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CABINET COUNCIL ON HUMAN RESOURCES

AGENT ORANGE WORKING GROUP

STATUS (TAB A)

FUNDING (TAB B)

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ON TWENTY-FIVE HHS STUDIES

Reports Received
up until February 1982

SCIENTIFIC ACTIVITY REPORT - SUMMARY - HHS/NIEHS
Agent Orange Working Group
January 26, 1982

1. Bioassy of Octachlorodibenzo-p-dioxin.
Terminated due to unavailability of purified chemical.

2. Carcinogenesis Bioassy of 2,3,7,8,-Tetrachlorodibenzo-p-dioxin (CAS no. 1746-01-6) in Swiss Webster mice (Dermal Study).
This compound found carcinogenic for B6C3P-1 mice and Osborne-Mendel rats producing liver and thyroid tumors.

3. Carcinogenesis Bioassy of 2,3,7,8,-tetrachloridibenzo-p-dioxin (CAS No. 1746-01-6) in Osborne-Mendel rats and B6C3F1 mice (Gavage Study).
This compound found carcinogenic for Swiss-Webster female mice producing tumors of the integument.

4. a. Bioassy of a mixture of 1,2,3,6,7,8- and a mixture of 1,2,3,7,8,9,- Hexachlorodibenzo-p-dioxins for possible carcinogenicity (Dermal Study).
Under the conditions of this bioassy, HCDD was not considered carcinogenic for Swiss-Webster mice.

b. Bioassy of a mixture of 1,2,3,6,7,8- and 1,2, 3, 7,8,9-Hexachlorodibenzo-p-dioxin for possible carcinogenicity (Gavage Study).
HCDD administered by gavage was carcinogenic for Osborne-Mendel rats and B6C3F1 mice producing tumors of the liver.

5. Comparitive species evaluation of chemical disposition and metabolism of 2,3,7,8,-tetrachlorodibenzofuran (TCDF) in rat, monkey, guinea pig and two strains of mice.
The speed of metabolism and excretion correlated inversely with the observed acute toxicity of TCDF in these species.

6. Neurotoxicity of 2,4-D in rodents.
Single oral doses of 2,4-D indicate a persisting effect (4-8 weeks) on fore-and hindlimb grip strength in male Fisher rats. Other neurobehavioral tests to measure the effects on sensory and motor functioning, affective behavior, learning, and memory have been undertaken.

7. Studies of the chemical disposition and metabolism of Octachloridibenzodoxin (OCDD).
Discontinued because chemical could not be purified.

8. Effects of "Agent Orange" components on male fertility and reproduction.
Sperm number and morphology, mating frequency, fertility efficiency, dominant letality, incidence of congenital malformations, viability of offspring and sisterchromatid exchanges are being measured in male mice fed large doses of the constituents of "Agent Orange" and will be published soon.

9. Mutagenicity Studies of TCDD, 2,4-D, 2,4,5-T and Esters of 2,4-D and 2,4,5-T.
The Ames test for point mutations, Drosophila tests for sex-linked recessive mutations and mammalion cell tissue culture tests for chromosomal aberrations are almost complete and have yielded negative results so far.

10. Implications of low level exposure to dioxins.
Two year dietary exposure to 5 and 50 parts-per-trillion TCCD will include clinical and behavioral evaluation of toxicity and fat biopsies to measure TCCD bioaccumulation in rehsus monkeys.

11. Mechanisms of toxicity of the chlorinated-p-dioxins.
In viro and in vitro metabolism of TCCD and examinations for the presence of receptor sites in different rodent species is in progress.

12. Research toward understanding the molecular level mechanism of toxicity of TCCD and related compounds.
An ongoing activity to determine the structure and electronic properties of the dioxin receptor in order to understand the mechanisms of toxicity.

13. Synthesis of selected tetrachlorodibenzo-p-dioxins and related compounds as analytical standards.
It is anticipated that another year will be necessary to have a minimum set of standards in hand before analytical method development can truly begin.

14. Matrix effect and sub parts-per-billion quantitative analysis of TCDD by mass spectrometry -- with special reference to milk.
This project is designed to validate the determination step for TCDD at low parts-per-trillion levels in environmental/ biological samples by high resolution gas chromatography and high resolution mass spectrometry.

15. Toxic actions of tetrachloroazobenzene and dioxins.
This project is designed to examine the pharmacokinetics and toxicologic, pathologic and biochemical changes with chronic exposure to TCAOB and TCCD using in viro and in vitro methods.

16. Xenobiotic induction of pleiotropic responses in liver. This project is an attempt to identify potentially toxic substances by their ability to induce certain hepatic enzymes before overt toxic effects are manifest.

17. Molecular, biochemical actions of chlorimated-p-dioxins. This project is designed to investigate biochemical mechanisms of TCDD toxicity in mammals via alterations in fatty acid metabolism.

18. Molecular basis of dioxin toxicity to keratinocytes. This project is designed to characterize the effects of TCDD on growth and differentiation of human skin cells in tussue culture.

19. Mechanism(s) for toxicity of chlorinated dibenzodioxins. This project is designed to measure interspecies variation in toxic metabolic and neural response to TCDD.

20. Establishment and maintenance of an International Register of persons exposed to phenoxy acid herbicides and contamenants.
An ongoing and long-term project which has begun only recently. preliminary contacts have been made with key individuals in Nordic countries and Italy and an international meeting will be held in the summer of 1982 to plan further efforts.

21. Investigation of a leukemia cluster in Madison County, Kentucky allegedly associated with pentachlorophenal-treated ammunition boxes at the Blue Grass Army Depot. (NIOSH: July 1981) (Report to come)

December, 1981

Summary of Dioxin Related Epidemiologic Studies at NIOSH

The National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control (CDC), D.H.H.S. is conducting two primary studies to ascertain effects of occupational exposure to dioxin-contaminated herbicides such as 2,4,5-T. 2,4,5-T has been heavily used domestically and was a major constituent of Agent Orange used in Vietnam.

22. I. NIOSH Dioxin Registry

Description: NIOSH is establishing a Dioxin Registry of people in the U.S. who have worked at the production of dioxin-contaminated materials such as 2,4,5-T. Since 1979, NIOSH has been collecting work history records dating back to the 1940's for the workers who were ever involved in making these materials at numerous production sites around the country. These records, along with information about the production processes, are being used to define the workers' exposure.

Status: At this time, data collection is close to completion and analyses are planned which will give some indication of whether the dioxin exposed workers die at a rate or from causes different from that expected for the U.S. population in general. Preliminary results from these analyses are expected in late 1983. In the future, other types of epidemiologic studies may be conducted with the NIOSH Dioxin Registry.

23. II. NIOSH Soft Tissue Sarcoma Investigation

Description: NIOSH also is investigating an association between occupational exposure to herbicides such as 2,4,5-T and the development of a malignant tumor known as soft tissue sarcoma. This association was first reported in 1979 in two epidemiologic studies from Sweden, and recently has been corroborated by a review at NIOSH of data from U.S. workers. Further epidemiologic study is required to confirm the association, and such studies are underway at NIOSH. In particular, NIOSH is beginning an epidemiologic case-control study for soft tissue sarcoma to ascertain whether a group of people with soft tissue sarcoma report occupational exposure to the suspect materials significantly more often than controls without the tumor.

Status: The study is under design, and results are not due until 1984.

24. The Birth Defects and Military Service in Vietnam Study

The Centers for Disease Control (CDC) has begun a study designed to determine if Vietnam veterans are at increased risk of having babies with serious birth defects. Since 1968 CDC has kept a registry of all babies born with defects in the greater metropolitan Atlanta area. The parents of 7500 of these babies will be interviewed. In addition, the parents of 3000 babies born during this same time without defects will also be interviewed. The major objective of this study will be to determine whether an unusually high proportion of fathers of babies born with defects served in Vietnam. Thus, information is being gathered about Vietnam service and a wide variety of other factors which may be associated with the occurrence of birth defects. If the study demonstrates that Vietnam veterans have an increased risk of fathering a child with a defect it will be desirable to try to determine if the increase is associated with Agent Orange exposure or with some other factor(s). The study is scheduled to be completed by September 1983.

25* Current Status of FDA Dioxin Methodology Development: Summary Statement for Inclusion in Memo from Dr. Cordle to CDC Dave Firestone, 12/28/81

FDA is currently concerned with developing improved methods for isolation, analysis and confirmation of TCDD and other dioxins in foods and feeds. Current projects include developments of a multi-column high performance liquid chromatographic (HPLC) procedure for cleanup of fish samples prior to capillary column GC/EC (gas chromatography with electron capture detection) examination and MID (multiple ion detection) GC/MS confirmation of the identity of the TCDD in the extracts, evaluation of the Fish and Wildlife Service extraction-cleanup procedure for 2,3,7,8-TCDD; and evaluation of the Dow extraction-cleanup procedure for 2,3,7,8-TCDD.

The multi-column HPLC extraction-cleanup procedure involves digestion of 20g fish tissue at room temperature in 20% KOH solution, hexane extraction, washing with concentrated sulfuric acid and cleanup of the hexane extract by passage through three tandem HPLC columns as follows: (a) Zorbax PMS 60 S (6.2 mm i.d. x 50 cm; 93/5/2 hexane/MeOH/ CH_2Cl_2; 1 mL/min.); (b) Zorbax C-8 (4.6 mm i.d. x 50 cm; 75/25 CH_3CN/H_2O; 2.4 mL/min.); and (c) Zorbax C-18 (4.6 mm i.d. x 50 cm; 100% CH_3CN; 1.2 mL/min). Both fortified (60 ppt TCDD for recovery determination) and unfortified samples are examined. Evaluation of the precision of the multi-column HPLC procedure was determined by quadruplicate analyses of fortified (60 ppt) and unfortified carp and catfish samples. Relative standard deviations of less than 15% were obtained. Recoveries of 2,3,7,8-TCDD obtained with the procedure averaged 57% (C.V. = 14%). The procedure is isomer specific for 2,3,7,8-TCDD. As little as ca 15 ppt of 2,3,7,8-TCDD can be detected and confirmed in fish tissue.

The Canadian Health Protection Branch and FDA recently completed a round-robin to check performance of laboratories conducting TCDD analyses. Four fish samples (a control sample and three trout samples containing 30-60 ppt of bioincurred TCDD) were analyzed by eight collaborating laboratories in the United States and Canada, each laboratory using its own methodology. Precision (relative standard deviation) of the analytical values from the eight reporting laboratories varied from 14% to 26% for the three trout samples, remarkably good for ppt level determinations.

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* No dollar amount reported.

SCIENTIFIC ACTIVITY REPORT -- FUNDING -- HHS

Agent Orange Working Group

Scientific Activity	Funding ($000)					
	FY 80	FY 81	FY 82	FY 83	FY 84	FY 85
1. Bioassay of Octachlorodibenzo-p-dioxin (NIEHS; Terminated)	-	-	-	-	-	-
2. Bioassay of 2,3,7,8-Tetrachloro-dibenzo-p-dioxin for possible carcinogenicity -- dermal study (NCI; Completed)	120	-	-	-	-	-
3. Bioassay of 2,3,7,8-Tetrachloro-dibenzo-p-dioxin for possible carcinogenicity -- gavage study (NCI; Completed)	120	-	-	-	-	-
4. Bioassay of a mixture of 1,2,3,6,7,8 and 1,2,3,7,8,9-Hexachloro-dibenzo-p-dioxins for possible carcinogenicity -- dermal and gavage studies (NCI; October 1980)	120	-	-	-	-	-
5. Comparative species evaluation of chemical disposition and metabolism of TCDF in rat, monkey and guinea pig (NCI/NIEHS; Completed)	48	-	-	-	-	-
5. Neurotoxicity of 2,4-D in rodents (NIEHS; December 1982)	9	27	-	-	-	-
7. Studies of the chemical disposition and metabolism of OCDD (NIEHS; Discontinued)	14	-	-	-	-	-
8. Effects of "Agent Orange" Components on Male Fertility and Reproduction (NTP; Completed)	95	-	-	-	-	-

Scientific Activity	Funding ($000)					
	FY 80	FY 81	FY 82	FY 83	FY 84	FY 85
9. Mutagenicity Studies of TCDD, 2,4-D 2,4,5-T and Esters of 2,4-D and 2,4,5-T (NIEHS; April 1981)	20	81	-	-	-	-
10. Implications of low level exposure to dioxins (NIEHS; August 1982)	122	293	-	-	-	-
11. Mechanism(s) of toxicity of the chlorinated p-dioxins (NIEHS; March 1981)	40	-	-	-	-	-
12. Research Toward Understanding the Molecular Level Mechanism of Toxicity of TCDD and Related Compounds (NIEHS; Indefinite)	55	55	55	55	55	55
13. Synthesis of Selected Tetrachlorodibenzo-p-Dioxins and Related Compounds as Analytical Standards (NIEHS; December 1981)	-	75	-	-	-	-
14. Matrix Effect and Sub Parts - per - Billion Quantitative Analysis of TCDD by Mass Spectrometry - with Special Reference to Milk (NIEHS; January 1982)	-	25	-	-	-	-
15. Toxic Actions of Tetrachloroazobenzene and Dioxins (NIEHS; April 1984)	-	77	53	57	-	-
16. Xenobiotic Induction of Pleiotropic Responses in Liver (NIEHS; January 1986)	-	184	123	132	143	153

Scientific Activity	Funding ($000)					
	FY 80	FY 81	FY 82	FY 83	FY 84	FY 85
. Molecular, Biochemical Actions of Chlorinated -p- Dioxins (NIEHS; December 1983)	-	54	36	38	-	-
. Molecular Basis of Dioxin Toxicity to Keratinocytes (NIEHS; August 1984)	-	76	48	48	-	-
. Mechanism(s) for Toxicity of Chlorinated Dibenzodioxins (NIEHS; June 1983)	-	60	29	-	-	-
. Establishment and Maintenance of an International Register of Persons Exposed to Phenoxy Acid Herbicides and Contaminants (NIEHS; July 1984)	-	310	-	146	-	-

SCIENTIFIC ACTIVITY REPORT -- FUNDING -- HHS

CABINET COUNCIL ON HUMAN RESOURCES

Agent Orange Working Group

Scientific Activity	Funding ($000)					
	FY80	FY81	FY82	FY83	FY84	FY85
Investigation of a leukemia cluster in Madison County, Kentucky allegedly associated with pentachlorophenal-treated ammunition boxes at the Blue Grass Army Depot (NIOSH; July 1981)	10	10	-	-	-	-
Dioxin registry (NIOSH; Dec. 1983)	75	72	126	126	100 1/	125 1/
Case control study for soft tissue sarcoma (NIOSH; Dec 1984)	-	-	230	70	70	-
Birth Defects and Military Service in Vietnam (CDC; Sept. 1983)	53	596	866	800*	-	-
FDA Great Lakes Study on Human Exposure (no funding information)						

1/ Funding Dependent on Registry Results

* (Approximate study cost, one-third each from HHS/VA/DOD

2/1/82

VETERANS ADMINISTRATION

AGENT ORANGE WORKING GROUP

Title of Activity	Funding		
	FY 80	FY 81	FY 82
1. Review and Analysis of Literature on Phenoxy Herbicdes and Dioxin	$ -0-	$122,000 (1)	$ -0-
2. Epidemiology of Agent Orange in Vietnam Veterans			
a. Contract for Study Design	-0-	-0-	133,900
b. Conduct of Study	-0-	-0-	4,379,000 (2)
3. TCDD Assay of Human Fat	7,000 (3)	-0-	-0-
4. CDC Birth Defects Study	-0-	216,352	122,048 (4)
5. Mortality Study	-0-	20,000 (5)	50,000 (5)
6. Urinary 6-Hydroxy Cortisol; Physiologic and Pharmacologic Studies (including Agent Orange)	34,750	37,800	41,580
7. Effect of TCDD on Lipid Metabolism Dioxins	26,611	20,513	22,564
8. Mechanisms of Dioxin Induced Toxcity Using the Chloracne Model	-0-	15,000	5,500

(1) Completed in FY 1981
(2) Available - not yet obligated
(3) Study completed in FY 1980
(4) Obligated - not yet expended
(5) Funding for contract with Medical Follow-up Agency, National Academy of Sciences

SCIENTIFIC ACTIVITY REPORT

AGENT ORANGE WORKING GROUP

January 21, 1982

Title of Activity:

1. Review and Analysis of Literature on Phenoxy Herbicides and Dioxin

2. Epidemiology of Agent Orange in Vietnam Veterans

3. TCDD Assay of Human Fat

4. Birth Defects and Military Service in Vietnam

5. Vietnam Veteran Mortality Studies

6. Urinary 6-Hydroxy Cortisol; Physiologic and Pharmacologic Studies (including Agent Orange)

7. Effect of TCDD on Lipid Metabolism

8. Mechanisms of dioxin induced toxicity using the Chloracne model

REVIEW AND ANALYSIS OF LITERATURE

ON

PHENOXY HERBICIDES AND DIOXINS

Public Law 96-151, enacted December 20, 1979, required the Administrator of Veterans Affairs to "conduct a comprehensive review and analysis" of the worldwide literature on Agent Orange and other phenoxy herbicides. The goal of this report was to present a balanced and critical review of the current state of published scientific literature relevant to the problem of exposure to herbicides, particularly, phenoxy herbicides used in Vietnam. The contract for this review was awarded to JRB Associates, Inc., of McLean, Virginia, and submitted in final form to the VA in October 1981. For the purpose of this review, JRB Associates used an expanding and reiterative search strategy and a scientific relevancy criteria. Over 1,400 documents were acquired and examined. About 1,200 were judged to fall within the relevant parameters. These documents underwent an extensive review and analysis and the report was prepared with a supporting bibliography.

The literature search is expected to assist researchers, both those in government and in the private sector, to identify opportunities for the systematic development of new knowledge based on what is already known and published.

Copies of the report have been provided to the House and Senate Veterans Affairs Committees (both of which have exercised close supervision of VA's response to veterans concerned about Agent Orange) and to the Board of Veterans Appeals.

Copies were sent also to the National Academy of Sciences (NAS), the Congressional Office of Technology and Assessment, VA's Scientific Advisory Committee on Herbicides and an interagency Agent Orange Working Group, all of which have been cooperating in the massive research effort. The VA has also given a copy of this report to the government of Australia.

EPIDEMIOLOGY OF AGENT ORANGE

IN

VIETNAM VETERANS

Public Law 96-151 charged the Veterans Administration to "design a protocol for and conduct an epidemiological study of persons, who while serving in the Armed Forces of the United States during the period of the Vietnam conflict, were exposed 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') to determine if there may be long-term adverse health effects in such persons from such exposure."

On May 1, 1981, the VA contracted with the Department of Epidemiology, School of Public Health, University of California at Los Angeles, to design the mandated research. Although offering information and assistance, the VA has avoided influencing the design. The initial draft design was sent to three groups for review, namely the Office of Technology Assessment, the Science Panel of the Agent Orange Working Group and the VA Advisory Committee on Health-Related Effects of Herbicides. The VA Advisory Committee has members from veterans organizations and thus provides a direct means to solicit comments from the veteran community. UCLA is to provide the protocol to the VA for peer review by January 25, 1982. Following this review, UCLA will have 30 days to resubmit the design for a further peer review. Upon completion of the review process, assuming that an acceptable design is ultimately accepted, action will be taken by the VA to initiate the conduct and monitoring of this research effort.

TCDD ASSAY OF HUMAN FAT

The purpose of the TCDD Assay of Human Fat (adipose tissue) was to initiate a small feasbility trial which would assist in determining whether TCDD could be measured in the fat tissue of Vietnam veterans and a control sampling of non-Vietnam veterans. The study required a surgical biopsy of specimens of abdominal fat extracted from research participants. The specimens were assayed by an ultra-high resolution mass spectrometer after gas-liquid chromatography. Specimens analyzed by the University of Nebraska were subsequently re-assayed by the Environmental Protection Agency. The analysis of adipose tissue from 20 Vietnam veterans claiming exposure to Agent Orange, 10 non-Vietnam veterans and 3 Air Force Officers having a documented exposure history to TCDD, revealed that exposure and health status did not correlate with detected levels of TCDD. Nevertheless, the results indicated that the assay method was feasible, but too delicate and difficult to be a useful assay method at this time.

THE BIRTH DEFECTS AND MILITARY SERVICE IN VIETNAM STUDY

In 1981 the Centers for Disease Control (CDC) initiated a study designed to determine if Vietnam veterans are at increased risk of having offspring with serious birth defects. Since 1968 CDC has kept a registry of all babies born with defects in the greater metropolitan Atlanta area. The parents of 7,500 of these babies will be interviewed. In addition, the parents of 3,000 babies born during this same time without defects will also be interviewed. Since the major objective of this study will be to determine whether an unusually high proportion of fathers of babies born with defects served in Vietnam, information will be gathered about Vietnam service as well as factors which may be associated with the occurrence of birth defects. If the study demonstrates that Vietnam veterans have an increased risk of fathering a child with a defect it will be desirable to try to determine if the increase is associated with Agent Orange exposure or with some other factor(s). The study is scheduled to be completed by September 1983.

VIETNAM MORTALITY STUDY

The Vietnam Mortality Studies are designed to analyze and compare death rates and cause-of-death profiles between veterans with service in Vietnam and comparable veterans with no service in Vietnam. The studies use existing computer records to assemble a cohort of veterans and determine their mortality experience. The studies also include independent validation of the computer data bases used in the studies. By using automated records, a large number (approximately six million) of veterans may be studied and results may be obtained relatively quickly and inexpensively. It should be noted however, that the mortality studies are not intended to provide definitive answers, but will instead provide mortality information which may prove useful primarily in suggesting areas for further scientific study. In addition, it is important to note that the mortality studies do not address phenoxy herbicide exposure, per se, but only service in Vietnam.

URINARY 6-HYDROXY CORTISOL: PHYSIOLOGIC AND PHARMACOLOGIC STUDIES (INCLUDING AGENT ORANGE)

6-hydroxy cortisol is a polar metabolite of cortisol formed in the endoplasmic reticulum of liver cells by mixed function oxygenase systems (MFOS) which are also responsible for the metabolism of many drugs and polycyclic hydrocarbons. The investigator has developed a sensitive radioimmunoassay for 6-hydroxy cortisol in human urine. He intends to utilize this method to further characterize the normal and abnormal physiology of 6-hydroxy cortisol, to investigate dogs and humans exposed to carcinogens such as those in cigarette smoke and to investigate the impact of 2,3,7,8-TCDD on hepatic microsomal induction.

The information will be used to determine whether urinary 6-hydroxy cortisol can be helpful in assessing any continuing effects of herbicides and TCDD in exposed humans.

EFFECT OF TCDD ON LIPID METABOLISM (DIOXINS)

Previous toxicological studies have demonstrated that TCDD given to guinea pigs and rats causes increases in the serum lipids. The objectives of this proposal are to study the effects of acute doses of TCDD on serum lipoproteins in guinea pigs, rats and rabbits. The overall plan is to characterize the lipoproteins, study lipoprotein synthesis and catabolism, and study adipose tissue mobilization of fatty acids in acute dosing experiments. Further studies will use chronic administration of TCDD to determine the effects of accumulation of the toxin on lipid metabolism as it is administered in sublethal amounts.

MECHANISMS OF DIOXIN INDUCED TOXICITY USING THE CHLORACNE MODEL

Because of the apparent selective sensitivity of follicular epithelial cells to polyhalogenated aromatic hydrocarbons, elucidating the mechanisms of toxicity for such cells may provide a better understanding of the mechanisms of toxicity in general.

In human beings, development of chloracne is the most sensitive indicator of exposure to toxic polyhalogenated aromatic hydrocarbons. The mechanism of pathogenesis of this disease is not known. It appears that epithelial cells lining the ducts of human sebaceous follicles are primary target organs and are reflected in an abnormal pattern of retention hyperkeratosis, comedones and chloracne.

To understand the mechanisms involved in this transformation, the investigator proposes to use experimental animals for in vivo, and human skin biopsies for in vitro studies to investigate the biochemical and metabolic parameters which may be affected upon exposure to 2,3,7,8-TCDD and to polychlorinated biphenyls (PCBs). Specifically, certain enzymatic markers will be monitored during experimentally induced chloracne in hairless mice and in rabbit ears. The effects of TCDD and PCB exposure will be examined on sebaceous follicle lipid biosynthesis and androgen metabolism in in vitro assays and on the cellular kinetics of follicular epithelial cells in tissue culture. An attempt will be made to identify the localization of these aromatic hydrocarbons in the skin by using radiolabeled tracers.

ENVIRONMENTAL PROTECTION AGENCY

SCIENTIFIC ACTIVITY REPORT -- FUNDING

Agent Orange Work Group

Title of Activity	Funding FY81	Funding FY82
1. Bacterial decomposition of TCDD (ORD: August 1982)	75K	75K
2. Evaluation of municipal waste combustors	100K	70K
3. Evaluation of large scale combustion sources	100K	100K
4. Investigation of bioavailability to fresh water fish of TCDDs in flyash	____	80K
5. Analysis of environmental samples for PCDDs and PCDFs	200K	225K

EPA'S RESEARCH RELATED TO AGENT ORANGE
October, 1981

Bacterial decomposition of TCDD

2,3,7,8-TCDD is generally very persistent once it escapes into the environment. This is particularly the case for 2,3,7,8-TCDD in soils, where the half-life of the substance is on the order of years. EPA is sponsoring a research project which seeks to isolate bacteria which are capable of degrading 2,3,7,8-TCDD much more rapidly.

Scientists have alreday successfully isolated a bacterium which will decompose 2,4,5-T, one of the principal components of Agent Orange. A similar technique is now being applied to the case of 2,3,7,8-TCDD.

Evaluation of municipal waste combustors

During the past few years a number of studies have shown that 2,3,7,8-TCDD and a number of other polychlorinated dibenzo-p-dioxins (PCDDs) can be emitted from facilities which are burning municipal wastes. The extent of these emissions and their significance has recently been evaluated by EPA in an interim analysis. After sampling five municpal waste combustors in this country, the Agency concluded that the levels found do not constitute a public health concern. Additional studies on such facilities are planned in the future.

Evaluation of large scale combustion sources

In addition to municipal waste combustors, EPA is investigating emissions from other large scale combustors; e.g., coal-fired power plants, for the presence of a variety of organic pollutants, including 2,3,7,8-TCDD.

Investigation of bioavailability to freshwater fish of TCDDs in flyash

TCDD emissions from combustion sources are often associated with particulate matter. Very limited toxicological studies have been performed using such material. It is known from lab work, however, that the TCDDs are difficult to remove chemically. Questions have been raised about whether or not the TCDDs could be removed by biological processes once they enter the body and thereby become available to exert a toxicological effect.

This research project will investigate a relatively simple biological system as a first step in addressing this

bioavailabilty question.

Analysis of environmental samples for PCDDs and PCDFs

EPA maintains an on-going program for the analysis of 2,3,7,8-TCDD and related compounds in environmental samples. During the coming year an increasing number of such samples are expected to come from "Superfund"-related activities; e.g., abandoned dump sites.

Department of Defense
Herbicide Orange Activities Summary

The primary research effort concerning the possible effects of Herbicide Orange and its contaminant dioxin is an epidemiologic investigation of health effects in approximately 1,200 Air Force Ranch Hand personnel who were heavily exposed to herbicides while performing fixed wing aircraft spray missions. This study is being managed by the United States Air Force Epidemiology Division of the School of Aerospace Medicine, located at Brooks Air Force Base, Texas. The retrospective phase of the epidemiology study has been initiated by an award of a contract to Louis Harris and Associates, Inc. on September 18, 1981 for the administration of the retrospective phase questionnaire. The Cross Sectional Study Phase contract was awarded on 3 December 1981 to the Kelsey-Seybold Clinic to conduct a maximum of 2,400 comprehensive physicals. The physicial examinations will include Ranch Hand members and a control group. The matching of a control group to the 1,264 Ranch Hand members was completed at a ratio of ten-to-one for the study. Matches were made by age, occupational category, and race. A one-to-one match for physical examinations was done and a five-to-one match for the ongoing mortality study has been completed. All physical examinations will be completed by the end of September 1982.

In the meantime the mortality study of Ranch Hand personnel has continued. To date,* the Air Force has knowledge of 58 deaths: 22-killed in action; 16-accidents (aircraft, motor vehicle, drowning); 3-suicides; 2-homicides; 2-malignant neoplasms; 1-endocrine, nutritional and metabolic diseases; and 1-symptoms, signs and ill defined conditions. The conclusions of the first round of questionnaires and physical examination will provide the basis for the remainder of the study. The study may continue for 20 years with follow-up examinations planned at 3, 5, 10, 15 and 20 years.

The Department of Defense has also been involved for almost two years in an extensive records search and information retrieval effort which has primarily been accomplished by the Army Agent Orange Task Force (AAOTF) located within the Adjutant General's Office. The AAOTF has accomplished extensive records screening and declassification actions on significant portions of the 40,000 linear feet of Vietnam military operational records. In support of the Agent Orange Working Group and its Science Panel the AAOTF has completed three detailed battalion studies directed

* As of November 18 1981

at determining ground troop operating locations in relation to distances from fixed wing herbicide spray missions and from perimeter spraying. The Marine Corps Historical office has also completed two similar Marine Battalion studies. The AAOTF has provided support to the Veterans Administration contractor representatives in their development of a protocol for an Epidemiology Study of Vietnam Veterans. Numerous briefings have been made by the AAOTF staff to veterans organizations, state veterans commissions and other Federal personnel involved in the Herbicide Orange research effort. The AAOTF and other service offices have provided many responses to individuals and organizations concerning veterans assignments and locations while in Vietnam.

In November 1981 the Department expanded its capability to be responsive to the Veterans Administration by establishing formally "Agent Orange Task Forces" in the Departments of the Navy and Air Force. In early December the manning of the Army AOTF was doubled with further expansion in personnel projected as the data and search requirements develop from the VA.

DEPARTMENT OF DEFENSE

Interagency Work Group on Phenoxy Herbicides and Contaminants

Title of Activity	Funding Thousands		
	FY80	FY81	FY82
Epidemiological Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicide Orange	380	1,550	3,900

Date: 9 November 1981

SCIENTIFIC ACTIVITY REPORT

Interagency Work Group on Phenoxy Herbicides and Contaminants

1. Title of activity: Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to "Herbicide Orange"

2. Agency responsible, including agency, component(s) directly responsible for activity: United States Air Force,
School of Aerospace Medicine,
Epidemiology Division
Data Sciences Division
Clinical Sciences Division

3. Statement of objective(s): The purpose of this investigation is to determine whether there are or will be long term health effects attributable to occupational exposure to Herbicide Orange and its contaminant TCDD.

4. Principal investigator(s):

George D. Lathrop MD, MPH, PhD
Colonel, USAF, MC
Chief, Epidemiology Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

William H. Wolfe, MD, MPH
Lt Colonel, USAF, MC
Chief, Disease Surveillance Branch
Epidemiology Division
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Brooks AFB, TX 78235

Clarence F. Watson, Jr., MD, MPH
Colonel, USAF, BC
Chief, Clinical Sciences Division
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Richard A. Albanese, MD, GS-15
Chief, Biomathematical Modeling Branch
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Patricia M. Moynahan, BSN, MS
Lt Colonel, USAF, NC
Chief, Epidemiologic Investigative Section
Disease Surveillance Branch
Epidemiology Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

5. Relationship of activity to other work group activities: Long term epidemiology done by the VA and NIOSH.

6. Statement of scientific method(s) to be used, including (as appropriate) administrative process(es): The scientific protocol has been reviewed by five scientific groups, the School of Public Health, University of Texas, Houston, the Air Force Scientific Advisory Board, the Armed Forces Epidemiological Board, the National Academy of Sciences, Board on Toxicology and Environmental Health Hazards and the Scientific Panel of the Interagency Work Group to study the possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants.

7. Status as of November 1981: The retrospective phase of the study has been initiated by award of a contract to Louis Harris and Associates, Inc. for administration of the retrospective phase questionnaire. The cross sectional phase of the study will be initiated with award of a contract. Contract award is anticipated by November 30, 1981.

8. Relevant review process(es), as applicable: The Scientific protocol has been reviewed by five scientific peer review groups. They are listed in 6 above. Additionally, an Advisory Committee has been appointed by the Department of Health and Human Services to monitor the first five years of the study.

9. List of Key interim project milestones (nature, description and projected dates of accomplishment) and project completion date:
Key milestones

Retrospective study phase	Project completion date 12 months after initiating questionnaire administration.
Cross Sectional Study Phase	19 months after administration the last physical examination.
Prospective study phase	Up to 21-22 years after initiation of the retrospective study phase.

Title of activity
Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to "Herbicide Orange"

Interagency Work Group

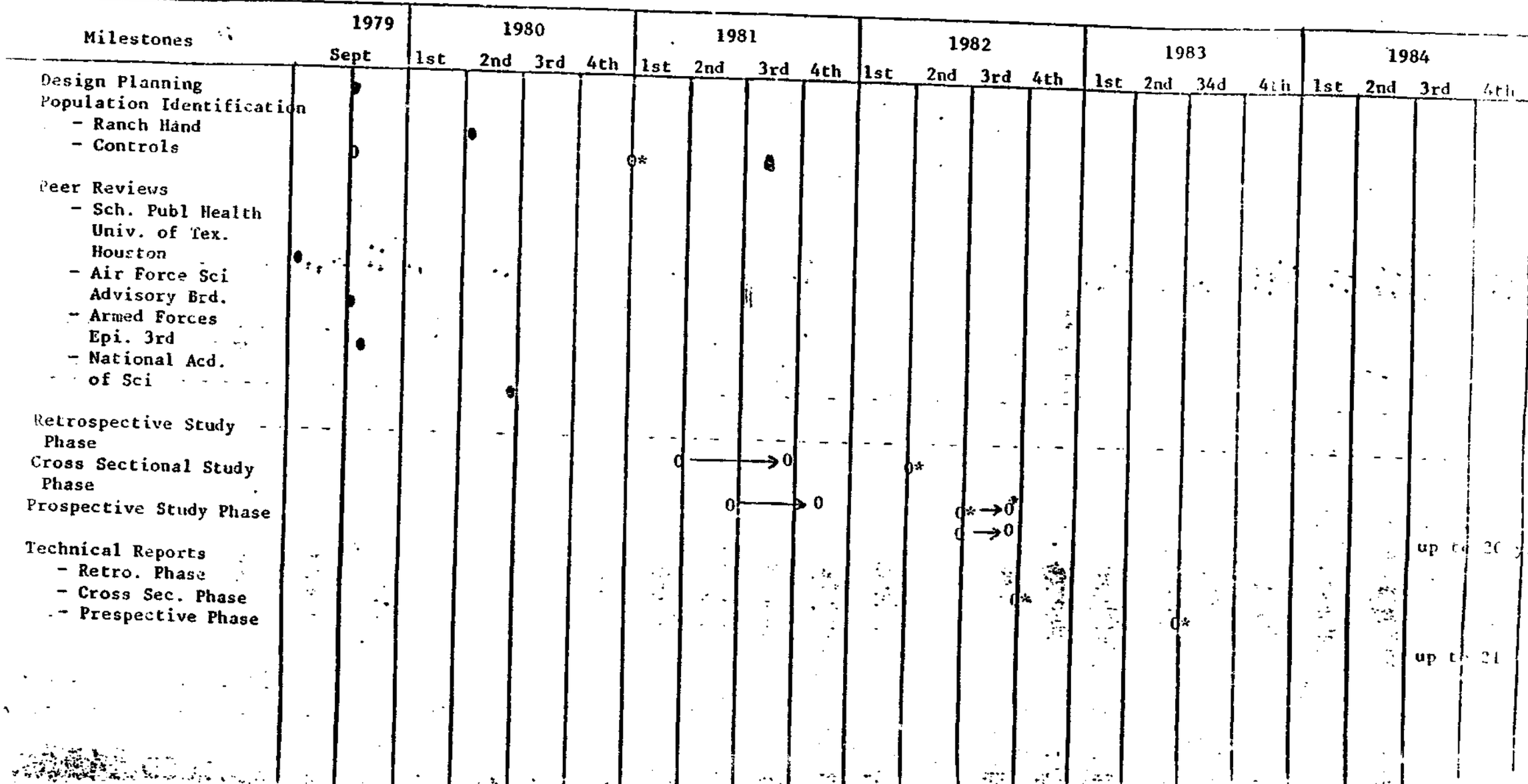
Phenoxy Herbicides and Contaminants

Date prepared
9 November

SCIENTIFIC ACTIVITY MILESTONE TIMETABLE

Projected Start 0 Accomplished ● Project Completion 0*

Calendar Years by Quarter



U.S. DEPARTMENT OF AGRICULTURE

SCIENTIFIC ACTIVITY REPORT -- FUNDING

Interagency Work Group on Phenoxy Herbicides and Contaminants

Title of Activity	Funding			
	FY80	FY81	FY82	FY83
1. Exposure Survey on Herbicides Including Phenoxys	100 K	230 K*	100 K*	
2. Use Survey on Herbicides Including Phenoxys	100 K	100 K	300 K*	
3. Survey of Phenoxy Herbicides Literature	4 K	4 K	4 K*	
4. Photolysis of 2,4,5-T	-	10 K	10 K*	
5. Biological and Economic Assessment of 2,4,5-T and Silvex	30 K	15 K	15 K*	

*Estimate - Includes USDA and State activities thru CSRC

DEPARTMENT OF AGRICULTURE

Interagency Work Group on Phenoxy Herbicides and Contaminants

Title of Activity	Funding		
	FY80	FY81	FY82
1. TCDD Residue Monitoring in Deer (Forest Service, Summer 1980)	$1,200*	0	0
2. 2,4-D Human Exposure Study (SEA-AR-NER-BARC-AEQI; December 1980)	85,000	2,000	0
3. Participation in Study of Herbicides and Spontaneous Abortions being Conducted by SRI International (October 1980)	100,000	0	0

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* All data collection completed in FY 79. Only report preparation to be done in FY 80.

NOTE: Proposed Epidemiology Feasibility Study among U.S. Forest Service Employees was cancelled.

Title of Activity:

TCDD Residue Monitoring in Deer

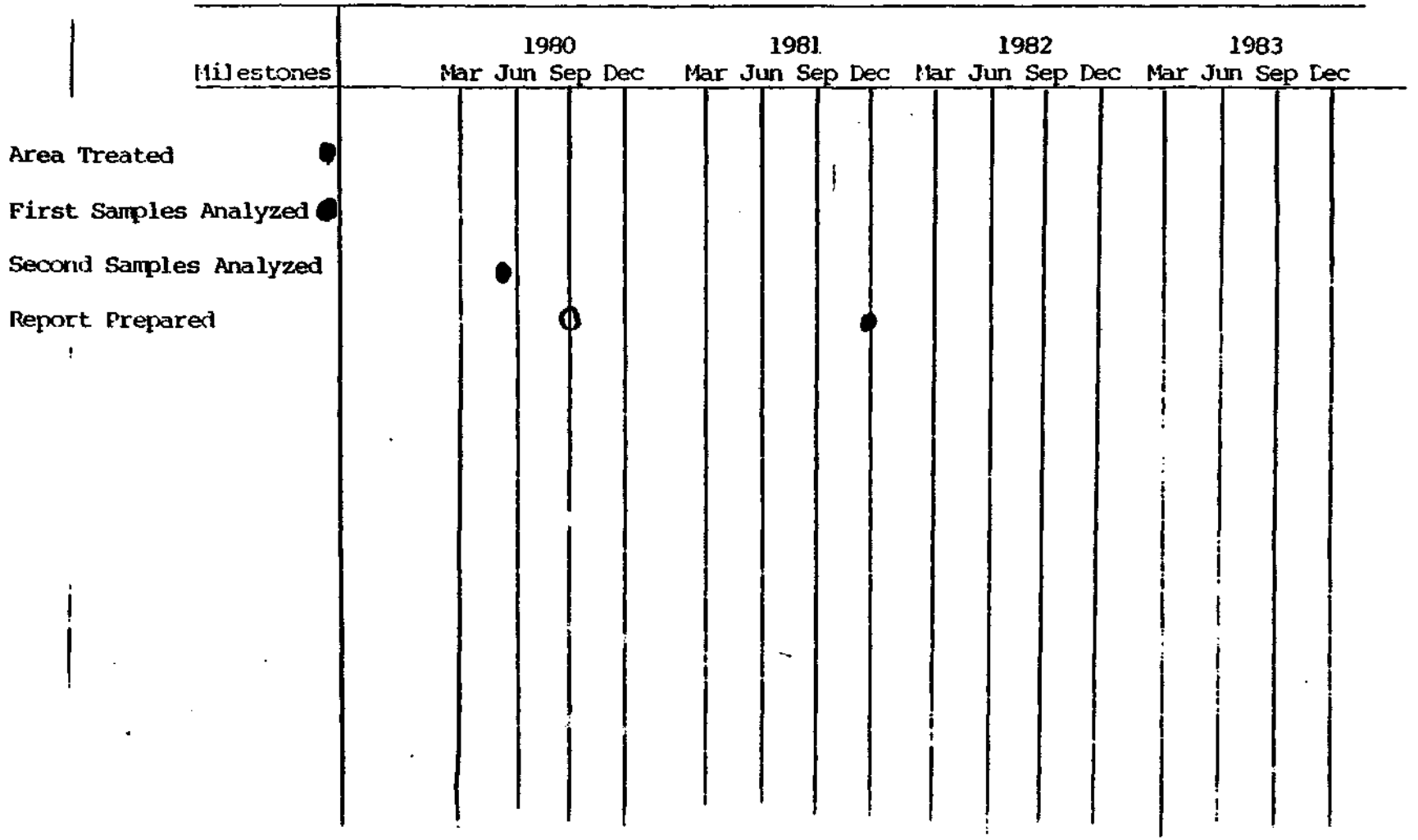
Interagency Work Group
Phenoxy Herbicides & Contaminants

Date:

August 1980

SCIENTIFIC ACTIVITY MILESTONE TIMETABLE

Projected O Accomplished ●



United States Department of Agriculture
Science and Education Administration
Agricultural Research Northeastern Region Beltsville Agricultural Research Center
Beltsville Maryland 20705

September 24, 1981

SUBJECT: Update - Scientific Activity Report

TO: L. Platt, Office of General Counsel, HHS

As requested, please find enclosed the subject report and funding levels for FY 81 and 82. Let me give you a status of these reports:

Title of Activity	Status
2,4-D Human Exposure Study	Completed
Herbicide Exposure to 2,4-D and Spontaneous Abortion	Completed
TCDD Residue Monitoring Study in Deer	Completed

The last study (TCDD Residue Monitoring Study in Deer) is complete, but a preliminary draft, subject to revision, is being submitted at this time. Consequently we must await a final draft before it can be officially concluded. Final reports are enclosed for the other two activities.

The U.S. Forest Service is considering funding a proposed study on Teratogenicity and Fetotoxicity of Environmental Chemicals to be conducted by Drs. H. Osterud and D. Campbell, University of Oregon Health Sciences Center in Portland, Oregon (enclosed).

I am pleased to note the Department of Agriculture has completed its activities in a timely fashion and can present the data to the Agent Orange Working Group for their consideration.

Philip C. Kearney

PHILIP C. KEARNEY, Chief
Pesticide Degradation Laboratory
Agricultural Environmental Quality Institute

Enclosures

cc:
A. Bertrand
D. Graham
W. Shaw
T. Kinney, Jr.

United States Department of Agriculture
Science and Education Administration
Office of the Administrator Agricultural Research
Washington, D.C. 20250

September 8, 1981

SUBJECT: Meeting with U.S. Forest Service, Region 5, on Blodgett Forest Deer Study on 2,4,5-T/TCDD

TO: Files

ATTENDEES: Brian Sturgess, FS
Larry Freeman, FS
John Borrecco, FS
Ralph Ross, ARS

PURPOSE

The subject study has been completed over one year. Recently EPA litigation attorneys requested additional data on bioaccumulation of TCDD in deer and elk. Questions were raised within USDA on the need for additional studies before the final reports of the various components from the Blodgett Forest Study have been completed and evaluated. Since I participated with the Forest Service in this study and was in San Francisco for other purposes, it was agreed that it might be worthwhile to inquire on the status of these reports.

FINDINGS

1. A final report from the FS will be written and forwarded soon. Hugh Black in Washington, along with John Borrecco (FS, Region 5) will assume the lead in preparing this report.

2. There are approximately 5 reports (segments of the overall study) which represent the total study.

3. Amalgamation of the reports is needed to determine the net effect of the study.

4. An administrative decision is needed to ascertain the need and mechanism on how these reports will be amalgamated.

5. The outcome of the overall study cannot be determined until this one final report is completed.

SUMMARY

The Forest Service and General Counsel should work together to determine how

these reports can be assembled. By copy of this memorandum and followup conversations with OGC and FS, hopefully, we can generate some action in this area.

Ralph T. Ross

RALPH T. ROSS
Assistant to Administrator

cc:
M. E. Carter, ARS
M. M. Breinholt, OGC
F. Honning, FS
W.C Shaw, ARS
T. J. Army, ARS
P. H. Kearney, ARS
B. Sturgess, FS
J. Borrecco, FS
R. E. Stewart, FS
D. A. Graham, FS