUBMITTED FOR PEER REVIEW ON MAY 27. THE PEER REVIEW IS BEING CONDUCTED BY THE CONGRESSIONAL OFFICE OF TECHNOLOGY ASSESSMENT AND BY THE SCIENCE PANEL OF THE AGENT ORANGE WORKING GROUP OF THE CABINET COUNCIL ON HUMAN RESOURCES. THE LATTER PANEL WILL CONDUCT ITS REVIEW WITH THE COOPERATION OF THE ADVISORY COMMITTEE

ON SPECIAL STUDIES WHICH IS PRINCIPALLY COMPOSED OF NON-FEDERAL SCIENTISTS.

THE COHORT FOR THE EPIDEMIOLOGY STUDY WILL REQUIRE THE IDENTIFICATION AND SELECTION OF SOME 30,000 VIETNAM VETERANS. WE ARE VERY PLEASED WITH THE SPIRIT OF COOPERATION AND SUPPORT BEING PROVIDED BY DEPARTMENT OF DEFENSE SECRETARY WEINBERGER TO EXPEDITE THAT PROCESS. STAFF, FUNDING, SPACE AND EQUIPMENT HAVE BEEN PLACED IN THE HANDS OF THE ARMY AGENT ORANGE TASK FORCE FOR THIS PURPOSE. MR. RICHARD CHRISTIAN, THE CHIEF OF THAT TASK FORCE WILL PROVIDE DETAILED TESTIMONY ON THOSE ACTIVITIES TODAY.

DATA COLLECTION FOR THE CDC BIRTH DEFECTS STUDY WILL BE COMPLETED BY THE END OF THIS YEAR WITH PRELIMINARY ANALYSIS EXPECTED SHORTLY THEREAFTER. THE REPRESENTATIVE FROM CDC WILL PROVIDE THE COMMITTEE WITH MUCH GREATER DETAIL ON THESE TOPICS.

SIMILARLY, THE CDC/NIOSH DIOXIN REGISTRY OF U.S. PRODUCTION WORKERS IS PRECEEDING ON SCHEDULE.

THE ESTABLISHMENT AND MAINTENANCE OF AN INTERNATIONAL REGISTRY OF SIMILAR WORKERS IN OTHER COUNTRIES APPEARS FEASIBLE. THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES MET WITH THE PRINCIPAL INVESTIGATOR FROM THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, AS WELL AS A SCIENTIFIC ADVISORY GROUP, ON MAY 29TH. THE DISCUSSION DEALT WITH THE DEVELOPMENT OF THE ACTUAL INTERNATIONAL REGISTRY AND A PROTOCOL FOR AN EPIDEMIOLOGY STUDY DERIVED FROM COHORTS OBTAINED FROM THE REGISTRY. IT WAS AGREED THAT FURTHER INFORMATION PRELIMINARY TO A FINAL DECISION IS REQUIRED. A MEETING FOR THAT PURPOSE HAS BEEN TENTATIVELY SCHEDULED FOR OCTOBER 13-14. THIS REGISTRY IF APPROVED, WILL BE COMPATIBLE WITH THE NIOSH DIOXIN REGISTRY, THUS IMPROVING THE NUMERICAL POWER OF MORTALITY AND OTHER DATA.

THE NATIONAL CANCER INSTITUTE IS CONDUCTING A CASE CONTROL STUDY OF LYMPHOMA AND SOFT TISSUE SARCOMA TO TEST THE ASSOCIATION BETWEEN THE USE OF HERBICIDES AND THE INCIDENCE OF LYMPHOMA AND SOFT TISSUE SARCOMA AMONG AGRICULTURE APPLICATORS IN KANSAS. THE INTERVIEW PHASE OF THIS STUDY IS 50% COMPLETE AND SHOULD BE 100% COMPLETE BY THE END OF SEPTEMBER WITH FINAL RESULTS EXPECTED BY THE SPRING OF NEXT YEAR.

ADDITIONAL STUDIES ARE BEING CONDUCTED IN THE STATES OF MINNESOTA AND IOWA WHERE INSECTICIDES ARE GENERALLY APPLIED SIMULTANEOUSLY WITH HERBICIDES TO CORN AND OTHER CROPS. A SIMILAR CASE CONTROL DESIGN IS BEING EMPLOYED IN THESE AREAS TO COMPARE PESTICIDE EXPOSURES IN GENERAL AMONG CASES OF LEUKEMIA AND LYMPHOMA AND SUITABLE CONTROLS. ALTHOUGH INFORMATION WILL BE OBTAINED ON HERBICIDE USE, WE MAY NOT BE ABLE TO SEPARATE POSSIBLE EFFECTS OF EXPOSURE TO HERBICIDES ALONE FROM THOSE EXPOSED TO HERBICIDES AND OTHER PESTICIDES. RESULTS OF THESE STUDIES SHOULD BE AVAILABLE IN LATE 1984.

THE VETERANS ADMINISTRATION IS ENGAGED IN A NUMBER OF STUDIES ON AGENT ORANGE EXPOSURE AND THE VIETNAM EXPERIENCE. FOR INSTANCE, A MORTALITY STUDY IS WELL UNDERWAY TO ANALYZE AND COMPARE DEATH RATES AND CAUSE-OF-DEATH BETWEEN VETERANS WITH SERVICE IN VIETNAM AND COMPARABLE VETERANS WHO DID NOT SERVE

THERE. ALSO, VA IS PLANNING A STUDY OF TWINS IN WHICH ONE SERVED IN VIETNAM AND THE OTHER DID NOT. VA EXPECTS TO HAVE ITS PROTOCOL COMPLETED, INCLUDING PEER REVIEW, BY OCTOBER. AS YOU KNOW, THE VA IS ENGAGED IN OTHER REGISTRY AND RESEARCH WORK, INCLUDING THE AGENT ORANGE REGISTRY AND DIOXIN-IN-FAT-TISSUE STUDIES. THE REPRESENTATIVE FROM THE VETERANS ADMINISTRATION WILL ELABORATE ON THESE TOPICS SHORTLY.

THE MORTALITY DATA FROM THE AIR FORCE RANCH HAND STUDY WILL BE AVAILABLE FOR PUBLIC RELEASE AFTER REVIEW BY THE ADVISORY COMMITTEE BY THE END OF THIS MONTH. IT WILL BE FOLLOWED WITH MORBIDITY DATA IN OCTOBER. AIR FORCE GENERAL MURPHY CHESNEY WILL BE PROVIDING DETAILED TESTIMONY ON THIS TODAY.

I APPRECIATE THE OPPORTUNITY TO PROVIDE THIS INTRODUCTION AND WOULD BE HAPPY TO RESPOND TO ANY QUESTIONS.

STATEMENT OF

FRANZ M. ENZINGER, M.D.

ARMED FORCES INSTITUTE OF PATHOLOGY

BEFORE THE COMMITTEE ON VETERANS AFFAIRS

UNITED STATES SENATE ON SOFT TISSUE SARCOMAS

18 May 1983

MR. CHAIRMAN AND MEMBERS OF THE COMMITTEE:

My name is Franz M. Enzinger. I am a pathologist and I am Chairman of the Department of Soft Tissue Pathology at the Armed Forces Institute of Pathology in Washington, D.C.

As consultant in soft tissue pathology to the military, Veterans Administration and civilian pathologists, I have had the opportunity to review and study a large number of soft tissue sarcomas, and over the past 24 years I have examined and diagnosed approximately 30,000 soft tissue sarcomas that were submitted for consultation to the Armed Forces Institute of Pathology. I also have been responsible for the preparation of an international classification of soft tissue tumors for the World Health Organization and for a textbook on the pathology of soft tissue tumors.

Although I cannot provide you with any new insight or specific information on the possible relationship of Agent Orange and soft tissue sarcomas, I would like to give you some background information on the occurrence, distribution and clinical behavior of these tumors.

Soft tissue sarcomas, compared to carcinomas and other forms of cancer, are relatively rare tumors. It is estimated that they account for about 0.8 to 1.0 percent of all cancers and that about 7000 to 8000 new cases are diagnosed each year in the United States. It has been suggested that there is an upward trend in the number of soft tissue sarcomas, but this is a true increase in part only and may reflect better access to medical facilities, better diagnostic capabilities and greater interest in this type of tumor. Incidence and distribution seem to be similar in different geographic regions of the world.

As the name indicates, soft tissue sarcomas usually arise in muscle, fat and fibrous connective tissue such as tendons or ligaments and less frequently in blood vessels and nerves that serve these tissues. Consequently, these tumors may occur anywhere, but the majority originates in the large muscles of the legs and arms where they often grow into poorly circumscribed, bulky tumors that infiltrate and destroy surrounding tissues. Despite their frequent large size and destructive growth, most of the tumors are painless and as a result recognition and therapy is often delayed for several months or even years. Soft tissue sarcomas occur at any age. About 15 percent affect persons younger than 15 years and about 35 percent persons 55 years or older. There is no particular sex prevalence. Some types are more common in men, others in women. There is no proven racial variation, even though the annual age-adjusted incidence rates have been reported to be higher for blacks than whites.

At the operating table, soft tissue sarcomas display a fairly uniform picture but when examined under the microscope they vary greatly in appearance and actually comprise a diverse and complex group of tumors rather than a single entity. At present, pathologists are able to recognize 25 major types

and about 120 subtypes of this tumor, but there are still other types of soft tissue sarcomas that are as yet not clearly defined. The latter frequently cause considerable problems in diagnosis and may require examination with sophisticated techniques such as immunohistochemical preparations or the electron microscope. The various types are named according to the predominant cellular elements and the resemblance of the tumor to normal tissue or its embryonic counterpart. The most common types of soft tissue sarcomas are malignant fibrous histiocytoma, liposarcoma and fibrosarcoma which together account for slightly more than 50 percent of all cases. Malignant lymphoma, Hodgkin's disease and leukemia, the malignant tumors of lymph nodes and blood-forming organs, are not counted among the soft tissue sarcomas.

The various types differ considerably in the grade of malignancy, and identification and diagnosis of the exact microscopic type and subtype is not only essential for prediction of the clinical course and therapeutic response but also for selection and planning of therapy - the important decision whether a given sarcoma should be treated by local excision, radical local excision or amputation and whether surgery should be combined with radiotherapy or chemotherapy. If adequate treatment is given, many soft tissue sarcomas, particularly those occurring in infants and children, are curable, but even with the best type of therapy 35 to 40 percent of all patients with this tumor die of metastatic disease within five years after diagnosis, often after they have recurred locally. Yet without doubt some progress has been made in the therapy of soft tissue sarcomas over the past 10 years and overall survival rates have increased by at least 10 to 15 percent.

As with other forms of cancer, very little is known about the various causes of soft tissue sarcomas. A hereditary or genetic factor plays a role in a small proportion of cases, the majority of which are patients that

develop sarcomas in a setting of neurofibromatosis. Such a factor is also suggested by the clustering of childhood sarcomas in some families. Moreover, there are sarcomas that seem to be induced by genetically determined or acquired immunodeficiency or therapeutic immunosuppression, a necessary procedure in organ tranplantation. Viruses are responsible for the induction of sarcomas in chicken, cats and mice, but there is no evidence so far that human viruses constitute a major risk factor in the development of soft tissue sarcomas. However, using the electron microscope, possible virus particles have been found in some cases.

There is even less reliable information on the significance of environmental factors. A small number of soft tissue sarcomas occur following radiation exposure, usually given as treatment for some other kind of malignant tumor, such as breast carcinoma or Hodgkin's disease. Most of the radiation-induced sarcomas are osteosarcomas, malignant fibrous histiocytomas and fibrosarcomas. Others develop in individuals who have a history of industrial or environmental exposure to vinyl chloride or asbestos. As a rule, specific risk factors, such as vinyl chloride, are associated with a single type of sarcoma (angiosarcoma) and none of the known risk factors seem to induce all types of sarcomas equally. Evaluation of the exact cause is often extremely difficult because of the possible effect of multiple environmental factors and the long time-lag or latent period between exposure and development of the tumor. Radiation induced soft tissue sarcomas, for example, frequently have a time-lag of 5, 10 or even more years. Asbestos related tumors may appear in some patients 30 or 40 years after the initial exposure.

As a soft tissue pathologist, I am of course familiar with the reported studies linking toxic, dioxin containing phenoxy herbicides with the development of soft tissue sarcomas. The suggested link, however, is mainly based on the observations of one group of Swedish investigators and there are other studies which viewed individually have not confirmed these findings. In my opinion, additional data are clearly necessary to resolve the question of a direct causal relationship between Agent Orange and soft tissue sarcoma. For this purpose, well-planned and carefully executed cooperative studies on a large number of patients with soft tissue sarcomas are needed.

Recently, the Veterans Administration has asked the Armed Forces Institute of Pathology to supply them with diagnoses and identification of at least 500 soft tissue sarcomas. Selection will be restricted to males who were diagnosed between 1975 and 1980 and were age 20 to 40 years at the time of diagnosis. These cases will be analyzed in regard to survival in Vietnam and exposure to various environmental factors and will be compared with two sets of matched controls of cancer and non-cancer patients. An epidemiologist and a biostatistician have been assigned to carry out this project.

I believe that this and other similar studies, that are currently being carried out, will make it possible to provide a satisfactory answer to the question whether or not exposure to Agent Orange plays a significant and specific role in the development of soft tissue sarcomas.

This concludes my statement, Mr. Chairman. I will be happy to answer any questions the committee may have.

RECORD VERSION

STATEMENT BY

FRANZ M. ENZINGER, M.D.

ARMED FORCES

INSTITUTE OF PATHOLOGY

BEFORE THE

COMMITTEE ON VETERANS AFFAIRS

UNITED STATES SENATE

NINETY EIGHTH CONGRESS

ON

JUNE 15, 1983

NOT FOR PUBLICATION UNTIL
RELEASED BY THE COMMITTEES
OF THE UNITED STATES SENATE
AND THE UNITED STATES HOUSE
OF REPRESENTATIVES

Comments on Porphyria Cutanea Tarda & Related Matters

Hyman J. Zimmerman, M.D.
Professor of Medicine
&
Director of Gastroenterology

George Washington University
School of Medicine and
Health Sciences

I have been invited by the Chairman to comment on the entity known as porphyria cutanea tarda henceforth referred to as PCT, to evaluate its possible service-connection and specifically the possible relationship to exposure to DIOXIN. In that context, I have also been asked to describe the known causes of PCT, its temporal evaluation, its clinical manifestations including any clinical clues to the etiology and the means for its treatment and its ultimate prognosis. I have also been asked to comment on the range of known effects of DIOXIN in the liver.

My personal background is shown in the attached C.V. In brief, I have long had a special interest in liver disease especially that induced by chemicals.

We might start with a definition of PCT. It is the least rare of a group of rare conditions collectively called the porphyrias because they are characterized by the presence in the blood and urine of compounds that may appear red or purple, (Porphyros = purple). Several of these conditions are accompanied by characteristic and dramatic skin changes induced by exposure to sunlight hence the cutanea in the name. PCT appears usually in mature or elderly adults while other porphyrias with cutaneous manifestations appear early in life, hence the term tarda. In contrast to all of the other porphyrias, PCT is considered acquired. While the other porphyrias are recognized to result from distinct, genetic abnormalities, i.e. hereditarily transmitted, PCT has been considered to be an acquired condition, i.e. the result of exposure to certain chemicals and other etiologic factors. In actuality, that is not quite true,

and there are several forms of PCT as shown in the following table.

Table I

ETIOLOGIC CATEGORIES OF PORPHYRIA CUTANEA TARDA (PCT)

NON-TOXIC PCT

SPORADIC - Most frequent type

Unusual response to common or uncommon disorder of the liver, i.e. alcoholic liver disease, estrogen-induced liver disease, "Bantu siderosis"

FAMILIAL - Very rare

ASSOCIATED with chronic renal failure

TOXIC PCT

Exposure to porphyrogenic compounds

Hexachlorbenzene

2, 4 D & 2, 4, 5-T

PCB's

D-Benzyl-P-Chlorophenol + 2-Benzyl-4-6 Dichlorophenol

DIOXIN

In this country, almost all cases of PCT are sporadic, i.e. isolated instances without familial involvement. About 70% of these sporadic cases have alcoholic liver disease and the PCT appears to be a complication of that disease. However, since only a tiny proportion, less than 1% of individuals with alcoholic liver disease develop PCT, it has been assumed that these individuals have a genetic predisposition to PCT exposed by the alcoholic liver disease. A second group of individuals with PCT are women who have been taking contraceptive steroid preparation or other individuals taking estrogenic compounds. Again, the tiny proportion of those exposed who develop PCT presumably reflect genetic predisposition. It has now become clear that there is also a tiny incidence of a truly genetic form of PCT. An additional category of PCT has been seen in patients with chronic renal failure who are being maintained on hemodialysis.

Most relevant to today's discussion, however, is the fact that there is indeed an acquired form of PCT caused by exposure to toxic chemicals. This entity is known as toxic PCT. Toxic PCT is associated with exposure to polychlorinated aromatic hydrocarbons. These toxic substances by their effect on one or more specific enzymes lead to an interference with the production of the heme portion of hemoglobin and as a consequence to the development of abnormal porphyrin compounds which lead to the clinical manifestations of the disease.

The clinical manifestations of PCT include its occurrence predominately in middle age or elderly persons, the development of abnormal skin fragility, blistering of skin exposed to the sun and striking increase in body hair. There is darkening and thickening of the skin, and the deposition of calcium in some of the scarred areas. Body and head hair loss may develop in areas of scarring and there may be loss of nails. Implicit in the relationship to sunlight, skin lesions are found predominately on the light-exposed areas of the face, arms, and back of the hands. In women, legs and feet are often involved. The increased fragility of the skin is the most common complaint of the patient and is seen most often on the back of the hands and forearms, areas which are subject to minor frequent trauma; the trauma leads to the skin being pulled away leaving areas that are denuded. In those instances of PCT associated with exposure to toxic chemicals there may also be a skin condition known as chloracne.

Some of the chemicals that have been incriminated in the pathogenesis of PCT are listed in Table I. During synthesis of these compounds, however, DIOXIN is regularly formed in small amounts and therefore is a regular contaminant of these agents. Furthermore, DIOXIN is the most potent porphyrinogenic agent known. Accordingly, it has been considered to constribute to or be responsible for the porphyria-inducing effects of the other agents listed in Table I. Specifically, DIOXIN has been implicated in the production of PCT in individual workers involved in the manufacture

of the herbicides 2, 4 D & 2, 3, 5-T. Extensive animal studies confirm the porphyrinogenic capacity of DIOXIN and of several herbicides and other chloroaromatic compounds which might contain dioxin.

While a DIOXIN-contaminated industrial environment has been incriminated in the development of PCT and while extensive DIOXIN contamination of external environments is well-established, the porphyrinogenic effects of an external environmental exposure to DIOXIN is less unequivocal. Nevertheless, I believe it to be possible, since serious hepatic disease has been seen in a variety of species (horses, dogs, rats) exposed externally to DIOXIN contaminated areas.

Duration of exposure to porphyrinogen chemicals and onset of PCT is uncertain. In an epidemic in Turkey, almost 30 years induced by ingestion of hexachlorbenzene contaminated wheat seeds, six months elapsed between initial exposure and the first evidence of PCT. Industrial exposure to DIOXIN can lead to PCT during or even several months after exposure and may progress for several years. If exposure is stopped, there is usually improvement and in most instances ultimately disappearance of the PCT.

Treatment of PCT consists of administration of small doses of a drug called chloroquine and of removal of excess liver iron by regular removal of blood. Other treatments have been described. Until treatment by iron removal is well underway, exposure to sunlight should be minimized. Outlook for health and survival in the treated patient is good.

Other forms of liver injury that DIOXIN can produce in experimental animals include necrosis (i.e. destruction) of liver tissue, and production of carcinoma. The relevance of these to man and the relevance of liver injury and PCT to exposure to DIOXIN remains to be evaluated by proper epidemiologic studies.

98TH CONGRESS
1ST SESSION

S. 786

To amend title 38, United States Code, to establish a service-connection presumption for certain diseases caused by exposure to herbicides or other environmental hazards or conditions in veterans who served in Southeast Asia during the Vietnam era.

IN THE SENATE OF THE UNITED STATES

MARCH 11 (legislative day, MARCH 7), 1983

Mr. PRESSLER introduced the following bill; which was read twice and referred to the Committee on Veterans' Affairs

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A BILL

To amend title 38, United States Code, to establish a service-connection presumption for certain diseases caused by exposure to herbicides or other environmental hazards or conditions in veterans who served in Southeast Asia during the Vietnam era.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "Vietnam Veterans Agent Orange Relief Act".

SEC. 2. The Congress finds that—

(1) certain adverse health effects occurring among persons who served in the Armed Forces in Southeast

Asia during the Vietnam era, and certain birth defects occurring among the children of such persons, as well as certain psychological effects, may be the result of the exposure of such persons during such service to phenoxy herbicides (including the herbicide known as agent orange) and the class of chemicals known as the dioxins produced during the manufacture of such herbicides or to other factors involved in such service including exposure to other herbicides, chemicals, medications, or environmental hazards or conditions; and

(2) a comprehensive review and scientific analysis of the literature covering studies relating to whether there may be long-term adverse health effects in humans from exposure to any of the class of chemicals known as the dioxins produced during the manufacture of the various phenoxy herbicides (including the herbicide known as agent orange), as required by section 307(a)(1)(B) of Public Law 96–151, has been completed and submitted to the Veterans' Administration.

SEC. 3. Section 312 of title 33, United States Code, is amended by adding at the end the following new subsection:

"(d)(1) For the purposes of section 310 of this title and subject to the provisions of section 313 of this title, in the case of a veteran who served in Southeast Asia during the Vietnam era and who after such service suffers from a dis-

ease described in paragraph (2)(A) of this subsection, such disease shall be considered to have been incurred in or aggravated by such service, notwithstanding that there is no record of evidence of such disease during the period of service, and providing that no other cause for such disease can be proven.

"(2)(A) The diseases referred to in paragraph (1) of this subsection are the following:

"(i) Soft-tissue sarcomas.

"(ii) Prophyria cutanea tarda.

"(iii) Active and residual chloracne and chloracne-form lesions.

"(iv) A disease listed in a regulation prescribed by the Administrator under subparagraph (B) of this paragraph.

"(B) The Administrator may determine, and prescribe by regulation, diseases (in addition to those listed in subparagraph (A) of this paragraph) that medical research has shown may be due to exposure to herbicides, chemicals, medications, or environmental hazards or conditions. The Administrator shall include in such regulations a specification of the standards used by the Administrator in making such determination.

"(3) Paragraph (1) of this subsection shall terminate on the first day of the first month beginning after the end of the one-year period beginning on the date the Administrator sub-

mits to the appropriate committees of Congress the first report required by section 307(b)(2) of the Veterans Health Programs Extension and Improvement Act of 1979 (Public Law 96–151; 93 Stat. 1098).".

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98TH CONGRESS
1ST SESSION

S. 991

To amend title 38, United States Code, to require regulations providing for the resolution of Veterans' Administration benefits claims based on certain exposures to herbicides containing dioxin, to ionizing radiation from detonations of nuclear devices, and to certain other hazardous substances, and for other purposes.

IN THE SENATE OF THE UNITED STATES

APRIL 6 (legislative day, APRIL 5), 1983

Mr. CRANSTON introduced the following bill; which was read twice and referred to the Committee on Veterans' Affairs

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A BILL

To amend title 38, United States Code, to require regulations providing for the resolution of Veterans' Administration benefits claims based on certain exposures to herbicides containing dioxin, to ionizing radiation from detonations of nuclear devices, and to certain other hazardous substances, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That (a) section 354 of title 38, United States Code, is amended—

(1) in subsection (b)—

(A) by striking out all beginning with "In" through "expedition, the" and inserting in lieu thereof "The"; and

(B) by striking out "such service" the first place it occurs and inserting in lieu thereof "a veteran's service on active duty"; and

(2) by adding at the end the following new subsection:

"(c)(1)(A) The regulations required to be prescribed by subparagraph (B) of this paragraph shall—

"(i) establish guidelines, standards, and criteria for the resolution of claims for benefits under laws administered by the Veterans' Administration where the benefit eligibility criteria include a requirement that a death or disability be service connected and the claim of service connection is based on a veteran's exposure during service on active duty—

"(I) in the Republic of Vietnam during the Vietnam era, to a herbicide containing dioxin,

"(II) in connection with such veterans' participation in the test of a nuclear device or with the American occupation of Hiroshima or Nagasaki, Japan, prior to July 1, 1946, to ionizing radiation from the detonation of a nuclear device, or

"(III) to another hazardous substance; and

"(ii) ensure that subsection (b) of this section is given full effect with respect to such claims.

"(B) The Administrator, in accordance with paragraphs (2) (A) and (B) of this subsection, shall develop and publish regulations implementing this subsection. Promptly after each occasion on which the Administrator prescribes or amends the substance of any such regulations, the Administrator shall submit to the appropriate committees of the Congress a report containing any recommendations for legislative action, including proposed amendments to section 312 of this title, if any, that the Administrator considers appropriate in light of such guidelines, standards, and criteria.

"(C) Regulations developed and published pursuant to subparagraph (B) of this paragraph shall include specification of any presumptions (including any presumptions regarding exposure and service connection) to be applied to the resolution of the claims to which the guidelines, standards, and criteria in such regulations apply.

"(2)(A)(i) The Administrator shall develop the regulations required by paragraph (1) of this subsection through a public review and comment process in accordance with the provisions of sections 553 (b) and (e), 556, and 557 of title 5.

"(ii) Not later than one hundred and twenty days after the date of the enactment of this subsection, the Administrator shall develop and publish in the Federal Register, for

public review and comment for a period of not less than thirty days, a proposed version of the regulations required by such paragraph for the resolution of claims for service connection based on exposures specified in subclauses (I) and (II) of subparagraph (A)(i) of such paragraph.

"(B) Not later than ninety days after the end of each such period of public review and comment, the Administrator shall publish in the Federal Register final regulations containing the guidelines, standards, and criteria (together with explanations of the bases for such guidelines, standards, and criteria) for resolving the claims involved.

"(C) The Administrator's compliance with the provisions of, and any regulations prescribed pursuant to, this subsection shall be subject to judicial review in accordance with the provisions of chapter 7 of title 5.

"(3) For the purposes of this subsection, the term 'hazardous substance' means a substance with respect to which the Administrator determines, pursuant to the regulations required by paragraph (1) of this subsection, that—

"(A) a significant number of veterans were exposed (i) while serving on active duty, and (ii) as the result of (I) the use of such substance by a branch of the Armed Forces for military purposes, including training and testing programs, or (II) the action of a hostile force; and

"(B) there is insufficient medical or scientific evidence (i) to determine whether exposure to the substance causes a disease which has resulted in a disability in the cases of a significant number of veterans, or (ii) to determine whether a level (or range of levels) of exposure experienced by significant numbers of veterans is sufficient to cause such disease.".

(b) Paragraph (3) of section 307(b) of the Veterans' Health Programs Extension and Improvement Act of 1979 (Public Law 96–151; 93 Stat. 1097), as added by section 401(b)(2) of the Veterans' Health Care, Training, and Small Business Loan Act of 1981 (Public Law 97–72; 95 Stat. 1061), is amended to read as follows:

"(3)(A) Not later than ninety days after the submission of each report under paragraph (2), the Administrator shall, based on the results described in such report and the comments and recommendations included therein and any other available pertinent information, develop and publish in the Federal Register, for public review and comment, a proposed version of the regulations required by paragraph (1) of subsection (c) of section 354 of title 38, United States Code, for the resolution of claims for service connection based on the exposure specified in subparagraph (B)(i)(I) of such paragraph.

98TH CONGRESS
1ST SESSION

S. 1651

To amend title 38, United States Code, to provide for presumptions of service connection to be established by the Administrator of Veterans' Affairs for certain diseases of certain veterans exposed to dioxin or radiation during service in the Armed Forces; to require the Administrator to develop, through a process of public participation and subject to judicial review, regulations specifying standards for and presumptions applicable to the resolution of claims for disability compensation based on such exposures; to require that such regulations address certain specified diseases; and to require that all claimants for Veterans' Administration benefits be given the benefit of every reasonable doubt in claims adjudications; and for other purposes.

IN THE SENATE OF THE UNITED STATES

JULY 20 (legislative day, JULY 18), 1983

Mr. CRANSTON (for himself, Mr. SPECTER, Mr. MITCHELL, and Mr. BIDEN) introduced the following bill; which was read twice and referred to the Committee on Veterans' Affairs

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A BILL

To amend title 38, United States Code, to provide for presumptions of service connection to be established by the Administrator of Veterans' Affairs for certain diseases of certain veterans exposed to dioxin or radiation during service in the Armed Forces; to require the Administrator to develop, through a process of public participation and subject to judicial review, regulations specifying standards for and presumptions applicable to the resolution of claims for disability compensation based on such exposures; to require that such

regulations address certain specified diseases; and to require that all claimants for Veterans' Administration benefits be given the benefit of every reasonable doubt in claims adjudications; and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That (a) this Act may be cited as the "Veterans' Dioxin and Radiation Exposure Compensation Standards Act".

(b) Except as otherwise expressly provided, whenever in this Act an amendment is expressed in terms of an amendment to a section or other provision, the reference shall be considered to be made to a section or other provision of title 38, United States Code.

SEC. 2. (a) Section 312 is amended by adding at the end the following new subsection:

"(c) For the purposes of section 310 of this title and subject to the provisions of section 313 of this title, the following diseases developed to a degree of disability of 10 per centum or more shall, subject to a specification pursuant to section 354(c)(2) of this title, be considered to have been incurred in or aggravated by such service, notwithstanding that there is no record of such disease during the period of service:

"(1) In the case of a veteran who served in the Republic of Vietnam during the Vietnam era and who, during such service, was exposed to a herbicide containing dioxin—

"(A) a soft tissue sarcoma, if so developed within thirty years from the date of last departure from the Republic of Vietnam during such service,

"(B) porphyria cutanea tarda, if so developed within one year from the date of last departure from the Republic of Vietnam during such service, or

"(C) chloracne, if so developed within one year from the date of last departure from the Republic of Vietnam during such service.

"(2) In the case of a veteran who, in connection with such veteran's participation in the test of a nuclear device or with the American occupation of Hiroshima or Nagasaki, Japan, prior to July 1, 1946, was exposed to ionizing radiation from the detonation of a nuclear device during such veteran's service—

"(A) a malignancy,

"(B) polycythemia vera, or

"(C) hypothyroidism or a thyroid nodule.

"(3) In the case of a veteran described in paragraph (1) or (2) of this subsection, any other disease that is specified in a regulation prescribed by the Administrator pursuant to section 354(c) of this title as being presumed to have been incurred in or aggravated by the service of veterans who were so exposed.".

(b) Section 354 is amended—

(1) in subsection (b)—

(A) by striking out all beginning with "In" through "expedition, the" and inserting in lieu thereof "The"; and

(B) by striking out "such service" the first place it occurs and inserting in lieu thereof "a veteran's service on active duty"; and

(2) by adding at the end the following new subsection:

"(c)(1)(A) The Administrator, in accordance with paragraphs (2) and (3) of this subsection, shall prescribe regulations to—

"(i) establish guidelines, standards, and criteria for the resolution of claims for benefits under laws administered by the Veterans' Administration where the benefit eligibility criteria include a requirement that a death or disability be service connected and the claim of service connection is based on a veteran's exposure during service—

"(I) in the Republic of Vietnam during the Vietnam era, to a herbicide containing dioxin, or

"(II) in connection with such veteran's participation in the test of a nuclear device or with the American occupation of Hiroshima or Nagasa-

ki, Japan, prior to July 1, 1946, to ionizing radiation from the detonation of a nuclear device; and

"(ii) ensure that subsection (b) of this section is given full effect with respect to such claims.

"(B) Promptly after each occasion on which the Administrator prescribes or amends the substance of such regulations, the Administrator—

"(i) shall determine whether, in light of such guidelines, standards, and criteria and other pertinent information, any legislative action related to the subject matter of such regulations is needed, and

"(ii) if the Administrator determines that any such action is needed, shall submit to the Committees on Veterans' Affairs of the House of Representatives and the Senate a report containing the Administrator's recommendations for such legislative action, including any proposed amendments to section 312 of this title, as the Administrator considers appropriate.

"(2) In the regulations required to be prescribed by paragraph (1)(A) of this subsection, the Administrator—

"(i) shall specify, based on medical and scientific evidence and after resolving every reasonable doubt in favor of the claimants, (I) which of the diseases listed in paragraphs (1) and (2) of section 312(c) of this title (with any modifications of the maximum periods of

time specified in such section) will be presumed to have been incurred in or aggravated during service, (II) which of such diseases will not be so presumed, and (III) which other diseases (and any maximum periods of time after departure from a specified geographic area or the date of separation from service within which any such other disease must have developed to a degree of disability of 10 per centum or more), will be presumed to have been incurred in or aggravated during service;

"(ii) shall specify any other presumptions (including any presumptions regarding exposure and service connection) to be applied to the resolution of such claims; and

"(iii) may not include a requirement that a veteran provide any information regarding such veteran's service in the Armed Forces other than the information included in such veteran's military service records.

"(3)(A) The Administrator shall develop the regulations required by paragraph (1)(A) of this subsection and any amendments to such regulations through a public review and comment process in accordance with the provisions of section 553 of title 5 and with such procedures, in addition to those required by such provisions, as the Administrator considers appropriate to enable persons other than Veterans' Adminis-

tration personnel to submit evidence, proposals, and arguments. Such process shall include (i) a public hearing, which shall be announced in the Federal Register not less than thirty days in advance of its commencement, shall be commenced not earlier than sixty days after proposed regulations or proposed amendments are published in the Federal Register, and shall afford interested parties an opportunity to make oral presentations and to comment on oral and written submissions from other parties, and (ii) consultations by the Administrator with an advisory committee appointed by the Administrator and composed of individuals with a demonstrated interest and experience relating to the subject matter of the proposed regulations or amendments. The period for public review and comment shall be completed not later than ninety days after proposed regulations or proposed amendments are published in the Federal Register.

"(B)(i) Not later than one hundred and twenty days after the date of the enactment of this subsection, the Administrator shall develop and publish in the Federal Register a proposed version of the regulations required by paragraph (1)(A) of this subsection.

"(ii) Not later than three hundred and thirty days after such enactment date, the Administrator shall publish in the Federal Register the final regulations (together with explana-

tions of the bases for the guidelines, standards, presumptions, and criteria contained therein) required by such paragraph.

"(C) Notwithstanding section 211(a) of this title or any other provision of law, the Administrator's compliance with the provisions of, and any regulations prescribed pursuant to, this subection shall be subject to judicial review in accordance with the provisions of chapter 7 of title 5.".

(c) Paragraph (3) of section 307(b) of the Veterans' Health Programs Extension and Improvement Act of 1979 (Public Law 96–151; 93 Stat. 1097), as added by section 401(b)(2) of the Veterans' Health Care, Training, and Small Business Loan Act of 1981 (Public Law 97–72; 95 Stat. 1061), is amended to read as follows:

"(3) Immediately after the submission of each report under paragraph (2), the Administrator, based on the results described in such report and the comments and recommendations included therein and any other available pertinent information, shall evaluate the need for any amendments to regulations prescribed pursuant to paragraph (1) of subsection (c) of section 354 of title 38, United States Code, for the resolution of claims for service connection based on the exposure specified in subparagraph (A)(i)(I) of such paragraph. To the extent that the Administrator determines that any amendments to such regulations are needed, the Administrator, not later than ninety days after such submission, shall develop

and publish in the Federal Register, for public review and comment, proposed amendments to such regulations.".

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98TH CONGRESS
1ST SESSION

H. R. 209

To require the Secretary of Health and Human Services to arrange for an independent epidemiological study of persons exposed to the chemical dioxin, used in the herbicide known as agent orange.

IN THE HOUSE OF REPRESENTATIVES

JANUARY 3, 1983

Mr. LONG of Maryland introduced the following bill; which was referred to the Committee on Energy and Commerce

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A BILL

To require the Secretary of Health and Human Services to arrange for an independent epidemiological study of persons exposed to the chemical dioxin, used in the herbicide known as agent orange.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. (a)(1) The Secretary of Health and Human Services (hereinafter in the Act referred to as the "Secretary") shall arrange, in accordance with section 2, for the conduct of an epidemiological study, based on available information and information furnished in accordance with section 3, to determine if and to what extent there may be long-

term adverse health effects in humans from exposure to any of the class of chemicals known as dioxins produced during the manufacture of the various phenoxy herbicides, and in other processes including the herbicide known as agent orange. Such study shall give particular attention to individuals who served as members of the Armed Forces of the United States in the Republic of Vietnam during the period of the Vietnam conflict but may include others who have been or may have been exposed to such chemicals when such inclusion is feasible and appropriate.

(2) The study required by paragraph (1) shall be continued for so long after the submission of the first report under section 4(b) as the Secretary determines to be reasonable in light of the possibility of developing through the continuation of such study significant new information on the long-term adverse health effects in humans of exposure to dioxins.

(b) The Secretary shall arrange, in accordance with section 2, for the conduct of a comprehensive scientific analysis of the existing literature covering other studies relating to whether there may be long-term health effects in humans from exposure to such dioxins or other dioxins.

SEC. 2. (a) The Secretary shall request the National Academy of Sciences (hereinafter in this Act referred to as the "Academy") to design, monitor the performance of, and analyze the data from a controlled epidemiologic study and

perform a review and analysis of all pertinent scientific literature as required by section 1 under an arrangement whereby the actual expenses incurred by the Academy directly related to the study and analysis will be paid by the Secretary. Performance of examinations or interviews will be coordinated by the Academy but performed by other appropriate institutions. If the Academy agrees to such a request, the Secretary shall enter into such an agreement with the Academy.

(b) If the Academy is unwilling to conduct the study required by section 1 under such an arrangement, then the Secretary shall enter into a similar arrangement with another appropriate public or nonprofit private entity to conduct such a study and analysis.

(c) Any arrangement entered into under subsection (a) or (b) for the conduct of the study required by section 1(a) shall require that reports on the study be submitted within such time as the Secretary may require to meet the requirement of section 4(b). Any arrangement entered into under subsection (a) or (b) for the conduct of the literature analysis required by section 1(b) shall require that the analysis be completed and reports on the study be submitted within such time as the Secretary may require to meet the requirement of section 4(a).

SEC. 3. The Secretary may request relevant information required by section 1(a) from any agency of the Federal Gov-

ernment, and the head of any agency from which such information is requested shall promptly furnish such information to the Secretary.

SEC. 4. (a) Not later than twelve months after the date of the enactment of this Act, the Secretary shall submit to the appropriate committees of Congress a report on the literature analysis conducted pursuant to section 1(b).

(b) Not later than twenty-four months after the completion of the protocol for the study required by section 1(a), and annually thereafter until the study is completed or terminated, the Secretary shall submit to the appropriate committees of the Congress a report containing—

(1) a description of the results thus far obtained under the study (including supporting data and other materials provided by the entity that conducted the study);

(2) the recommendations, if any, of such entity for legislative and administrative action; and

(3) such comments on the results of the study and recommendations for legislative and administrative action as the Secretary considers appropriate.

SEC. 5. The study and literature analysis required to be conducted by section 1 shall be conducted in lieu of the study and literature review and analysis required to be conducted by section 307(a) of Public Law 96–151 (93 Stat. 1097).

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98TH CONGRESS
1ST SESSION

H. R. 331

To amend title 38, United States Code, to waive the one-year limitation on claims for compensation from the Veterans' Administration for disabilities and diseases incurred in or aggravated by military service in the case of claims by veterans who served in Southeast Asia during the Vietnam era for compensation for disabilities resulting from exposure to the phenoxy herbicide known as "agent orange", or other phenoxy herbicides.

IN THE HOUSE OF REPRESENTATIVES

JANUARY 3, 1983

Mr. ROE introduced the following bill; which was referred to the Committee on Veterans' Affairs

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A BILL

To amend title 38, United States Code, to waive the one-year limitation on claims for compensation from the Veterans' Administration for disabilities and diseases incurred in or aggravated by military service in the case of claims by veterans who served in Southeast Asia during the Vietnam era for compensation for disabilities resulting from exposure to the phenoxy herbicide known as "agent orange" or other phenoxy herbicides.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That section 312 of title 38, United States Code, relating to presumptions relating to certain diseases and disabilities, is

amended by adding at the end thereof the following new subsection:

"(d) For the purposes of section 310 of this title and subject to the provisions of section 313 of this title, in the case of any veteran who served in the active military, naval, or air service in Southeast Asia during the Vietnam era, any disability or disease of such veteran attributable to or caused by exposure to a phenoxy herbicide shall be considered to have been incurred in or aggravated by such service, notwithstanding that there is no record of such disability or disease during the period of service of such veteran or that such disability or disease did not become manifest until more than one year after such veteran was discharged or otherwise released from service.".

SEC. 2. The amendment made by the first section of this Act shall apply to compensation paid under chapter 11 of title 38, United States Code, after September 30, 1983.

O

98TH CONGRESS
1ST SESSION

H. R. 1135

To amend title 38, United States Code, to waive the one-year limitation on claims for compensation from the Veterans' Administration for disabilities and diseases incurred in or aggravated by military service in the case of claims by veterans who served in Southeast Asia during the Vietnam era for compensation for disabilities resulting from exposure to the phenoxy herbicide known as agent orange or other phenoxy herbicides.

IN THE HOUSE OF REPRESENTATIVES

FEBRUARY 1, 1983

Mr. DOWNEY of New York introduced the following bill; which was referred to the Committee on Veterans' Affairs

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A BILL

To amend title 38, United States Code, to waive the one-year limitation on claims for compensation from the Veterans' Administration for disabilities and diseases incurred in or aggravated by military service in the case of claims by veterans who served in Southeast Asia during the Vietnam era for compensation for disabilities resulting from exposure to the phenoxy herbicide known as agent orange or other phenoxy herbicides.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That section 312 of title 38, United States Code, relating to presumptions relating to certain diseases and disabilities, is

amended by adding at the end thereof the following new subsection:

"(d) For the purposes of section 310 of this title and subject to the provisions of section 313 of this title, in the case of any veteran who served in the active military, naval, or air service in Southeast Asia during the Vietnam era, any disability or disease of such veteran attributable to or caused by exposure to a phenoxy herbicide shall be considered to have been incurred in or aggravated by such service, notwithstanding that there is no record of such disability or disease during the period of service of such veteran or that such disability or disease did not become manifest until more than one year after such veteran was discharged or otherwise released from service.".

SEC. 2. The amendment made by the first section of this Act shall apply to compensation paid under chapter 11 of title 38, United States Code, after September 30, 1980.

O

98TH CONGRESS
1ST SESSION

H. R. 1382

To provide that any award by the Veterans' Administration of compensation for a disease or disability in a veteran resulting from exposure to agent orange shall be retroactive to the date the veteran first applied to the Veterans' Administration for compensation for such disease or disability.

IN THE HOUSE OF REPRESENTATIVES

FEBRUARY 10, 1983

Mr. DOWNEY of New York introduced the following bill; which was referred to the Committee on Veterans' Affairs

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A BILL

To provide that any award by the Veterans' Administration of compensation for a disease or disability in a veteran resulting from exposure to agent orange shall be retroactive to the date the veteran first applied to the Veterans' Administration for compensation for such disease or disability.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That any award of compensation by the Veterans' Administration to a veteran under chapter 11 of title 38, United States Code, for a service-connected disease or disability incurred or aggravated due to exposure to the herbicide commonly known as agent orange shall be retroactive to the date

of the initial application of that veteran for compensation for such disease or disability.

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98TH CONGRESS
1ST SESSION

H. R. 1961

To amend title 38, United States Code, to provide a presumption of service connection for the occurrence of certain diseases related to exposure to herbicides or other environmental hazards or conditions in veterans who served in Southeast Asia during the Vietnam era.

IN THE HOUSE OF REPRESENTATIVES

MARCH 8, 1983

Mr. DASCHLE (for himself, Mr. PANETTA, Mr. BONIOR of Michigan, Mr. EDGAR, Mr. LONG of Maryland, Mr. WILLIAMS of Ohio, Mr. RICHARDSON, Mr. APPLEGATE, Mr. GARCIA, Mr. KASTENMEIER, Mr. OLIN, Mr. SMITH of New Jersey, Mr. MOAKLEY, Mr. OTTINGER, Mr. WHITEHURST, Mr. BARNES, Mr. KASICH, Mr. LELAND, Mr. FEIGHAN, Mr. RATCHFORD, Mr. DUNCAN, Mr. FORD of Michigan, Mr. SMITH of Florida, Mr. FRANK, Mr. TALLON, Mr. YOUNG of Alaska, Mr. MURTHA, Mr. STARK, Mr. MORRISON of Connecticut, Mr. OWENS, Mr. SIMON, Mr. ROE, Mr. FAUNTROY, Mr. MITCHELL, Mr. SCHEUER, Mr. STUDDS, Mr. DORGAN, Mr. LAFALCE, Mr. ERDREICH, Mr. CORRADA, Mr. ECKART, Mr. FORD of Tennessee, Mr. TRAXLER, Mr. SPRATT, Mr. WILLIAMS of Montana, Mr. OBERSTAR, Ms. MIKULSKI, Mr. PERKINS, Mr. LOWRY of Washington, Mr. MCKINNEY, Mr. HERTEL of Michigan, Mr. WIRTH, Mrs. SCHNEIDER, Mr. LANTOS, Mr. MARTINEZ, Mr. BERMAN, Mr. SHANNON, Mr. KILDEE, Mr. D'AMOURS, Mrs. COLLINS, Mr. FOGLIETTA, Mr. LEVINE of California, Mr. WEISS, Mr. HARRISON, Mr. FAZIO, Mr. MINETA, Mr. STOKES, Mr. DWYER of New Jersey, Mr. MURPHY, Mr. WEAVER, Mr. MCHUGH, Mr. HOWARD, Mr. DURBIN, Mr. MARKEY, Mr. BATES, Mr. SEIBERLING, Mr. VENTO, Mr. BORSKI, Mr. DONNELLY, Mr. SUNIA, Mr. MRAZEK, Mr. ADDABBO, Mr. RODINO, Mrs. KENNELLY, Mr. BEREUTER, Mr. DELLUMS, Mrs. BOXER, Mr. EDWARDS of California, Mr. JEFFORDS, Mr. BROWN of California, Mr. SHARP, Mr. PENNY, Mr. FISH, Mr. ASPIN, Mr. KEMP, Mr. FLORIO, Ms. OAKAR, Mr. GORE, Mr. HARKIN, Mr. OXLEY, Mr. DE LUGO, Mr. MCCLOSKEY, Mr. GUNDERSON, Mr. GILMAN, Mr. KOGOVSEK, Mr. TORRICELLI, Mr. HORTON, Mr. DIXON, Mr. EVANS of Illinois, Mr. MILLER of California, Mr. WOLPE, Mr. GLICKMAN, and Mr. SLATTERY) introduced the following bill; which was referred to the Committee on Veterans' Affairs

A BILL

To amend title 38, United States Code, to provide a presumption of service connection for the occurrence of certain diseases related to exposure to herbicides or other environmental hazards or conditions in veterans who served in Southeast Asia during the Vietnam era.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "Vietnam Veterans Agent Orange Relief Act".

SEC. 2. The Congress finds that—

(1) certain adverse health effects occurring among persons who served in the Armed Forces in Southeast Asia during the Vietnam era, and certain birth defects occurring among the children of such persons, may be the result of the exposure of such persons during such service to phenoxy herbicides (including the herbicide known as Agent Orange) and the class of chemicals known as the dioxins produced during the manufacture of such herbicides or to other factors involved in such service including exposure to other herbicides, chemicals, medications, or environmental hazards or conditions; and

(2) a comprehensive review and scientific analysis of the literature covering studies relating to whether there may be long-term adverse health effects in

humans from exposure to any of the class of chemicals known as the dioxins produced during the manufacture of the various phenoxy herbicides (including the herbicide known as Agent Orange), as required by section 307(a)(1)(B) of Public Law 96–151, has been completed and submitted to the Veterans' Administration.

SEC. 3. Section 312 of title 38, United States Code, is amended by adding at the end the following new subsection:

"(d)(1) For the purposes of section 310 of this title and subject to the provisions of section 313 of this title, in the case of a veteran who served in Southeast Asia during the Vietnam era and who after such service suffers from a disease described in paragraph (2)(A) of this subsection, such disease shall be considered to have been incurred in or aggravated by such service, notwithstanding that there is no record of evidence of such disease during the period of service.

"(2)(A) The diseases referred to in paragraph (1) of this subsection are the following:

"(i) Soft-tissue sarcomas.

"(ii) Porphyria cutanea tarda.

"(iii) Active and residual chloracne and chloracneform lesions.

"(iv) A disease listed in a regulation prescribed by the Administrator under subparagraph (B) of this paragraph.

"(B) The Administrator may determine, and prescribe by regulation, diseases (in addition to those listed in subparagraph (A) of this paragraph) that medical research has shown may be due to exposure to herbicides, chemicals, medications, or environmental hazards or conditions. The Administrator shall include in such regulations a specification of the standards used by the Administrator in making such determination.

"(3) Paragraph (1) of this subsection shall terminate on the first day of the first month beginning after the end of the one-year period beginning on the date the Administrator submits to the appropriate committees of Congress the first report required by section 307(b)(2) of the Veterans Health Programs Extension and Improvement Act of 1979 (Public Law 96–151; 93 Stat. 1098).".

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