Uploaded to the VFC Website

February 2014

This Document has been provided to you courtesy of Veterans-For-Change!

Feel free to pass to any veteran who might be able to use this information!

For thousands more files like this and hundreds of links to useful information, and hundreds of "Frequently Asked Questions, please go to:

Veterans-For-Change

Veterans-For-Change is a A 501(c)(3) Non-Profit Organizaton
Tax ID #27-3820181
CA Incorporation ID #3340400
CA Dept. of Charities ID #: CT-0190794

If Veterans don't help Veterans, who will?

We appreciate all donations to continue to provide information and services to Veterans and their families.

https://www.paypal.com/cgi-bin/webscr?cmd=_s-xclick&hosted_button_id=WGT2M5UTB9A78

Note: VFC is not liable for source information in this document, it is merely provided as a courtesy to our members & subscribers.

10. R&D and Exploratory Development Programs on Defoliant/Anticrop Agents and Systems

A. Department of the Army, Fort Detrick

1. Technical Aspects of Defoliation and Vegetation Control Program

Prior Status

A brief history of Fort Detrick's role in the Army R&D program on agents and dissemination systems for defoliation is given in Fort Detrick Miscellaneous Publication 33, "Information Manual for Vegetation Control in Southeast Asia" by K. R. Irish, R. A. Darrow and C. E. Minarik. A detailed history of all activities in chemical and biological plant control is available in Fort Detrick Miscellaneous Publication 37, 1970 (Secret).

By 1967 agents ORANGE, BLUE and WHITE were in operational use in the RANCH HAND program in RVN for defoliation and crop destruction coordinated by MACV. An initial order of eight UH-1B/D (AGRINAUTICS) helicopter spray systems had been made available to Army divisional commanders for defoliation and anticrop activities.

Field requirements had developed for methods of controlling grasses and other vegetation in perimeters of base camps and other military installations in RVN, and for ground-based portable disseminators for control of enemy crop areas.

By October 1967, Plant Sciences Laboratories at Fort Detrick had completed a Special Defoliant Development Program involving investigations of rapid acting desiccants and defoliants.

Chronology

Aerosol Disseminator (ENSURE 210)

September 1967. An aerosol can device was developed at Fort Detrick for evaluation as handheld dissemination device for agent BLUE.

October 1967. Fort Detrick representative in RVN for evaluation of test device under field conditions.

26 August 1968. ENSURE requirement withdrawn.

Soil-Applied Herbicide (ENSURE 86)

September 1967. ENSURE requirement was received by Fort Detrick for a pelleted or granular material to be applied directly

6701

to soil or dissolved and applied as foliage spray for control of vegetation in perimeter areas in RVN. Minimal period of vegetation control was established as 1 year. The Fort Detrick proposal of a 2-year program of research with available materials such as bromacil and monuron, was indicated by USARV as too costly and required too much time.

June 1968. The earlier ENSURE 86 requirement was converted to an R&D program objective as it will require more than 1 year to satisfy certain critical requirements.

September 1968. A test and evaluation program of soil-applied herbicides including bromacil and Tandex was in progress at several CONUS locations by Plant Sciences Laboratories personnel. Contract research was initiated in Hawaii with the University of Hawaii and with Texas A&M University in evaluation of aerial dissemination equipment for granular herbicides.

January 1969. Tests of Kenapon (a dalapon ester for grass control) in Vietnam and by Fort Detrick CONUS were reviewed. Fort Detrick strongly advised against introduction of Kenapon into RVN as a vegetation control agent and recommended continuing use of BLUE for grass control.

August 1969. Bromacil and Tandex were reported as most effective chemicals for grass control in the CONUS and contract research programs.

March 1970. Recent field and greenhouse tests have shown that mixtures of bromacil and picloram mixtures are antagonistic resulting in less herbicidal effect than in separate treatments.

June 1970. The Fort Detrick R&D program for control of grasses was expanded to include growth retardant chemicals, with the objective of maintaining a low grass cover to reduce erosion. None of the materials in the current test program are considered militarily useful.

October 1970. Publication of Fort Detrick Technical Memorandum 212 "The lateral and vertical movement of four herbicides applied to a grassland soil" (ORANGE, WHITE, picloram, bromacil).

June 1971. Soil analysis of areas treated with BLUE at rates up to 12 gal/acre showed no movement of cacodylic acid to depths below the surface 4-inch soil layer.

Field tests and evaluations were continued with soil-applied herbicides and growth retardants. Bromacil has been found best on clay soils and Tandex on sandy soils for control of subtropical grasses.

Current Status

Fort Detrick data on chemical structure-biological activity of 30,000 compounds has been computerized so that searches can be made in a matter of 1 or 2 minutes that formerly took hours.

Pinolene, a resin polymer, increases the effectiveness of 2,4-D and other herbicides and presumably extends the period of herbicide absorption.

Combinations of Ethrel, an ethylene-releasing compound, and the desiccant endothall are being evaluated as nonherbicidal defoliants.

Evaluations are being made of the effects of extremely low dosages of ORANGE, BLUE, and WHITE on crop plants to assist in appraisal of crop damage claims.

References

See Section X.

2. Administrative Aspects of Defoliation/Vegetation Control Program

Background

The Army R&D program on herbicides and defoliants was started in 1943 with the establishment of Crops Division at Camp Detrick. Following a phase-out in 1957-58, the Division became active in defoliation and vegetation control research associated with the Vietnam operations.

On 1 Oct 1967, Crops Division became a Directorate with Dr. C. E. Minarik as Director, Plant Sciences Laboratories. The former Biological and Chemical Branches of Crops Division were given divisional status as Plant Pathology and Plant Physiology Division, respectively, and a third, Field Projects and Support Division, was added.

Following the Presidential announcement of 25 Nov 1969 (Appendix L), activities in the Plant Pathology Division were directed toward defensive aspects only. Under guidance from AMC, the FY 71 RDT&E Program Structure recommended research on chemical agents to be designated as Vegetation Control Investigations, Chemical under three tasks: (i) Vegetation Control Technology, (ii) Effectiveness, Employment and Dissemination Studies and (iii) Ecological Aspects of Vegetation Control. Task iii was new in the program and added because of the current concern on ecological effects of herbicide use.

6703

Chronology

24 July 1970. AMC requested MUCOM for alternative plans and recommendations for transfer of the Vegetation Control Program from Fort Detrick including: (a) total program at Edgewood Arsenal (EA), (b) total program execution at Dugway Proving Ground (DPG), and (c) program execution at EA with specified outdoor experimental activities (plots) at DPG. The proposed program to be funded at a level of $500,000 annually should have the following objectives:

(a) Maintain a scientific and technological base to provide assistance to DA on vegetation control.

(b) Evaluate commercial herbicides for military use.

(c) Evaluate commercial dissemination equipment for military use.

(d) Conduct RDT&E on materials and equipment not available from commercial sources.

September 1970. AMC provided guidance to MUCOM that transfer of Vegetation Control Program would be made to Edgewood Arsenal.

12 October 1970. Detailed plans for relocation of the Vegetation Control Program at Edgewood Arsenal by 30 June 1971 submitted to AMC as Annex II of recommended reorganization of Fort Detrick activities.

16 October 1970. Alternative plans suggested by CO, Fort Detrick to AMC involving the retention of the Vegetation Control Program at Fort Detrick facilities in view of the high cost of proposed transfer and the lack of suitable greenhouse, laboratory, and test plot facilities at EA.

March 1971. Dr. Minarik announced that a waiver had been granted through FY 72 for the proposed move of the Vegetation Control Program from Fort Detrick to Edgewood Arsenal. As of that time the administrative status of the program was undecided.

4 April 1971. Personnel and administrative jurisdiction of the Plant Pathology Division of Plant Sciences Laboratories were transferred from Department of Army to Plant Sciences Division, Agriculture Research Service, US Department of Agriculture. This Epiphytology Research Laboratory will remain in the previously occupied facilities at Fort Detrick and will conduct defense-oriented research on biological antiplant agents.

6704

June 1971. As of 25 June 1971 the Vegetation Control Program was placed under the administrative direction of Edgewood Arsenal. Staff and use of facilities will continue at Fort Detrick.

References

Irish, K. R., R. A. Darrow and C. E. Minarik. December 1969. Information manual for vegetation control in Southeast Asia. Misc. Publ. 33, Department of Army, Fort Detrick. AD 864 443.

Mattie, V. Z. November 1970. History of Crops Division--Plant Sciences Laboratories, 1943-1969 (U). Misc. Publ. 37. Department of Army, Fort Detrick (Secret). AD 512 829.

3. Technical and Administrative Aspects of Biological Anticrop Program

Status

A general synopsis of biological anticrop agents and systems up to the time of President Nixon's statement of 25 Nov 1969 renunciating biological warfare-may be found in the Secret publication dated November 1969, Biological Agents and Munitions Data Book, Technical Memorandum 74, Department of the Army, Fort Detrick.

Chronology

October 1969. Executive Order 11490, dated 29 Oct 1969, prior to President Nixon's 25 Nov 1969 announcement on CBW, assigned responsibility for defense of crops and livestock against CBW agents to US Department of Agriculture.

November 1969. Removal of offensive biological warfare R&D under President Nixon's announcement eliminated the program on offensive biological anticrop R&D conducted by the Plant Pathology Division of Plant Sciences Laboratories at Fort Detrick (Appendix L).

March 1970. Concensus of opinion in military agencies was that the Plant Pathology program at Fort Detrick should be transferred to US Department of Agriculture. The current program of that Division, as reported by Dr. [redacted], is being continued on a defensive basis and geared to USDA requirements to protect the principal crops of the United States. Primary crops under consideration are wheat, corn and soybeans.

June 1970. Defensive aspects of the Plant Pathology Division program will be funded by Army for FY 1971.

December 1970. Demilitarization plans for biological anticrop agents announced.

April 1971. Personnel in Plant Pathology Division at Fort Detrick transferred to US Department of Agriculture. Full funding and administration of defensive R&D program in biological antiplant studies to be assumed by USDA as of 1 July 1971.

B. AIR FORCE, AFSC (AFATL AND ADTC)

1. Stull Bifluid System

Status

Flight test evaluation of Stull Bifluid and ORANGE was made at Eglin AFB at the request of DDR&E. An earlier evaluation of the Stull system reported by AFATL had shown no advantage of Stull Bifluid over ORANGE.

In the 1968-69 test, studies of the biological effectiveness of Stull Bifluid and ORANGE were conducted by Plant Sciences Laboratories at Fort Detrick and determinations of spread factors and other physical data on the two agents were made by the Physical Sciences Division at Fort Detrick. Flight tests at Eglin AFB showed no significant difference in spray characteristics and consequent biological effectiveness between the Stull and A/A45Y-1 systems.

Fort Detrick data showed no signficant difference in biological effectiveness between Stull Bifluid and ORANGE. It was further shown by droplet studies that attempts to control spray drift by increasing droplet size would drastically reduce agent efficiency.

References

Hurtt, W. and R. A. Darrow. October 1968. Biological effectiveness of Stull Bifluid and ORANGE. Tech. Rept. AFATL-TR-68-122. Armament Development and Test Center, Eglin AFB, Florida.

Hurtt, W., R. A. Darrow, R. E. Klein, E. T. Harrigan, and W. R. Wolf. March 1969. Comparison tests of defoliants, Vol. II. Final Rept. 12 Jun-12 Sep 68. Tech. Rept. ADTC-TR-69-30. Vol. 2. Armament Development and Test Center, Eglin AFB, Florida.

Klein, R. E. and E. T. Harrigan. March 1969. Comparison tests of defoliants. Tech. Rept. ADTC-TR-69-30, Vol. 1. Armament Development and Test Center, Eglin AFB, Florida. (For Official Use Only)

2. Gel Stabilized Defoliants

Concept: Feasibility study to determine if gel stabilization ameliorates undesirable characteristics of otherwise potentially

useful defoliant/herbicide chemicals and improves methods of delivery of defoliants.

Status: Contract (PR 69-501) was initiated with Monsanto Research Corporation in December 1969. Thixotropic gels of several agents prepared under this contract were tested at Eglin AFB. Feasibility of technique was established.

Reference:

Long, R. L., et al. (Monsanto Research Corp.). September 1970. Gel stabilized defoliants. Tech. Rept. AFATL-TR-70-98. Air Force Armament Lab., Eglin AFB, Florida.

3. Ecological Studies at Eglin AFB

Status

The intensive applications of PURPLE, ORANGE, BLUE, and WHITE at Test Area C-52A at Eglin AFB have provided an excellent opportunity for evaluation of the ecological effects of high rates of herbicide application on vegetation wildlife and aquatic organisms.

Surveys of vegetation in the vicinity of the grid area (C-52A) conducted under a contract with the University of Florida showed a rapid disappearance of damage attributable to the heavy applications in 1963-64 and significantly less effect from the 1969 series of tests.

Soil residue studies have been made on areas receiving heavy applications of PURPLE and ORANGE in 1963-64 and more recent tests with BLUE and WHITE in 1967-68.

Dioxin analysis by the US Department of Agriculture laboratory at Beltsville of soil samples taken from grid areas receiving heavy applications of herbicide showed no dioxin present at any depth (December 1970). Bioassay analysis of samples to depths of 8 ft were repeated in June 1971 with no dioxin found.

A summary report on the ecological studies reported at the March 1971 meetings is given in Appendix K.

References

Ward, D. B. June 1970. Ecological records on Eglin AFB Reservation--Conclusion. Tech. Rept. AFATL-TR-70-55 (Univ. of Florida). Air Force Armament Laboratory, Eglin AFB, Florida.

Lehn, P. J., et al. August 1970. Studies to determine the presence of artificially induced arsenic levels in three freshwater

6707

streams and its effect on fish species diversity. Tech. Rept. AFATL-TR-70-81. Air Force Armament Laboratory, Eglin AFB, Florida.

C. NAVY: NAVAL AIR SYSTEMS COMMAND

See Section III.B. Dissemination Systems.

6208

V. R&D GOALS AND REQUIREMENTS

A. PROPOSED R&D GOALS

Items suggested by Dr. C. E. Minarik, US Army, Fort Detrick with partial inputs (1-8) by COL H. C. Kinne, based on experience as MACV J-3 Chemical Operations Division Officer (Sep 1970 Minutes).

1. True defoliant - nonherbicidal to preserve valuable lumber and provide minimal ecological disturbances.

2. More effective grass killer for large tropical grasses.

3. Faster acting defoliant for priority photo or visual reconnaissance.

4. Growth retardant for grasses on perimeters and mine fields without violating prohibition on soil sterilants.

5. Herbicide that promotes flame burning of grasses in standing water.

6. Herbicide effective at significantly lower rates of application.

7. Nonvolatile defoliant for contact use in densely populated areas.

8. Herbicide providing increased duration of effect for border stripping without violating prohibition on soil sterilants.

9. Nonarsenical rice agent.

10. Herbicide effective on bamboo.

11. Determine metabolic breakdown products in plants, soils, and water.

12. Determine persistence in tropical soils and water.

13. Determine biological activity of breakdown products in fish and wildlife.

14. Conduct ecological surveys in defoliated areas in cooperation with Vietnamese scientists.

15. Improve herbicide activity by formulation modification.

16. Investigate drift control through use of particulated agents.

17. Explore naturally occurring defoliants in fungi, bacteria, viruses, and insects.

B. ARMY REQUIREMENTS

In September 1970 minutes, Mr. [redacted] B6 CBR Agency, CDC, indicated that the following items were in preparation by US Army:

1. Revision of Qualitative Materiel Developments Objective (QMDO) for Antiplant Agent/Dissemination Systems, applicable to Army 85.

2. Small Developments Requirement for an Army Air Defoliant Dissemination System to include equipment suitable for mounting on vehicles, river boats and Army aircraft to disseminate insecticides, defoliants and anticrop agents.

C. AIR FORCE REQUIREMENTS

Required operation Capabilities (ROC) developed by Air Force during 1968-71 included principally:

1. Modular external dispenser of liquid defoliants and herbicides for high performance aircraft (PAU-8/A).

2. Modular disseminator with internal tank for liquid herbicides, insecticides and fertilizers for various low-performance cargo aircraft (PWU-5/A).

D. NAVY REQUIREMENTS

The Navy has no stated herbicide requirements (June 1971).

6710

VI. DEFOLIANT/HERBICIDE OPERATIONS IN RVN

Prior Status

The defoliation and crop destruction program conducted by 7th AF under operation *RANCH HAND* and coordinated by MACV reached maximum operational status in 1967 with more than 1,700,000 acres sprayed. Army units were also conducting limited-area applications of defoliants and herbicides using UH-1 dissemination system (eight AGRINAUTICS units) and limited ground-based equipment. Three agents, ORANGE, WHITE, and BLUE were supplied under AF procurement.

Chronology

January - August 1968. Herbicide policy review conducted in RVN by US Embassy-MACV to determine policy guidelines. Technical support in policy review was provided by Fort Detrick (four position papers prepared by Dr. Minarik and Dr. Darrow) and a short-term ecological survey was conducted by Dr. F. H. Tschirley of US Department of Agriculture.

1968-69. Conversion of RANCH HAND aircraft from C-123B to C-123K with addition of two jet engines.

January 1969. Twenty-one additional AGRINAUTICS spray systems ordered for UH-1 Army aircraft.

15 April 1970. Use of ORANGE in RVN temporarily suspended by Deputy Secretary of Defense Packard.

May 1970. Herbicide Reporting System (HERBS) established by MACV to process herbicide mission data and record all available information.

June 1970. Inactivation of 12th Special Operation Squadron, 7th AF, for RANCH HAND operations with reduction in general operational level in defoliation program.

December 1970. White House statement indicated a phase-out of herbicide operations by mid-1971 with current restriction of defoliation to perimeters of fire bases and US installations. (See Sec. VII.B.)

February 1971. Ambassador Bunker and General Abrams announced termination of crop destruction program. (See Sec. VII.B.)

Current Status

As of June 1971, decisions on the nature and conditions of use of herbicides in RVN were still pending at higher headquarters.

6711

References

Warren, W. F. August 1968. A review of the herbicide program in South Vietnam (U). CINCPAC Scientific Advisory Group Working Paper No. 10-68. CINCPAC Scientific Advisory Group, FPO San Francisco 96610. (Secret)

Irish, K. R., R. A. Darrow, and C. E. Minarik. December 1969. Information manual for vegetation control in Southeast Asia. Misc. Publ. 33. Department of the Army, Fort Detrick, Frederick, Md.

Comments on the operational program in RVN are reported in the following subcommittee minutes:

May 1969	COL H. C. Kinne
Dec 1969	MAJ [redacted] b6
Jun 1970	COL Bruce Whitesides
	MAJ [redacted] b6
	Dr. [redacted] b6
Dec 1970	Dr. [redacted] b6
Jun 1971	Dr. [redacted]

6712

VII. DEFOLIATION/ANTICROP POLICIES AND PROGRAMS

A. CHRONOLOGY

30 June 1967. Creation of Defoliants/Anticrop Systems Subcommittee of Joint Technical Coordinating Group for Chemical/Biological.

21 September 1967. Initial meeting of Defoliants/Anticrop Systems Subcommittee of JTCC/CB at Fort Detrick; LT [redacted] USAF, Chairman. b6

February 1968. Press release by Department of Defense of summary of Midwest Research Institute report on assessment of ecological impact of herbicides used for defoliation and crop destruction in RVN (Appendix M).

August 1968. Comprehensive herbicide policy review of RVN operations completed by American Embassy-MACV recommending general continuation of program.

April 1969. Engineering development programs at Eglin AFB transferred from Air Force Armament Laboratory (AFATL) to Armament Development and Test Center (ADTC). Exploratory and advanced development mission remained with AFATL.

June 1969. President Nixon requested a review by the Arms Control and Disarmament Agency and the State and Defense Departments of chemical and biological warfare.

29 October 1969. Dr. [redacted] b6 Science Adviser to the President, announced partial curtailment of the use of 2,4,5-T based on results of laboratory studies by Bionetics Research Laboratories for National Cancer Institute showing 2,4,5-T to cause teratogenic or fetal deforming effects in laboratory animals. (Appendix F). Associated action by the Department of Defense was to restrict the use of 2,4,5-T (component of ORANGE) to areas remote from population.

25 November 1969. President Nixon renounced any resort to chemical and biological warfare and promised to destroy US stockpiles of such weapons (Appendix L). Riot control gases and defoliants were not included.

December 1969. Dioxin reported by Dow Chemical Company to be a possible source of teratogenic effects of 2,4,5-T.

15 April 1970. Departments of Agriculture, HEW, and Interior announced restriction on use of 2,4,5-T in populated areas and on food crops (Appendix G). Deputy Secretary of Defense Packard

announced temporary suspension of the use of ORANGE (comprised of 2,4,5-T and 2,4-D).

19 June 1970. Department of Interior bans all use of 2,4,5-T on public lands administered by Interior Department.

October 1970. Defense Appropriation Act (Public Law 91-441, 7 Oct 1970) specifies that the National Academy of Sciences conduct a survey of the ecological effects of use of herbicides with a report to Congress and the President 1 March 1972.

26 December 1970. White House announced a phase-out of herbicide operations in RVN with restriction on use to perimeters of fire bases, US installations or remote unpopulated areas. Ban for herbicide ORANGE remains in effect. (See Sec VII, B.)

February 1971. Ambassador Bunker and General Abrams announced the termination of crop destruction program in RVN.

May 1971. Authorization by US Army Materiel Command for continuation of Vegetation Control program at Fort Detrick under administrative responsibility of Edgewood Research Laboratories at Aberdeen Proving Ground.

May 1971. Initiation of DDR&E-sponsored Study on Military Utility of Herbicides by Engineer Strategic Studies Group to be completed by 15 December 1971.

B. DISCUSSION TOPICS AND PUBLIC RELEASES

Note: Restricted principally to subcommittee meetings held subsequent to May 1969 in which representatives of CINCPAC, MACV, and JCS participated. Items are referenced to minutes of specific meetings.

May 1969

CINCPAC

Intelligence reports on effectiveness of defoliation and anti-crop missions in RVN.

Disposal of washing and flushing water at herbicide loading sites.

Evaluation of future capabilities of RVN forces to conduct defoliation.

Nature and quantity of future stockpiles of defoliants.

6714

MACV

Increase in use of helicopters for defoliation and crop destruction missions. Continued use of ORANGE in UH-1 systems by elimination of paint-softening problem by use of lard or grease coating on aircraft.

Payment of claims for alleged herbicide damage to rubber trees in RVN.

Indorsement of intensive vegetation control program by field commanders; benefits derived from defoliation missions.

December 1969

CINCPAC

Feasibility of transfer of defoliant capability to VNAF.

MACV

Reaffirmation of August 1968 Herbicide Policy Review plan for defoliation targets.

Cut back in RVN defoliation operations in spite of remaining defoliation requirements.

New defoliation targets consisting of fields for cattle raising, Rome-plowed areas and waterway clearing in the Delta.

Problems involved in use of high performance aircraft for defoliation.

June 1970

MACV

Inactivation of 12th SOS in RANCH HAND operations.

Immediate requirement for collection and collation of all technical data in RVN resulting from herbicide operations.

Strong military requirement existent for defoliant to use at fire support bases and base camp perimeters.

7th AF

Problems in handling defoliation material because of allocation of herbicides to ARVN on arrival in RVN.

Operational problems for 12th SOS, 7th AF because of tri-mission responsibilities and requirement to deconfigure and reconfigure aircraft for spray missions.

Closer scrutiny of pollution problems resulting from RVN defoliation program.

Requirement to retrain AF crews involved in herbicide missions with diminished frequency of missions.

PACAF

Use of herbicides in vegetation control on base perimeters in PACAF area. Limitations are: Proximity to agricultural crops, living quarters of local nationals, design of the perimeter defense system, and unsuitability of the three chemical agents permitted for use in RVN.

Cessation of tests with Kenapon for tropical grass control with increased public concern over use of herbicides.

September 1970

JCS

Current status of herbicide program as outlined in letter by D. J. Dooley, Deputy Assistant Secretary of Defense to Senator C. E. Goodell, 14 August 1970 (Appendix N).

Current MACV programmed sortie rate for herbicide operations.

Status of WHITE supplies following suspension of ORANGE on 15 April 1970.

Changes in approval authority for herbicide operations.

Rejection by US Senate of proposed amendment to Defense Appropriation Bill to terminate herbicide operations in RVN.

AFLC

Mr. [redacted]66 representing SAAMA/SFQT, discussed the impact of the interim guidelines for Federal Agencies under the National Environmental Policy Act (NEPA). The guidelines state that at the inception of a major action, or in the continuation of an existing program initiated prior to the passage of the NEPA, if appraisals indicate that (1) a significant adverse environmental effect will result from a proposed action, or, (2) a proposed action is likely to be controversial with respect to environmental effects, a five-point draft environmental statement must be prepared and submitted to the Council on Environmental Quality.

Activities or actions of the following types should be assessed carefully for the necessity of preparing an environmental statement:

(1) Initiation of development of new weapon systems.

(2) Programs for weapons testing.

(3) Large-scale training operations.

(4) Programs for utilization of pesticides and herbicides.

(This is only a partial list.)

Preparation of an Environmental Impact Statement must include the following information:

(1) Total impact of proposed action on environment.

(2) State any adverse environmental effects which cannot be avoided.

(3) List alternatives to proposed actions.

(4) Assessment of the action's cumulative and long-term effects is required.

(5) An inventory of all irreversible and irretrievable commitments of natural resources.

December 1970

Army

Development and activation of HERBS (Herbicide Reporting System) to record on computer tape by ADP techniques all pertinent data from available records of spray missions in RVN.

CINCPAC

(1) Spray Operations in Vietnam

(a) Available assets dedicated to herbicide program

(b) Current and future spray sortie rates

(c) Herbicide materials available

(d) UC-123 defoliation operations

6717

(2) Herbicide Review - Saigon

(a) Tasking by Ambassador

(b) Committee membership

(c) COMUSMACV position

(d) Present status of final report

(3) Suspension of BLUE Shipments

(4) Vietnamization Program

(5) ORANGE Stockpile in Vietnam

(6) Herbicide Stockpiles Elsewhere in PACOM-US Government Restricted Materials Thailand and Okinawa (Kadena)

JCS

Status of Vietnamization as related to the herbicide program.

Future consideration by Senate of Geneva Protocol.

Possible action by MACV relative to stocks of ORANGE in RVN.

Recent statements of policy concerning the defoliation program in RVN are given in the following two releases:

(1) White House Statement issued on Saturday, 26 Dec 1970:

"In response to the President's direction to reduce the use of herbicides in Vietnam, the Secretary of Defense has reported the following actions to the President:

"--Steps are being taken to assure that there will be strict conformance in Vietnam with policies governing the use of herbicides in the United States.

"--Ambassador Bunker and General Abrams are initiating a program for an orderly, yet rapid phase-out of the herbicide operations.

"--During the phase-out, the use of herbicides in Vietnam will be restricted to the perimeter of fire bases, in US installations, or remote unpopulated areas.

"--The ban on herbicide known as "ORANGE" remains in effect."

6718

(2) 29 Dec 1970 statement of Jerry W. Friedheim, Acting Assistant Secretary of Defense for Public Affairs:

"Secretary of Defense Melvin R. Laird has, as we have previously reported, taken steps to insure that herbicide usage in South Vietnam will conform to the policies governing usage in the United States. As a result, the stresses and risks involved in South Vietnam will be no greater than those sustained by the United States population and the United States environment in normal peacetime activities.

"Deputy Secretary David Packard last spring restricted all use of defoliant ORANGE, and that ban remains in effect. In addition, at that time use of other defoliants (BLUE and WHITE) was strictly limited to areas remote from population.

"General Abrams is now initiating in South Vietnam an orderly phase-out of the herbicide operations to be completed by next spring.

"It is important to note that estimated herbicide coverage for 1970 through September is 75% less than that for the same period in 1969."

On 20 Feb 1971, Ambassador Bunker and General Abrams publicly announced the end of the use of chemicals to destroy crops in RVN. Limited herbicide operations would continue in remote jungle areas away from heavily populated centers but would be limited to spraying from helicopters and ground machines, in a manner currently authorized within the United States within the guidelines set forth by the US Department of Agriculture.

CINCPAC

Defoliation as a method to achieve interdiction.

Requests by MACV to use herbicides at fire bases.

Current status of helicopter defoliation in RVN.

Visit of ESSG team at CINCPAC and RVN.

Conditions of remaining stockpile of herbicides in Vietnam.

JCS

Discussion of the chronological sequence of events concerning herbicide policies and programs in RVN which have taken place since the December 1970 subcommittee meeting. Decisions on the nature

6719

and conditions of use of herbicides and defoliants are still pending at higher headquarters since the suspension on the use of ORANGE in April 1970, by Deputy Secretary of Defense Packard.

C. POLICY STATEMENT ON HERBICIDES BY ARMED FORCES PEST CONTROL BOARD

The following statement from Minutes, March 1970, Item 2.f., quoted by Mr. Vandeventer, SAAMA, presents the policy of the Armed Forces Pest Control Board in relation to use of herbicides in maintenance and tactical situations:

"The Armed Forces Pest Control Board (AFPCB) has an express interest in herbicides used for the control of noxious vegetation in the operation and maintenance of military installations. Weed control is conducted by personnel specifically trained in the use of herbicides and is usually directed toward the control of specific plants while leaving desired species. Other uses of herbicides entail soil sterilization in restricted areas wherein any vegetation may be undesirable, i.e. perimeter fences, parking lots, adjacent to building and POL areas. Such use requires a variety of herbicides with specific properties of selectivity, minimal animal toxicity, persistency and ease of handling. The use of weed control agents by installation maintenance engineers should be considered apart from the strictly tactical use of these and other herbicides by Operation RANCH HAND. The AFPCB has a vital concern with the safe, effective use of herbicides by Department of Defense personnel in the maintenance of military installations. Tactical use of herbicides is not the concern of this Board."

6720

VIII. SURVEYS AND ORGANIZATION ACTIVITIES RELATED TO DEFOLIATION/ANTICROP

A. AAAS HERBICIDE ASSESSMENT COMMISSION

Prior Status

At its Dec 1966 annual meeting, the American Association for Advancement of Science (AAAS) adopted a resolution initiated by Dr. E. W. Pfeiffer, University of Montana in which AAAS: (1) Expresses concern on the long-range consequences of the use of biological and chemical agents on the environment; (2) establishes a study committee; and (3) volunteers cooperation of AAAS with government agencies in evaluation of defoliation programs which modify the environment and affect ecological balance on a large scale.

In Sep 1967, AAAS President [redacted], b6 suggested to Secretary of Defense McNamara that the National Academy of Sciences conduct a study of short- and long-range effects of military use of chemical agents that modify the environment. Dr. [redacted], DDR&E, responded for DOD that a nonprofit research organization b6 would review and assess the information and that National Academy of Sciences would be asked to review the study. The review and assessment of ecological effects of extensive or repreated use of herbicides was conducted by Midwest Research Institute (MRI) and final report submitted in December 1967 (see reference, W. B. House et al. 1967). Reviews of the MRI reports by NAS and AAAS indicated a need for factual information on ecological affects of herbicide use and particularly of repeated or heavy herbicide applications such as military defoliation in Vietnam.

Chronology

March-April 1968. At the invitation of US State Department and MACV, Dr. [redacted], b6 Agricultural Research Service, USDA, participated in the 1968 American Embassy-MACV Herbicide Policy Review and conducted a 30-day ecological survey of the effects of Vietnam defoliation. His report was published in Science 163:779-786, 21 Feb 1969. Dr. Tschirley had previously served as project leader for ARS defoliation tests in Puerto Rico and Texas conducted under ARPA Order 424. His report represents the first ecological survey of defoliation in Vietnam.

July 1968. AAAS Board of Directors in a series of reports in the 19 July issue of Science recommended that a field study of defoliation be conducted in Vietnam under auspices of United Nations. Four supplementary statements by various Board members expressed minority and divergent viewpoints on the proposed study and continuation of the military defoliation program.

December 1968. AAAS Board of Directors at its December meeting announced that the AAAS "would participate in the study of the use of herbicides in Vietnam" and authorized the formation of an ad hoc committee to prepare specific plans for conduct of such a field study.

March 1969. Dr. [redacted] b6, University of Washington, and Dr. E. W. Pfeiffer (initiator of AAAS commitment in Vietnam defoliation study) made a 15-day ecological survey in Vietnam with funds supplied by the Society for Social Responsibilities in Science.

December 1969. Dr. [redacted] b6 Harvard University biologist, was named head of a committee to prepare plans for a field study of defoliation in Vietnam with $50,000 in funds supplied by AAAS.

March 1970. Dr. [redacted] b6 Chairman, appointed Dr. Arthur H. Westing, Department of Biology, Windham College, Putney, Vermont, as Director of AAAS Herbicide Assessment Commission.

June 1970. A planning conference sponsored by the AAAS Herbicide Assessment Commission (HAC) was held at Woods Hole, Massachusetts to develop plans for a survey of ecological effects of defoliation in RVN. Twenty-one specialists attended the meeting. Dr. [redacted] b6 b6 Fort Detrick participated. Trip report by participant [redacted] International Economist, Foreign Economic Development Service, US Department of Agriculture is included as Attachment 6 of Minutes, Dec 1970 Subcommittee Meeting. The report summarizes the significant social, ecological and economic consequences desired from the use of herbicides in Vietnam.

August 1970. Four representatives of the AAAS, HAC spent about 6 weeks in South Vietnam on a preliminary or "feasibility" survey of ecological effects of defoliation. Members of the group were Dr. [redacted] b6 Dr. [redacted] Dr. [redacted] b6 Harvard Medical School and Mr. [redacted] graduate student, Department of Biology, Yale University. A report of the survey was given at the subsequent AAAS annual meetings in Dec 1970 and excerpts published in Sierra Club Bulletin 56(4):4-9, April 1971 (Appendix O).

December 1970. Report of the AAAS Herbicide Assessment Commission was presented 29 Dec at the AAAS meetings in Chicago, including presentations by Meselson, Constable and Westing on the August 1970 survey. At the same meeting a AAAS Panel Session was held on "Implications of Continued Military Use of Herbicides in Southeast Asia, Dr. Herbert Scoville, Jr., Chairman. Participants were: [redacted] b6 b6 [redacted] US Department of Agriculture; General William Stone, US Army retired, formerly CG, ACSTOR; [redacted] Department of b6

6722

Government, Harvard University; [redacted] b6 Professor of Law, University of Wisconsin; Honorable Richard D. McCarthy, US House of Representatives; and [redacted] b6 Harvard University. Details of the meeting and transcribed recordings of the panel session are given in Minutes, March 1971, as Inclosures 3 and 4.

January 1971. Release of an unpublished summary "Background Material Relevant to Presentations at the 1970 Annual Meeting of the AAAS" prepared by Dr. Meselson, Dr. Westing and Dr. [redacted] b6 including discussions of land and peoples of South Vietnam (pp. 8-13). military use of herbicides in South Vietnam (pp 14-22), and herbicide toxicology, stillbirths and birth defects (pp 23-47). The August 1970 feasibility survey of the AAAS Commission examined birth records in Vietnamese hospitals to evaluate the "feasibility of demonstrating any change in pattern of births that might have resulted from exposure to 2,4,5-T or its contaminant, dioxin, reported to be teratogenic under certain laboratory conditions in certain animals." Comparisons were made with data presented in the earlier Cutting report on stillbirths and birth defects in Vietnam (December 1970).

April 1971. Publication of an article by John Constable and Matthew Meselson "The Ecological Impact of Large Scale Defoliation in Vietnam" in Sierra Bulletin for April 1971 (Appendix O). This article contains much of the information presented at the Dec 1970 AAAS meetings.

Current Status

The AAAS Herbicide Assessment Commission is continuing to function. No formal report of the Commission has been made available.

References

House, W. B. et al. December 1967. Assessment of ecological effects of extensive or repeated use of herbicides. Midwest Research Institute, Kansas City, Missouri. Final Report 15 Aug-1 Dec 67. Contract DAHC 15-68-C-0119, ARPA Order 1086, 369 pp. AD 824 314.

Orians, G. H. and E. W. Pfeiffer (Interview with). 1969. Mission to Vietnam. Parts 1 and 2. Scientific Research June 9, 1969, pp. 22-23, 27-28, 30; June 23, 1969, pp. 26-27, 29-30.

Tschirley, F. H. 21 February 1969. An assessment of ecological consequences of the defoliation program in Vietnam. Science 163:779-786.

Cutting, R. et al. December 1970. Congenital malformations, hydatiform moles and stillbirths in the Republic of Vietnam, 1960-1969. Dept. of Defense unnumbered report. 29 pp. Govt. Printing Office, Washington, D. C.

6723

B. NATIONAL ACADEMY OF SCIENCES ECOLOGICAL SURVEY

Prior Status

In March 1967 the Board of Directors of American Association for Advancement of Science (AAAS) created an ad hoc Committee on Environmental Alteration with Dr. Rene Dubos, Rockefeller University, Chairman. The committee recommended that continuing studies of the effects of chemical and biological warfare agents on soil, biota and human health be conducted by the National Academy of Sciences.

In September 1967, AAAS President [redacted] suggested to Secretary of Defense McNamara that the National Academy of Sciences-National Research Council (NAS-NRC) conduct a study of short- and long-range effects of [redacted] chemical agents which modify the environment. Dr. [redacted] DDR&E, responded for DOD that a nonprofit research organization would review and assess the information followed by a review by NAS-NRC. Midwest Reseach Institute prepared this review, released in December 1967. A NAS-NRC panel headed by Dr. A. S. Crafts, University of California, reviewed the MRI report pointing out the general need for factual information on ecological consequences of herbicide use, particularly of repeated or heavy applications. (Subsequent actions were taken by AAAS in the establishment of a Herbicide Assessment Commission to evaluate the ecological effects of Vietnam defoliation, see AAAS, VIII. A.)

Chronology

October 1970. Defense Appropriation Act (Public Law 91-441, 7 Oct 1970) passed specifying that the National Academy of Sciences conduct a survey of the ecological effects of use of herbicides. A report was to be made to Congress and the President by 1 March 1972 in this legislation developed by Senator Thomas J. McIntyre. Funding for the survey was to be provided by the Department of Defense.

December 1970. Initial plans for the National Academy of Sciences survey were developed by DDR&E. The survey by NAS is to be conducted on a contract basis for DOD in three phases involving a 6-month period for orientation and review of available data, 6 months in-country survey and 6 months for preparation of final report. (Minutes, Dec 1970, Item 7.g.)

March 1971. Dr. Anton H. Lang, Director MSU/AEC Plant Research Laboratory at Michigan State University, has been named chairman of the NAS [redacted] ecological survey of the defoliation program in RVN. Mr. [redacted] DDR&E, is project officer for DOD on the contract; [redacted] and Dr. [redacted] are assistant project officers on the DOD committee assisting NAS. Preparations and actions to be taken by DOD personnel in support of the National

6724

Academy of Sciences ecological survey were outlined at a meeting at CINCPAC, 8-10 Feb 1971.

The NAS Committee will submit an interim report by 1 Jan 1972 as specified under the Defense Appropriation Act. Funds provided for the contract include $50,000 to initiate the survey and $750,000 for the survey and report to be completed in FY 1972.

June 1971. Dr. [redacted] Chairman of the NAS Committee on Ecological Survey, completed selection of members of the committee. Following a planning meeting scheduled for July, survey work in RVN will be initiated. Dr. [redacted] Staff Officer for the NAS Committee, has assembled more than 350 references dealing with the defoliation problem and its ecological aspects.

Current Status

The NAS ecological survey is in progress. An extension of time has been requested beyond the original scheduled completion date for preparation of reports.

A companion study to the NAS effort is in progress by the Engineer Strategic Studies Group (ESSG) dealing with the military utility of herbicides (see VIII. C.).

C. DDR&E STUDY ON MILITARY UTILITY OF HERBICIDES BY ESSG

Prior Status and Background

Public Law 91-441, 7 Oct 1970, requires the Secretary of Defense to contract with the National Academy of Sciences (NAS) for a comprehensive investigation to determine the ecological and physiological effects of the defoliation program carried out in South Vietnam. By 1 March 1972, the Secretary of Defense is required to transmit the NAS study (together with his comments and recommendations) to the President and the Congress. To assist the Secretary in presenting a complete and balanced report it is necessary to evaluate the military advantages and disadvantages of herbicides.

To satisfy this requirement and an associated study required by NSSM 112 on the potential military utility of herbicides by all military services in other possible areas (theaters of operations) around the world, DDR&E selected the Engineer Strategic Studies Group (ESSG) to conduct the study which is scheduled for completion by 15 December 1971.

Chronology

May 1971. Prospectus and plan of work completed by ESSG. Study team departed for CINCPAC and MACV to begin data collection phase of plan.

6725

July 1971. ESSG study team returned from travel and data collection in RVN.

Current Status

Study in progress with scheduled date of 15 Dec 1971 for completion of final report. A copy of the prespectus was included as Inclosure 3, Minutes 9-10 June 1971.

6726

IX. SUBCOMMITTEE RECOMMENDATIONS AND SUBSEQUENT ACTION

September 1967

Recommendations:

a. Revision of specifications for Agent ORANGE to include the infrared test for quality of product. (Air Force)

b. Consideration of development of a large capacity system for dispensing granular or pelleted chemicals. (Air Force)

Action:

a. Air Force Purchase Description AFPID 6840-1 issued for interim use in procurement specified quality control tests by infrared analysis (Minutes, Sep 1968, Item 4.b.). A later amendment dated 10 Feb 1970 to AFPID 6840 dated 2 Jan 1970, specifies gas-liquid chromatographic techniques for analysis of ORANGE (Minutes, Mar 1970, Item 2.d.).

b. No exploratory development or design has been conducted by Air Force of a dissemination system for granular or pelleted chemicals. However, both Navy and Army have developed similar systems for aerial dispersal of granules or pellets from UH-1 helicopters (PAU-5(XM-1). The Army version was type classified in Sep 1969 by US Army Medical Equipment R&D Laboratory, Fort Totten, New York (Minutes, Dec 1969, Item 3).

June 1968

Recommendations:

a. Establishment of procedures which will insure a feedback of information on defoliation and anticrop operations in Vietnam.

b Resolution of the controversy on the Federal Stock Classification for the defoliation agent ORANGE and obtain a fully coordinated Purchase Description without undue delay.

Action:

a. Representatives of CINCPAC and MACV concerned with the herbicide and defoliation program were invited to participate in the subcommittee meetings starting with the May 1969 meeting.

b. The controversy between Air Force and Army concerning the Federal Stock Classification of herbicides and defoliants was resolved

on 8 Aug 1969 in a memorandum from Assistant Secretary of Defense (Installation and Logistics) to Air Force and Defense Supply Agency which directed the management transfer of agents ORANGE, WHITE, and BLUE to Air Force under FSC 6840. Subsequently, Air Force Purchase Description AFPID 6840, dated 2 Jan 1970, and Amendment No. 1, dated 10 Feb 1970, were used in procurement contracts for ORANGE (Minutes, Mar 1970, Item 2.d.).

June 1970

Recommendations:

a. MACV with the assistance of USARPAC should be tasked with the responsibility of collecting, analyzing, and recording all pertinent technical data on herbicide operations in RVN. Data should be collected on all targets sprayed and include. Date, time, herbicide used, and results achieved, if known. PACAF and/or CINCPAC should be tasked with the responsibility of collating this RVN herbicide data and evaluating results from a military and civilian viewpoint. The data should be collected and recorded as soon as possible to prevent its loss due to suspension of herbicide operations or withdrawal from RVN.

b. Difficulties reported by MACV and 7th AF with handling supply and administration of herbicide material in RVN indicate the need for control of this material by a single US agency in RVN. Either MACV or 7th AF should be designated as material manager.

Action:

a. Plans for collecting and recording technical data on herbicide operations in RVN have been formalized and funding was provided by listing the program as a line item in the Defense Appropriation Bill for FY 71. The Herbicide Reporting System (HERBS) was established by MACV in May 1970 (Minutes, Dec 1970, Item 3.e.).

b. Because of a 1962 pact, the RVN own all defoliant agents in-country and no single US Agency could control the material. In the opinion of CINCPAC this recommendation is being partially fulfilled.

September 1970

The following recommendations were made by the subcommittee to SAAMA (AF) for disposal of chemical herbicide raw material components in contractor facilities:

a. The chemical compounds 2,4-D and 2,4,5-T are components of herbicide ORANGE. Quantities of these compounds have been held at contractor's locations pending their use in fabrication of additional

6725

ORANGE. Current EPA consumption rates have been radically decreased resulting in an over supply of ORANGE and a restriction has been placed on further use of ORANGE. Consequently these components are no longer required. The recommendation by the Joint Technical Coordinating Group, Subcommittee is, therefore, that disposal be made of these components.

b. Disposal of these components should be investigated as follows:

(1) First, queries should be made to see if any agency has use for the components in their present form. Agencies queried should include, but not necessarily be limited to, (i) Department of Interior regarding possible use on forest or rangeland, (ii) Department of Agriculture regarding possible use in forests, (iii) US Army Engineers regarding use in waterways, on rights-of-ways or military installations, and (iv) MACV, to see if 2,4-D alone could be used during the suspension of use on herbicide ORANGE.

(2) Second, should none of these agencies have a use for the components, destruction by incineration is required. In this regard the following must be determined:

(a) The contractors (particularly Dow who possesses a destruction facility) should be queried as to capability and cost of destruction of components.

(b) AMC should provide information on the transportable detoxification/demilitarization facility being constructed for chemical agent detoxification. This facility might be capable of incinerating these components at their storage location.

(c) Other DOD incineration facilities capable of accomplishing this task should be located and costs of transportation to those sites calculated.

c. Upon receipt of the information discussed above, a cost-effective decision can be made and the most economical means of disposal determined.

Action:

The contractor surplus inventory of unmixed components of ORANGE and of BLUE remains in storage at Kelly AFB. Government agencies such as the US Forest Service, Bureau of Reclamation, etc. with a requirement for 2,4-D and 2,4,5-T, utilize only low-volatile esters and are not potential customers for the contractor inventory. A proposal from Anaul Company to purchase the entire supply of BLUE at its original cost to the Government

6729

was not accepted because of DSA surplus property restrictions. A related AF proposal recommending incineration for the Gulfport stockpile of ORANGE received nonconcurrence at higher headquarters (Minutes, June 1971, Items 3.a.(1) and (2)).

December 1970

Recommendations (with designated action agency and personnel):

a. Technical Order 42-C-1-17 on use of herbicides, should not be revised at this time to eliminate reference to ORANGE herbicide. (Action - SAAMA, Mr [redacted] b6

b. A decision on the use of disposal of ORANGE herbicide now stored at Gulfport, Mississippi and in SEA should be expedited. (Action - JCS (J5), COL H. C. Kinne)

c. Herbicide spray equipment removed from C-123 aircraft in Vietnam should be identified and held in Vietnam pending future decisions on Vietnamization or resumption of C-123 operations. (Action - CINCPAC, Dr. Warren)

d. The normal butyl ester of 2,4-D contract termination inventory material is recommended for use in SEA in place of WHITE for defoliation and crop control. Technical details on use, application, and identification should be worked out between SAAMA/SFQT and Fort Detrick, Dr. [redacted] (Action - SAAMA, Mr. [redacted] b6 b6

Action:

a. Recommendation was for no action.

b. Decision at Command level has not been reached concerning disposition of the ORANGE stockpile at Gulfport, Mississippi (Minutes, June 1971, Item 3. a(1)). No action has been taken on the recommendations for disposal of ORANGE in RVN to a plan submitted by JCS to Deputy Secretary of Defense Packard on 23 Apr 1971 (Minutes, June 1971, Item 4.b.).

c. No information available.

d. No supply support is being given to SEA activities. Apparently use of WHITE and BLUE has been reduced to a minimum or these herbicides are no longer being used (Minutes, March 1971, Item 3.b. (2)). With the curtailment of WHITE and BLUE, no requirement remains for any substitute such as 2,4-D ester.

6730

V. TECHNICAL REPORTS AND MANUALS ON USE OF DEFOLIANTS AND HERBICIDES

Air Force

U. S. Air Force. AFTO, SAAMA. November 1966. Use of herbicides. Tech. Manual T.O. 42C-1-17. San Antonio Air Materiel Area, Kelly AFB, Texas.

A revision to this technical order was cancelled and not distributed.

Darrow, R. A., R. R. Irish and C. E. Minarik. August 1969. Herbicides used in Southeast Asia. Tech. Rept. SAO)-TR-69-11078. Prepared by Plant Sciences Laboratories, Fort Detrick under contract FD-2053(M)-11073. San Antonio Air Materiel Area, Kelly AFB, Texas. AD 864 443

Young, A. L. and B. C. Wetherton. March 1970. Military herbicides and insecticides. Tech. Notes AFATL-TN-70-1. Air Force Armament Laboratory, Eglin AFB, Florida.

Army

Irish, K. E., R. A. Darrow and C. E. Minarik. December 1969. Information manual for vegetation control in Southeast Asia. Misc. Publ. 33. Department of the Army, Fort Detrick, Maryland. AD 864 443

Radke, R. O. and R. A. Darrow. October 1970. The lateral and vertical movement of four herbicides applied to a grassland soil (Tech. Memo. 212). Department of the Army, Fort Detrick, Maryland. AD 876 554

Darrow, R. A., et al. January 1971. Field evaluation of desiccants and herbicide mixtures as rapid defoliants (Tech. Rept. 114). Department of the Army, Fort Detrick, Maryland. AD 880 685

6731

APPENDIX A

LETTER OF INSTRUCTION FROM JTCG/CB FOR THE FORMATION OF THE SUBCOMMITTEE ON DEFOLIANTS/ANTICROP SYSTEMS

C O P Y

SMUEA-CC 30 June 1967

SUBJECT: Formation of Defoliants/Anti-Crop Systems Subcommittee of the JTCG/CB

TO: LT [redacted] b6
Air Force Armament Labs (AFATL)
C/B Division (ATC)
Eglin Air Force Base, Florida 32542

1. The Joint Technical Coordinating Group for Chemical/Biological (JTCG/CB) is a joint military service coordinating group organized in accordance with DoD Instruction 5160.5. Its purpose is to insure complete inter-service awareness at the technical working level of the total research and development program in the area of chemical and biological munition and defense systems and related materiel. The chairman of the JTCG/CB is:

COL N. Cox
Air Force Armament Labs (AFATL)
C/B Division (ATC)
Eglin Air Force Base, Florida 32542

2. Recently service interest and activity in defoliant and anti-crop agents/systems have experienced a considerable upswing. They are of considerable inter-service interest since the Army has the prime responsibility for agent development and procurement/production whereas the delivery systems for the most part are of Air Force and Navy interest.

3. It is imperative that a mechanism be set up to afford for the rapid and complete inter-service exchange of information concerning all aspects in this field. To this end, the JTCG/CB has constituted the

C O P Y

6738

COPY

SMUEA-CC
SUBJECT: Formation of Defoliants/Anti-Crop Systems Subcommittee of the JTCG/CB

30 June 1967

JTCG/CB Defoliants/Anti-Crop Systems Subcommittee. You have been nominated by COL N. Cox, USAF, to chair subject subcommittee. Other members, as nominated by their respective services, are shown on Incl. 1.

4. It is requested that you convene members of your subcommittee as soon as possible at site of your choice and draft charter and modus operandi for your subcommittee and submit to the JTCG/CB for review and approval. Sample subcommittee charter is attached as Incl. 2. COL N. Cox, USAF, is available to render assistance to you in this formulative phase.

5. For information, inclosed is copy of DoD Instructions 5160.5, Incl 3, and charter of the JTCG, CB, Incl 4.

4 Incl
as

[redacted]
Executive Secretary
JTCG/CB

Cys furn:
Mr. [redacted]
Dr.
Mr.
Mr.
Mr.
Mr.
Mr.
Mr.
COL

2

COPY

64

6733

BATCH 521 FSA JUS0069

APPENDIX B

JOINT TECHNICAL COORDINATING GROUP FOR CHEMICAL-BIOLOGICAL DEFOLIANTS/ANTI-CROP SYSTEMS SUBCOMMITTEE CHARTER

I. PURPOSE:

The purpose of this document is to define the mission, composition and functioning of the CB Joint Technical Coordinating Group subcommittee on Defoliants/ Anti-Crop Systems.

II. REFERENCE:

Department of Defense Instruction Number 5160.5, 7 February 1964.

III. MISSION:

A. General:

To effect detailed Interservice RDT&E program coordination at the technical level on CB incapacitating agents and weapons systems.

B. Specific:

Review in-house and contract programs to preclude unnecessary duplication of R&D effort.

1. Assure timely exchange of technical information in research, development, test, evaluation, logistics, production, and procurement.

2. Recognize and identify parallel or joint development efforts and recommend adoption of common requirements and military characteristics.

3. Resolve identified problems by mutual agreement and refer problems not amendable to higher authority, as necessary, through individual Service channels.

IV. COMPOSITION:

A. The subcomittee will consist of two representatives each from the Army, Navy and Air Force and one from the Marine Corps knowledgeable of their Services' research and/or development of CB agent/weapon systems. Subcommittee members will be appointed by each Service member of the JTCG.

B. The subcommittee will rotate its chairmanship on an annual basis and the chairman shall be of the corresponding Service which provides the chairman for the JTCG (e.g. 1967 - Air Force; 1968 - Navy; 1969 - Army).

C. The chairman shall designate an Executive Secretary to serve during the chairman's tenure of office.

D. The subcommittee representatives will designate individuals within their respective organizations to assist and participate in committee meetings as required.

V. FUNCTIONING:

A. The committee meeting will be arranged for by the chairman who will be responsible for the presentation and submission of an agenda and the submission of copies of documents to be discussed to all representatives at least three weeks in advance of the scheduled meeting.

B. Meetings will be held on a quarterly basis.

C. Meetings will include quarterly reports by members sufficient in scope to accomplish the mission of the subcommittee.

D. Minutes of the meeting will be the responsibility of the Executive Secretary of the subcommittee.

E. Any program recommendations of the subcommittee involving policy will be submitted to the JTCG for approval.

F. The subcommittee will provide the JTCG with a quarterly report of proceedings and any other reports deemed appropriate.

JOINT TECHNICAL COORDINATING GROUP FOR CHEMICAL-BIOLOGICAL
DEFOLIANTS/ANTI-CROP SYSTEMS SUBCOMMITTEE
CHARTER

APPROVED:

[redacted] b6
Plans & Read Opns Ofc
Ft Detrick Frederick, Md

[redacted] b6
Dir/Plant Sci Lab
Ft Detrick Frederick, Md.

[redacted] b6
Cust Rel & Cmdty Mgmt Ofc
Edgewood Arsenal, Md.

[redacted] b6
Naval Air Sys Cmd
Washington, D.C.

[redacted] USAF b6
(AFCB)
Eglin AFB, Fla

[redacted] b6
San Antonio Air Material Area
Kelly AFB, Texas

6736

APPENDIX C

COPY

STATE OF THE ART ON ANALYSIS OF "ORANGE"

The present Ft. D trick specification adequately covers a widely accepted precise method for determining total chlorine in an organic chloro-derivative (the Parr bomb method). For this specification, a suitable alternative for determining total chlorine is the more convenient sodium biphenyl method. The basic limitation of both methods is that no structural conformation is possible.

Infra-red techniques have served well as the choice method for characterizing structural groups of isomers in organic compounds for the past 20 years. The Plant Sciences Laboratory has been using a modern infrared spectrophotometer for analysis and identification of chemicals relating to various areas of Crops research. Currently, quantitative analysis of "Orange" is being contemplated in this laboratory. The infrared method is outstanding in its ability to provide a rapid qualitative analysis, but for quantitative purposes, it does not approach the accuracy of the Parr bomb. The Parr bomb fails to show what kind of chloride has been determined, and the infrared method fails to show how much of its indicated components are present without running the necessary standardization curves.

Since the biological activity of Orange is absolutely dependent upon a specific organic configuration, a direct analysis for these structures is highly desirable. IR analysis can qualitatively detect 2,4-D and 2,4,5-T esters, as well as appreciable amounts of certain inactive impurities, if present in significant amounts. Thus the Parr bomb or sodium biphenyl methods cannot do. With proper standardization procedures, IR techniques can provide quantitative analysis to a reliability of ±5%, according to methods described in the literature.

At present, 4 or 5 producers of Orange have used IR analysis for D & T esters, but not for routine production of Orange. In 2,4-D analysis, 3 different absorption peaks have been used for quantitative work, in which height of the peak from a hand-drawn baseline is related to amount of material present. Two different peaks have been used for 2,4,5-T analysis in different methods; in another variation, a T-peak is measured with 2,4-D in the reference cell. Although there appears to be great variability in IR procedures, no other method offers such highly specific analysis for the two main components in as short a time

COPY

COPY

(20 minutes), without separation of components. In addition, the presence of impurities or gross departures from the desired composition can be detected at the same time.

Gas chromatography may be considered as an alternate technique, but it is much more tedious and time-consuming to get set up. When set up, the gas chromatograph would be more or less restricted to analyzing only these herbicides and related compounds. With IR, the equipment would be available for other uses.

In conclusion, the present specification could include an additional paragraph suggesting the use of IR spectra for more specific identification of main components and detection of significant impurities.

31 Jan 68

COPY

6738

APPENDIX D

C O P Y

Preliminary notes, 2 Dec 1970 on INCINERATION OF ORANGE
WJW to CEM

Combustion experiments have indicated that the safest way to destroy large quantities of Orange is by incineration at a chamber temperature of around 900°C (1652 F). At much lower temperatures (100-200°C) there is a remote chance of dioxin formation, and FDA studies have indicated that the dichlorodioxin from 2,4-D derived phenol is as teratogenic as the tetrachlorodioxin from phenolic decomposition of 2,4,5-T. Recent mutagenic apprehensions from these dioxins thus rule out any alternative to high-temperature disposal.

Research on incineration of liquid pesticides is being conducted by Drs. [redacted] and [redacted] at Mississippi State University under USDA Grant No. 12-14-100-9182 (34). They reported briefly on "Incineration" at the National Working Conference on Pesticide Disposal, held at the National Agricultural Library at Beltsville on June 30-July 1, 1970. Mrs. Ruth Fyne at NAL provided a copy of the Proceedings of this Conference, and is making an ardent effort to obtain for us any subsequent reports by Shuman and Stojanovic. She informed us that no reports would be released at present to anyone but the granting agency (USDA) or Mississippi State University, so she is serving as our Liaison Officer in this case.

The July report on the experiments at Mississippi cited input rates of 0.66 to 2.34 gallons per hour of various pesticides, none identified except malathion (which in a xylene formulation had up to 4 GPH input rate). The next "Incineration" report in these NAL Proceedings (pp. 108-119) by Dr. [redacted] showed that no decomposition products were found from 2,4-D and a number of other pesticides at incinerating (pyrolyzing) ranges. These were the only incineration reports, and both were just preliminary.

We requested "any printed information or brochures" on incineration from the seven company addresses cited by Edgewood Arsenal. [redacted] response (from Tailor & Co., Bettendorf, Iowa) included these remarks: "We are presently finishing the Mustard Gas Disposal System. The paper enclosed is based on our work in the ill-fated Weldon Spring Chemical Herbicide project cancelled by the Government last year." None of his numerous enclosures gave specific mention

C O P Y

C O P Y

or attention to incineration of chlorinated herbicide, so we will acknowledge with a request for more details. One of his papers ("The Zoned CVX Reactor") on page 8 cited an erection cost of $875,000 for a system incinerating "Chemical Waste".

The Mustard Gas Disposal System, for which Tailor was the successful bidder, called for 24 hr/day incineration at 1250-1600°F of 580,000 gallons of crude and purified mustard (dichlorodiethyl sulfide) at feed rates of 0.25 to 3.0 gallons per minute (roughly a year of 24 hr/day burning of the total). Orange incineration should be directly comparable, with only 30% instead of 44% chlorine, and no sulfur. The 1 gpm continuous feed is 525,000 gal/year. Soda ash in our case should serve as well as dilute liquid caustic on mustard, since the removal of HCl should be easier than that of SO_2, a weaker acid gas. (The specified pollution limits for mustard effluent were 0.1 ppm max. SO_2 at ground level from a 55 ft. minimum stack height, vs. 0.015 ppm for HCl.) The 1250° to 1600°F incinerating range is adequate for safe disposal of Orange.

The first remark in the response from the [redacted] Company was that "direct flame incineration, as a means of pollution abatement, is gaining world-wide acceptance for the first time." To get additional guidance from this company we must return their "Pollution Abatement Section Data Sheet," and will fill in very rough figures comparable to those in the mustard disposal. (The writer from John Zink Pollution Research was A. Kim Reyburn.)

The response from Copeland Systems Inc., Oak Brook, Ill., by their General Sales Manager, acknowledged "that some years ago we completed the design for a facility for waste disposal from a Riverside Orange plant, but since the plant was not built, the waste disposal facility of course was not needed also. The point I am trying to make is that we have the capability to incinerate chlorinated pesticides and recover the hydrochloric acid." We will give them the same rough figures noted above for additional comments.

Thermal Research & Engineering Corp., Conshohocken, Pa., responded with comments from Evans Andreacola, Asst. Sales Manager, calling attention to one unit that "is used many times for the incineration of chlorinated hydrocarbons," and another where "an incinerator and separate scrubber system is used for incineration of chlorinated hydrocarbons," plus "a brief discussion on handling of halogenated compounds."

C O P Y

C O P Y

No replies have been received as yet (2 Dec. AM) from Teller Environmental Systems in New York, NY; Combustion Equipment Associates, also New York, NY; and VOP Air Correction in Darien, Conn.

C O P Y

APPENDIX E

COPY

DEPARTMENT OF DEFENSE
Armed Forces Pest Control Board
Forest Glen Section, WRAMC
Washington, D. C. 20012

Office of the Executive Secretary
AFPCB

15 March 1971

MEMORANDUM FOR: Director of Logistics, JCS-J4
ATTN: Colonel C. H. Sunder

SUBJECT: Advisory Statement on Disposal of Herbicide-Orange

1. Reference: DoD Directive 5154.12 dated 21 August 1968, subject: The Armed Forces Pest Control Board.

2. In accordance with requests for technical assistance within the scope of reference, paragraph 1, the Armed Forces Pest Control Board arranged an informal conference for the purpose of discussing methods of disposal for herbicide orange. The minutes of this meeting are attached as inclosure 1.

3. One method of disposal which was prominently discussed during the informal conference involved the construction and use of special pesticide incinerator equipment. In order to gain information as to what might be required for an operation of this nature, Dow Chemical Company was invited to present an informal resume of experience with disposal of pesticides by incineration. The results are summarized in inclosure 2.

4. In a follow-up action to the informal conference, Colonel C. H. Sunder, Mr. [redacted] and Mr. [redacted] visited the Construction Battalion Center, Gulfport, Mississippi, on 4 March 1971. The question of identification by each manufacturer was resolved. This may have some significance in the final disposition of the herbicides as indicated in inclosure 1, paragraph 9.a.

COPY

6742

C O P Y

AFPC3 15 March 1971
SUBJECT. Advisory Statement on Disposal of Herbicide-Orange

5. In view of the above data, the current recommendations for disposal of herbicide orange are as follows:

a. That action for immediate disposal of herbicide orange be withheld pending the following:

(1) Release of the President's Scientific Advisory Committee Report on 2,4,5-T to be released in the immediate future.

(2) Completion of the National Academy of Science Study on 2,4,5-T. Completion of this study is expected within 45-60 days.

(3) Action of the Environmental Protection Agency on the continued registration of 2,4,5-T. A formal position statement is expected by the end of March 1971.

These actions when complete will indicate what future uses of 2,4,5-T will be acceptable and may result in a sharp change in present policy.

b. That the possibilities for the use of approved incineration for disposal of herbicide orange be explored as suggested in inclosure 2, or by possible existing in-house capabilities modified as needed.

c. That the information contained in inclosure 3 be reviewed by herbicide specialists of the Department of Agriculture to provide a more accurate assessment of the dioxin content within each drum lot.

d. That a small amount (not to exceed 10,000 gallons) of herbicide orange from drum lots having very low dioxin content be reserved for use on military installations.

e. That dilution of herbicide orange to safe limits of dioxin content or reprocessing be utilized in the event that a wider latitude of 2,4,5-T uses are permitted in the future.

FOR THE CHAIRMAN:

[redacted]
Lt Colonel, MSC
Executive Secretary

66

3 Incl
1. Min of Inf Conf 24 Feb 71
2. Dow Chem Co ltr 8 Mar 71
3. Table of approx quan CBC ctr Armed Forces Pest Control Board

2

C O P Y

74

6743

COPY

MINUTES OF INFORMAL CONFERENCE ON DISPOSAL PROBLE
HERBICIDE ORANGE

1. On 24 February 1971 a conference was held at the suggestion of Col. Maurice G. Patton, OSD, Health and Environment Office to have the AFPCB consider the problem of the disposal of approximately 800,500 gallons of the tactical herbicide-orange, located at the US Navy Construction Battalion Center, Gulfport, Mississippi.

2. Attendees at the meeting were Capt. [redacted], Chairman AFPCB, LTC [redacted], Executive Secretary, AFPCB, Maj. [redacted], Entomology Consultant, Pesticides, OTSG, Army, Mr. [redacted], Chairman, Working Group on Pesticides, Mr. [redacted], Entomology Section, OCE, DA, Col. C. H. Sunger, JCS-J4, JCS (Dir. Logistics), LTC [redacted], JCS, Chem & Nuc, [redacted], AF RREY, Civ Engr Environ. Protect., [redacted], AF-SSSKE, Fuels Branch of Supply, [redacted], USDA, Pesticide Coordinator, Mr. [redacted], NAVFAC, Herbicide Committee, Mr. [redacted], OCE, Mr. [redacted], Representative, Dow Chemical.

3. Problem Background - The reported finding that the content of the contaminants (dioxins) in 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) were toxic to man and potentially teratogenetic, caused the suspension of the tactical use of herbicide orange in the Republic of Viet Nam. As a result, significant quantities of orange are in DOD stockpile awaiting disposal action.

4. Specific Problem - Mr. [redacted] reported that AF-SSSKE, Fuels Branch of Supply, is responsible for the procurement of tactical herbicides and has been tasked with the responsibility of developing a plan for the disposal of these herbicides. Specifically, Mr. [redacted], Deputy Secretary of Defense, has asked for practical alternative solutions to the problem including the pros and cons of each when considering their economic and political implications. This report is due to the Secretary of Defense by 15 April 1971.

5. The meeting was called to order by Capt. [redacted] and the general problem as reviewed in paragraph 1 and 3 was presented. It was further stated that although the AFPCB has limited involvement with tactical herbicides, COL. Patton requested help with the problem from the herbicide committee of the AFPCB.

6. Mr. [redacted] then enlarged on the specific problem at Gulfport (paragraph 4.). He stated that he had first been contacted by

COPY

Inclosure 1 to Appendix E

6744

BATCH 521 FSH USUW4

COPY

personnel responsible for storage area at CMCSH, Gulfport, for technical guidance on what could be done with the 15,000 plus drums of herbicide. Mr. Hutton contacted Dow Chemical Company about the problem and they agreed to study possible methods of disposal and make informal recommendations. One major problem area was indicated in that all of the drums were repainted over the manufacturer's label, therefore, the manufacturer's and batch numbers cannot be identified. Mr. Hutton further stated that there were considerably more than 800,000 barrels of orange in question in the supply pipeline and the solution to the Gulfport problem might also consider this supply. He also reported that the Working Group on Pesticides, at the present time, has no specific requirements for considering the "orange" disposal problem.

7. Colonel Sunder, JCS-J4, reviewed the request made to his office by Mr. Packard, as also indicated in paragraph 4. above. JCS-J4 has asked the AF and CIA-PAC for input on the problem by 15 March. Their suspense to Secretary Packard is 15 April 1971.

8. Mr. [redacted] b6 reported that there is a vigorous thrust on the disposal of nonmetallic pesticides by incineration at Mississippi State University. This USDA funded research has developed a successful closed loop disposal incinerator capable of totally detoxifying most pesticides. He also indicated that the political impact of this problem (Toxicity of 2,4,5-T) will be rekindled by a report forthcoming in the Food and Chem News. This journal has scooped the President's Scientific Advisory Committee's (PSAC) report and has published extracts from it which could largely exonerate the uncontaminated 2,4,5-T. There are two other studies of considerable national significance in progress concerning the future of 2,4,5-T. One is being conducted by the National Academy of Sciences - National Research Council under the chairmanship of Dr. Wilson. It is understood that the hearings for this Committee are in progress now. The other review is being conducted by the new Environmental Protection Agency as a result of a court hearing which requested banning action. Should these studies concur in the findings of the PSAC report, we may anticipate that there will be an easing of restrictions on 2,4,5-T.

9. Dr. Fred Tschirley, Pesticide Coordinator with the USDA presented information on the toxicity studies on 2,4,5-T:

a. The amount of toxic impurity dioxins varied greatly with different manufacturers from 0 to over 100 PPM.

COPY

6745

COPY

b. The dioxin impurity comes from "dirty" trichlorophenol.

c. The dioxin impurities are a family of compounds but the 2,3,7,8-tetrachlorodibenzo-p-dioxin is extremely toxic. (Acute oral).

(1) LD-50 in guinea pig is .0006 µg/kg
(2) LD-50 in male rats - .021 µg/kg
(3) LD-50 in female rats - .045 µg/kg

d. TCDD was found to be highly teratogenic in female rats. Rats dosages at the rate of 0.03, 0.125, 0.5, 2.0 and 8.0 µg/kg/day were teratocidal (killed the fetus in the mother rat). A dosage of 2.0 µg/kg was teratogenic (produced effects in offspring) and highly but not completely feticidal.

e. TCDD has been found - in limited studies - to be persistent in the soil - 55% recovered in 720 days. However, samples of soil taken at Eglin AFB were negative for TCDD, even though the soil is routinely treated with orange.

f. TCDD is quite immobile in soil - there was very little movement in different soil types which were continuously flushed with water.

g. TCDD is photolytic degraded (destroyed by ultraviolet light). TCDD in methanol was destroyed by ultraviolet light with a half life of 3.5 hours. No tests have been run on the effect of ultraviolet light on TCDD in water or spread on various soil types.

h. TCDD is translocated from the soil into plants - Soy beans and Oats grown in soil treated at an extremely high dosage (40,000 times a 2 lb/acre rate assuming a 1 PPM dioxin content). ^{14}C-TCDD was used in these experiments - detection sensitivity of .01 PPM. A very important fact in these studies was that no TCDD could be detected in the mature fruits of these plants - either the oats nor the soybeans showed detectable quantities of ^{14}C-TCDD. Therefore, plant up-take is not a significant factor.

i. Dr. Tschirley's recommendations:

(1) Determine manufacturer if identification is possible
(2) Hold on any action until the expert committee reports are available (NAS-NRC ANCEPA)
(3) Since TCDD is immobile in soil, it presents little hazard and therefore, some of the 2,4,5-T supply could be used in right-of-way maintenance.

6746

COPY

10. Mr. [redacted] b6 Dow Chemical Co., at the request of Mr. Hutton, presented Dow's viewpoint of the problem. Dow considered four alternatives to the orange problem:

1. Use it for base maintenance
2. Sell to a chemical company for remanufacturing
3. Contract for its disposal
4. Destruction by the Government

Mr. [redacted] b6 indicated that Dow has discussed the following considerations:

(1) They could not repurchase the supply. About 2/5 of the orange at Gulfport is Dow, and this portion cannot be identified because the drums have been repainted.

(2) They do not recommend remanufacturing the o[illegible]ge into a more usable herbicide. The 2,4,5-T used in orange is the butyl ester which has a higher volatility than the iscoctyl ester used in the standard registered commercial product. The butyl ester may not even be registered. (Note: Dr. Tschirley later confirmed registration of butyl ester compounds.)

(3) Dow can design and construct an incinerator system to destroy the orange. The contract would be on a "turn key" basis either as a GO-GO or GO-CO system (Government owned/Government operated or Government owned/contractor operated).

a. General description of the Dow system for incinerating orange:

(1) Closed loop with scrubbers and filters prior to air emission.

(2) Waste water from the system requires secondary water treatment.

(3) Solid waste; ash, filter collection, etc., would require disposal.

(4) Capacity, 3-5 gal/min.

(5) Tentative cost 1 million dollars.

COPY

(6) Time to construct and test -- Approx. 12 mo.

(7) All stages of the system will require continuous monitoring of all input and all output emissions; to air, water and solid. The monitoring equipment will be built into the system.

b. Dow has been operating similar system at their home office. This incinerator can handle most chemical wastes and has a flow rate of 10 gal/min. The system has been in operation for 10 years. They are currently constructing a similar plant with a 5 gal/hr capacity for the 3-M Co.

c. Dow agreed to have their engineers consult with the Environmental Offices of the Armed Services on the specific specifications of the incinerator in order to insure their compliance with EPA standards.

11. Discussion -

a. Can the manufacturers of the drums be identified? The reports are negative unless the OD paint can be removed. It was suggested that this problem could be reviewed at Gulfport during the following week as several members of the Group would be at the AFPCB meeting being held nearby.

b. What are the combustion products of the dioxin, TCDD? This will need further evaluation.

c. What is the current use level of 2,4-D/2,4,5-T on military bases? An answer is being sought, but it is believed to be low.

d. Are there ICC restrictions on the movement of orange? NO, but the political impact of the shipment of large quantities of orange would be significant. Further, extensive repackaging would be required to insure its safe shipment without leakage.

e. When will the reports or actions on the hazard of 2,4,5-T by the PSAC, National Academy of Sciences and EPA be published? They are reported to be due about 18 March, but the committees are requesting extensions.

f. Can a DOW type incinerator handle materials other than orange? YES, but each material must be identified prior to incineration since there will be different operating conditions for each compound.

6748

COPY

g. How long will it take to dispose of the 800,000 gal. of orange at Gulfport using a 3-5 gal/min. system? Approximately 1 year.

12. Recommendations -

a. Hold immediate action pending PSAC, NAS, and EPA reports.

b. Investigate procedures to purchase and construct a suitable incinerator.

c. Determine quantity which could be used on bases.

d. Determine manufacturer by amount, dioxin content.

e. Remanufacture to the isooctal ester or other material.

f. Recommend application of similar action on VN supplies of herbicide.

g. Indicate there could be the political impact of movement in interstate commerce.

6749

~~CONFIDENTIAL~~

DECLASSIFIED
20 MAY 1996
Auth: 1 May 1996 Ltr
From IMAC-R
8th US Army Command

(C)
(4) Because of the dangers to the civilian economy inherent in the use of defoliants, study of the problem is continuing at this headquarters. In the meantime, clearance of vegetation must be continued by ordinary means. Defoliants will be used by the Eighth Army Engineer in selected areas experimentally under careful control as a part of the solution of this problem.

ACTIONS REQUIRED:

(c) High priority further studies will be made by the Eighth Army Engineer of the following areas to improve future DMZ operations.

2. The feasibility of using herbicides for clearance of vegetation in the DMZ and area immediately south of the DMZ.

DOWNGRADED TO CONFIDENTIAL
IAW DoD DIR 5200.10

Extracted from HQ EUSA Ltr, EAGO-O, 9 Feb 67, subj: Special Analysis of the DMZ and Contiguous Operations (U) (SECRET)

6750

UNCLASSIFIED

b. (U) Clearance of Vegetation and Foliage in the DMZ Area (U)

This study is the result of the defoliation questions posed by the DMZ study.[5] The CVF Study was begun on 15 February and continued throughout the reporting period. The Engineer, Eighth US Army, has been designated with the study responsibility. As of 30 Jun 67, the status was:

(1) Terms of Reference – Approved by CINC, published 28 Feb 67, modified 11 Apr 67.[6]

(2) Political Implications – CINC directed on 11 Apr 67 that a joint Embassy/UNC/USFK message be sent to Washington giving details and requesting guidance on the proposed use of herbicides in Korea. A reply was received from SECSTATE on 24 May 67 requesting additional information. As of 30 Jun 67, the staff action for another joint reply was underway and implementation of the program had been stopped until SECSTATE/SECDEF permission was granted.

DECLASSIFIED IAW DoD DIR 5200.10

b. Clearance of Vegetation and Foliage in the DMZ Area: Reference is made to page 3 of the July – September 1967 Engineer Submission to the Historical Report. Revised plans for test applications were received from I Corps (Group) and FROKA.[3] Test applications were made at 9 locations totalling 80 acres. Two chemicals were used, Monuron, a growth retardant and 2,4,d a defoliant. Due to the lateness of the growing season, only marginal data has been obtained. Additional data is expected during the 1968 growing season. Due to an anticipated increase of NK infiltration, full scale application in 1968 is contemplated and will be predicated upon approval of plans and chemical availability.

DECLASSIFIED IAW DoD DIR 5200.10

testing dates back to July 67

Extracted from Eighth Army historical files.

UNCLASSIFIED

b. ~~(Confidential)~~ Clearance of Vegetation and Foliage in the DMZ Area (U). Reference is made to page 5 of the January - June 1967 Engineer Submission to the Historical Report. The Study continued during the reporting period with the following significant activity.

(1) Terms of Reference - no change[4]

(2) Political Implications - During the reporting period, messages were again exchanged between the country team and STATE/DEFENSE. These resulted in further delay of the study while additional information on political and social implications was provided. On 13 September 1967 STATE/DEFENSE was informed that the ROK Prime Minister supported the program and STATE/DEFENSE concurrence for the test program was given on 20 September 1967.

(3) Test Plans - No change

(4) Implementing Instructions - As a result of the 20 September concurrence, implementing instructions were issued on 30 September 1967 to I Corps (Gp) and First Republic of Korea Army (FROKA). Revised plans are due from these units.[5]

DECLASSIFIED IAW DoD DIR 5200.10

Extracted from Eighth Army historical files.

6758

10 October 1968

~~Confidential~~ UNCLASSIFIED

DEPARTMENT OF THE ARMY
U.S. ARMY ADVISORY GROUP, KOREA
OFFICE OF THE SENIOR CHEMICAL ADVISOR
APO SAN FRANCISCO 96302

EAAKORD/CML

MEMORANDUM FOR RECORD

SUBJECT: Summary 1968 Vegetation Control Tests

Subject to General Declassification Schedule
Declassify on 30 Dec 1975

SIGNIFICANT EVENTS

1. Chemicals were sent from the Plant Sciences Laboratory, Fort Detrick, Maryland, to the Republic of Korea for the purpose of testing their effectiveness in the control of vegetation.

2. 15 July - Dr. [redacted] b6, Mr. [redacted] b6 and LT [redacted] b6 arrived in the Republic of Korea, TDY from the Plant Sciences Laboratory, Fort Detrick, Maryland.

3. Travel in the 2nd U.S. Infantry Division was banned until 23 July 1968 because of rain.

4. 23-24 July - Test plots #1, 2 and 3 were made in the third Brigade, 2nd Division area.

5. 23-25 July - Republic of Korea Vegetation Control Program was reviewed by visits to the 2nd U.S. Infantry Division area and the 28th ROK Division area.

6. 26 July - Dr. [redacted] b6, Mr. [redacted] b6 and LT [redacted] b6 departed to return to Fort Detrick.

7. 14 August - Test plot #4 was made in the 4th Brigade 2nd U.S. Infantry Division area.

8. 22 August - Test plot #5 was made in the 4th Brigade 2nd U.S. Infantry Division area.

9. 26-27 August - Test plots #6, 7 and 8 were made in the 4th Brigade 2nd U.S. Infantry Division.

10. 30 September Mr. [redacted] b6 and LT [redacted] b6 from Fort Detrick returned to Korea.

11. 2-3 October - All test plots were reviewed.

12. 3 October - Test plot #9 was applied in the 3rd Brigade 2nd [redacted] Infantry Division area.

UNCLASSIFIED

5 MAY 1975 [redacted] b6 reviewed [redacted] b6

6753

BLANK PAGE

~~CONFIDENTIAL~~ UNCLASSIFIED

[redacted] b6

SUBJECT: Summary 1968 Vegetation Control Tests

DESCRIPTION OF TEST PLOTS

Test Plot #1 - 23 July 1968 - All listed chemicals applied except Urox Oil concentrate. Two subplots of 100 sq ft each were made of each concentration of each chemical. Total: 28 subplots of 100 sq ft each.

Test Plot #2 - 24 July 1968 - Only the solids were used here. One subplot of 100 sq ft each chemical. Total: 8 subplots of 100 sq ft each.

Test Plot #3 - 24 July 1968 - Only the liquids were used in this plot except Urox Oil concentrate. One subplot of 100 sq ft per concentration of each chemical. Total: 6 subplots of 100 sq ft each.

Test Plot #4 - 14 August 1968 - All listed chemicals applied. One subplot of 200 sq ft per concentration of each chemical. Total: 16 subplots of 200 sq ft each.

Test Plot #5 - 22 August 1968 - Test Plot #6, 7 & 8 - 26 & 27 August 1968 - Test Plot #9 - 3 October 1968 - all listed chemicals applied in each plot. Each plot contains one subplot of 400 sq ft per concentration of each chemical. Total each plot: 16 subplots of 400 sq ft each.

RESULTS

So far, all the test chemicals appear to be effective. It is impossible to tell the long range effect of these chemicals, but a better idea can be had next spring or summer. The test plots were selected to cover a large variety of terrain, vegetation and moisture levels.

The liquids all began to take effect about the same time and are always much quicker than the solids. Chlorosis may begin within two weeks after application of the liquids. Speed of effectiveness seems to vary with the amount of rainfall. More rain makes the chemicals effect more quickly.

At this point one of these best prospects appears to be tandex in either the liquid or solid form. Its effectiveness and the ease with which it can be used should result in a minimum of waste and makes it appear excellent for long range vegetation control. However, as stated before the duration of the effectiveness will be the key factor in determining which chemical would actually be best.

UNCLASSIFIED

[redacted]
LT, Cml C
Deputy Cml Advisor b6

~~CONFIDENTIAL~~

6755

[illegible]

1969 Requirements for [redacted] 66

3287

RFTCZYUW RUADXAE0082 2641721-CCCC--RUHHHQA.
ZNR RUAMHC 2894 2641015
ZNY CCCCC
R 200234Z SEP 68
FM CGUSAEIGHT SEOUL KOREA
TO RUHHRGA/CINCUSARPAC FT SHAFTER HAWAII
INFO RUHHHQA/CINCPAC
BT
~~C O N F I D E N T I A L~~ EA 98293 GO-VTA
SUBJ: VEGETATION CONTROL (U)
1. (U) REFERENCE SECRET MSG JCS 2658, SUBJ AS ABOVE, DATED 4 MAR 68.
2. (C) THIS HEADQUARTERS IS STUDYING THE FEASIBILITY OF CONTINUING DEFOLIANT OPERAZIONS AUTHORIZED IN REF MSG. INFORMAL INFORMATION REPORTED BY PERSONNEL OF PLANT SCIENCES LABORATORIES, FORT DETRICK, MARYLAND, INDICATES THAT USE OF SOIL APPLIED HERBICIDES ON HAND IN RVN IS NOT CURRENTLY AUTHORIZED.
3. (C) AUTHORIZATION TO EMPLOY DEFOLIANTS CITED IN REFERENCE ABOVE DOES NOT PLACE RESTRICTIONS AS TO TYPES OF HERBICIDES TO BE EMPLOYED. REQUEST THIS HEADQUARTERS BE ADVISED OF POSSIBILITY OF SOIL APPLIED HERBICIDES, EXCESS IN RVN, BEING FURNISHED THIS COMMAND AT NO COST, TO PLAN CONTINUATION OF VEGETATION CONTROL PROGRAM BEGINNING 15 APR 69
GP-4
BT

~~CONFIDENTIAL~~

CINCPAC COMMUNICATION CENTER - INCOMING

300190

[illegible]	[illegible]	[illegible]	C/S 101	DEP C/S 102	DEP C/S 103	PA	J1 SEC 104	PERS J1	INT J2	OPS J3	LOG J4	PLN J5	CAS J6	PEG J11	CPMP J12	LEGL J13	PIO J14	PACT J15	MED J16	[illegible]	EAO	B/S	IPC	DPR	MOC	IOPC	NSF	[illegible]
[illegible]	Y		X	X	X	X	X		X	C	X	X				X	X			X	X			X				X

CTNR 3287/20 TOR 201726Z OPR 90 DTG 200234Z SEP 68

6756

2087

PTTCZYUW RHMSMVA0060 3060805-CCCC--RUHHHQA. **PRIORITY**
ZNY CCCCC
P 010620Z NOV 68
FM COMUSMACV
TO RUHHRGA/CINCUSARPAC
INFO RUHHHQA/CINCPAC
RHMAAVA/CG USARV LONG BINH
RHMMAFA/CG III MAF DA NANG
RUAMWC/CG USAEIGHT SEOUL KOREA
BT
C O N F I D E N T I A L 32546
SUBJ: HERBICIDES(U)
REF: CINCUSARPAC 2027 DTG 272254Z SEP 68 (U)
1. (C) SOIL STERILANT TELVAR (MONURON) FSN 6840-514-0644 ON HAND AND EXCESS IN SVN IS APPROXIMATELY 2,000 FIBER DRUMS, 150 POUNDS EACH, WHICH IS SUFFICIENT QUANTITY TO TREAT APPROXIMATELY 1,600 ACRES.
2. (C) THIS AMOUNT OF TELVAR CAN BE PROVIDED USAEIGHT ON NON-REIMBURSABLE BASIS. RECOMMEND THAT ANY REQUIRED SHIPPING INSTRUCTIONS BE PROVIDED DIRECTLY TO CG, III MAF, INFO THIS HEADQUARTERS
GP-4
BT

NNNN#

CONFIDENTIAL

CINCPAC COMMUNICATION CENTER - INCOMING

300140

CINC 100	EXEC ASST 1001	F/LT 1002	C/S 101	DEP C/S 102	DEP C/S 103	FA	JT SEC 104	PERS 11	INT 12	OPS 13	LOG 14	PLN 15	CEC 16	PEG 171	COMM 172	LEGL 173	PID 174	PROT 175	MED 176	IPP	EAD	R/S	IRC	OPR	MSC	102C	NSG	
X	X		X	X	X	X	X		X	e	X	X				X	X			X	X			X				X

CWO W CTNR 2087/01 TOR 010845Z OPR 92 DTG 010620Z NOV 68

MACV 32546

6757

CINCPAC
COMMUNICATION CENTER

COPY NR.....
//CLASSIFIED MESSAGE FORM//

CONFIDENTIAL

CWO pass AMEMBASSY SAIGON 38211/191300Z SEP 68

(2395/20), (SECRET), as indicated, GP-4.
Control Number Classification

201200W SEP 68 ORIG: [redacted] 39667
(Time Prepared) b6

CONFIDENTIAL

300000

FROM: CINCPAC

ACTION:

INFO: OXOSXXXC
OXOBXCEKK
PXXXX
JCS

CLASSIFICATION: CONF | ORIGINATOR: J3A12 | RELEASER: J3A

CLEAR WITH: J3A1 [redacted] b6

PRECEDENCE

PRECEDENCE: ROUTINE

CVO [redacted] b6 32 LR 2654 CHNL NR [redacted] b6 TOO 2101 Z RTR DTG 2012

										O										X					

6758

COPY # 1 OF 2 5756

5756

716-39
99198

17 FEB 68 0354

UNCLASSIFIED

SECRET

BACC

FSA 68BACC-01123

RVN

Declassified
2 Mar 94
acc

68BACC-01123

TRANS:
POE - POC
$10.375 per DR

UNCLASSIFIED

SECRET

6759

RM

SECURITY CLASSIFICATION: UNCLASSIFIED ~~SECRET~~ C

RESERVED FOR COMMUNICATION CENTER 99495 114-57

Declassified 2 May 74 (CC)

UNCLASSIFIED

TYPE MSG: BOOK | MULTI x | SINGLE

PRECEDENCE

ACTION: ~~ROUTINE~~

INFO

DTG 27/2145Z FEB 68

FROM: SAAMA KELLY AFB TEX

TO: COMUSMACV COC7 AFG MSS TMA RVN

INFO: AFLC/MCSFF

CSAF/AFSSSEE

CG USARV LOGN BINH VIETNAM

CG 1ST LOG CMD TAN SON NHUT VIETNAM

FSA

UNCLASSIFIED

~~SECRET~~ C SAO

SPECIAL INSTRUCTIONS

Downgraded to Confidential 26 Feb 71 (CC)

1. a. Reference CSAF/AFSSSEE 170112Z Feb 68.

b. Request 610 drums of Herbicide Blue and 350 drums Herbicide Orange, cited in reference a, be released to U S Army from Saigon RVN stocks. Army contact for transportation is Col Roscoe Goodell O. C. Traffic Management Agency, MACV, Saigon RVN.

2. Request this headquarters and info addressees be notified date product is released to the Army. GP-4.

O	
OO	[redacted] b6
OT	[redacted] 2/27 b6
OR	[redacted] 27 Feb 68
OM	[redacted] b6
OS	[redacted] 2/2
OP	[redacted] b6
SM	[redacted] b6

DATE	TIME
27	1115
MONTH	YEAR
FEB	1968
PAGE NO.	NO. OF PAGES

DRAFTER — TYPED NAME AND TITLE: Mr. [redacted] IM Specialist SAORR/jdk b6

PHONE: 6119

RELEASER — SIGNATURE: signed

TYPED (or stamped) NAME AND TITLE: Acting Deputy Director of AF Aerospace Fuels

SECURITY CLASSIFICATION: ~~SECRET~~ C UNCLASSIFIED

REGRADING INSTRUCTIONS: SAO-68-036

DD FORM 173 NOV 63 REPLACES EDITION OF 1 MAY 55 WHICH MAY BE USED

6760

9693

UNCLASSIFIED

COPY # 1 OF 2

CCN

*************12 MAR 68 07 06**********

714-56
99494
(C)

[illegible] 67 [illegible]
BACC

A/2m

```
[illegible]
PTTSZYUW RUMSCM3598 0720060-SSSS--RUWTDUA.
ZNY SSSSS
DE RUMSMA 16300 0720515
ZNY SSSSS
P 120405Z MAR 68
FM COMUSMACV
TO [illegible]/CG USAEIGHT SEOUL
[illegible]/COMUSKOREA
[illegible]/OA
[illegible]/CSAF
[illegible]/SAAMA KELLY AFB TEXAS
[illegible]/CINCUSARPAC
[illegible]/CINCPAC
[illegible]/CG USAMC
[illegible]/CG RED RIVER ARMY DEPOT TEXARKANA
[illegible]/CG USARV LBN RVN
[illegible]/CG 1ST LOG COMD LBN RVN
[illegible]/AFLC
[illegible] 07069 FROM MACT[illegible] AFLC FOR [illegible]
SUBJ: PROJECT [illegible] (U)
REF: A. CSAF DTG 170112Z FEB 68 (S) (NOTAL)
     B. SAAMA KELLY AFB TEX DTG 272146Z FEB 68 (S) (NOTAL)
     C. [illegible] DTG [illegible] MAR 68 (S) (NOTAL)

PAGE 2 RUMSMA 16300 S E C R E T
1. (S) REF A DIRECTED TRANSFER OF FOLLOWING HERBICIDES TO U.S.
ARMY FROM SAIGON RVN STOCKS AND SUBSEQUENT MOVEMENT TO [illegible]
[illegible] 20 MARCH 1968:
   A. [illegible] DRUMS OF HERBICIDE, BLUE.
   B. [illegible] DRUMS OF HERBICIDE, ORANGE.
2. (S) REF B [illegible] DATE HERBICIDE RELEASED TO U.S. ARMY
[illegible] REQUESTED LIFT INFORMATION ON SAME.
3. (S) HERBICIDE SPECIFIED ABOVE LOADED ABOARD SS JOPLIN
VICTORY AT SAIGON ON 9 MARCH 1968. TOTAL OF 960 DRUMS LOADED IN
[illegible] 5, UPPER TWEEN DECK.
4. (S) SS JOPLIN VICTORY, VOYAGE NUMBER F81055, ETD [illegible]
[illegible] AND ETA INCHON, KOREA 20 MARCH 1968.
GP-4
```

689ACC-01493

FSA

Regr. 6c
Regr. [illegible]

Downgraded to Confidential
12 Mar 71 (OL)

Declassified
2 Mar [illegible]

UNCLASSIFIED

689ACC-01493

****

6761

6236 [redacted] b6
714-23
99491
ACTION O

A/cg

****

* UNCLASSIFIED 30 MAR 68 09 52 *

****

30 MAR 68 11 19
DACC

PTU00051
RTTEZYUW RUMSCMU0105 0880000-EEEE--RUWTOUA.
ZNY EEEEE
DE RUMSMA 4300C 0891445
ZNY EEEEE
R 291019Z MAR 68
FM COMUSMACV
TO RUAMWC/CG USAEIGHT SEOUL
INFO RUAMAC/COMUSKOREA
RUEPDD/DA
RUEFHQA/CSAF
RUWTOUA/SAAMA KELLY AFB TEXAS
RUHHHQA/CINCUSARPAC
RUHHHQA/CINCPAC
RUCLPGA/CG USAMC
RUWTUA/CO RED RIVER ARMY DEPOT TEXARKANA
ZEN/CGUSARV LBN RVN
ZEN/CO 1ST LOG COMD LBN RVN
RUWWFIA/AFLC WCSFF

FSA

UNCLAS E F T O 08861
SUBJ: PROJECT OBP
REF: COMUSMACV CITE 07267 DTG 140606Z MAR 68 (S) 68RACC-0152T-0
REQUEST FURNISH INFO PARA TWO (2) REF MSG.
BT

[redacted] b6
Please run down msg cited and let me know what's going on — [redacted] b6

ACTION To: [redacted] b6 [redacted] b6
COPY To: O
SUSPENSE:
From: O Date: 2 Apr
AUTHORITY: [redacted] b6 [redacted] b6

****

* UNCLASSIFIED E F T O *

****

I-68-915

6762

99490

THIS MESSAGE IS SUSPECTED DUPLICATE. DETERMINE IF PREVIOUSLY RECEIVED PRIOR TO TAKING ACTION.

2307
UNCLASSIFIED

ACTION [redacted]
INFO O-OT 66

14 MAR 68 1933

~~SECRET~~ Confidential

14 MAR 68 1909

BACC

SP [redacted] b6

This copy for OR
Suspected Duplicate

FSA

Downgraded to Conf 12 Mar 71

[redacted] b6

Declassified 2 May 72

UNCLASSIFIED ~~SECRET~~

[redacted] b6

CONFIDENTIAL

COPY 1

68BACC-01528

6763

9193

[redacted] b6

PP 0097
SD --RTTUZYYY RUHHROD\0253 1012150-\UUUU\--\RUWTNIA\.\\\+DE RUAMWC \1674 1011345

RTTUZYYY RUHHROD0253 1012150-UUUU--RUWTNIA.
DE RUAMWC 1674 1011345 11 APR 68 02 06 BACC
ZNR UUUUU ZFD RUWTNIA
P 1012202 APR 68
FM CGUSAEIGHT
TO RUMSMA/COMUSMACV
INFO ZEN/COMUSKOREA
RUEPWC/DA
RUEFHGA/CSAF
RUWTWIA/SAFMA KELLY AFB TEXAS
RUHHRSA/CINCUSARPAC
RUHHNGA/CINCPAC
RUEDMAA/CGUSAMC
RUWTLCA/CG RED RIVER ARMY DEPOT TEXAS
RUMSVA/CGUSARV LAM PVN
RUMSLC/CSOME LOG COMD LBN RVN
RUEDFIA/AFLC PCSFE
BT 5
UNCLAS EA 27256 GL-SKZ
SUBJECT: PROJECT [redacted]
1. REFERENCES:
A. COMUSMACV MSG 07267, DTG 140806Z MARCH 68.
B. COMUSMACV MSG 08860, DTG 291019Z MARCH 68.

THIS MESSAGE IS SUSPECTED DUPLICATE. DETERMINE IF PREVIOUSLY RECEIVED PRIOR TO TAKING ACTION.

Reference Occ 6936

PAGE 2 RUAMWC 1674 UNCLAS
2. INFORMATION REQUESTED PARA 2 REF ALPHA IS AS FOLLOWS:
ATA OF SSC/PLT VICTORY WAS 1300 HRS 20 MARCH 1968 AND
POL SS JOPLIN VICTORY WAS ENCHOR
BT

FSA

106903

6764

COMPARISON OF ASSESSING LEVELS OF 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN IN SELECTED POPULATIONS BY BIOMONITORING AND EXPOSURE INDICES

Larry L. Needham, Donald G. Patterson, Jr., and Wayman E. Turner

National Center for Environmental Health, Centers for Disease Control and Prevention, 4770 Buford Highway, Atlanta, GA 30341 USA

Introduction

Epidemiologists are frequently concerned with relating human exposure with health outcomes. Accurate assessment of this relationship requires accurate assessment of both components- exposure and health outcomes. In this presentation we will examine the assessment of human exposure using populations potentially exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD or dioxin) as the example chemical. Traditionally, epidemiologists have developed exposure indices for the assessment of exposure. These indices consist of at least two primary factors: the concentration of the dioxin in the media that humans contact and the time (duration or frequency) of that contact. However, these exposure indices may or may not correlate with the measured levels of dioxin in those humans; this measured level is generally considered the gold standard for assessing human exposure to chemicals such as dioxin, which has a half-life that has been calculated as 7.6 years,[1] and thus can be measured in heavily exposed people long after undue exposure has ceased. In this presentation we will relate the exposure index that was derived by epidemiologists with measured levels of dioxin.

Methods and Populations

In our laboratory we have measured the internal dose levels of dioxin in adipose tissue and serum samples from the general population and in populations potentially exposed to dioxin. These methods are based on the most accurate and precise approach for measuring these chemicals- namely, high-resolution gas chromatography/high-resolution mass spectrometry with quantification using the isotope-dilution technique.[2] The potentially exposed populations include selected residents of the State of Missouri, U.S.; industrial workers in U.S.; U.S. Army ground troops in Vietnam; U.S. Air Force veterans of Operation Ranch Hand in Vietnam; herbicide sprayers in New Zealand; and residents of Seveso, Italy.

The selected adult residents of Missouri centered around the spraying of oily material containing high levels of dioxin on roadbeds and horse arenas for dust control during the early 1970s; soil levels were measured at levels greater than 500 parts-per-billion (ppb). The exposure index defined an exposed individual as one potentially exposed to soil dioxin levels of 20-100 ppb for two or more years or to soil levels greater than 100 ppb for six or more months. Adipose tissue samples were collected in 1985.

The U.S. industrial workers were potentially exposed to dioxin as a result of working in plant sites that synthesized 2,4,5-trichlorophenol, which produces parts-per-million levels of TCDD, or used the 2,4,5-trichlorophenol, which contained dioxin, to make additional chemicals, such as 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and hexachlorophene. Various exposure indices were developed and compared to serum dioxin levels that were measured several years after the occupational exposure ceased.

6765

RISK ASSESSMENT

The U.S. Vietnam veterans and New Zealand sprayers were potentially exposed to dioxin from the spraying process or from residues of the spray on environmental matrices. Seven different exposure indices, including two based on self-reports, were developed for assessing exposure to the Army ground troops, who were enlisted men serving in III Corps military region in 1967/1968. The exposure index for each member of Operation Ranch Hand was based on the following equation: concentration of dioxin in Agent Orange during one's tour multiplied by the number of gallons of Agent Orange sprayed during one's tour divided by the number of men in one's specialty during that person's tour of duty. The serum samples for the initial study of 150 Ranch Hand members and 50 controls were collected in 1987. The original exposure index and additional ones were later compared to serum dioxin levels in the entire available Ranch Hand cohort. The exposure index for the New Zealand sprayers was based on the number of years that one sprayed 2,4,5-T. This cohort consisted of nine sprayers, but they had a wide range of years spraying.

The residents of Seveso, Italy were potentially exposed to dioxin as a result of a malfunction on July 10, 1976, at a 2,4,5-trichlorophenol manufacturing plant, which resulted in several kilograms of dioxin as well as larger amounts of other chemicals being cast over several hectares. The exposure index was based zones, which, in turn were based on dioxin soil levels and vegetation and animal deaths. The serum specimens were collected in 1976.

Results

The Missouri incident:[3-5]

- Adipose tissue levels ranged from 2.8-59.1 parts-per-trillion (ppt) in residents; 5.0 to 577 ppt in horse riders in arenas; nondetectable to 20.2 ppt in controls.
- 35 % of those deemed to have been exposed had dioxin levels at or below the 95th percentile of the controls.
- There was no significant relationship of dioxin adipose tissue levels and eating homegrown vegetables, gardening, mowing lawn, playing in yard, walking or other activities related to exposure to soil.
- The only significant variable found ($p=0.029$) was whether the person resided in the sprayed area from 1971-1973, which was during or soon after the actual time of spraying.

The U.S. industrial workers:[6,7]

- Levels measured ranged from 2 to 3390 ppt; maximum extrapolated level ranged to over 30,000 ppt.
- In two plants, duration (years) of exposure in plant areas where TCDD contamination was possible was highly correlated with serum dioxin levels. Thus, duration of exposure was used as the exposure index for the entire occupational cohort.

The U.S. Army ground troops:[8]

- Distributions of measured dioxin levels in 646 Vietnam and 97 non-Vietnam veterans were similar, with a mean and median in each group of about 4 ppt.
- Two veterans had levels greater than 20 ppt. Exposure in Vietnam cannot be ruled out.
- Dioxin levels did not tend to increase with increases in any of the seven exposure indices.
- The low serum dioxin levels were consistent with previously reported serum dioxin levels for ground troops.[9]

Members of Operation Ranch Hand:[10-13]

- Dioxin levels of Ranch Hands from initial study: mean- 49 ppt; median- 26 ppt; 62% above 20 ppt; highest value- 313 ppt; in controls, mean and median- 5 ppt.
- Poor correlation of serum dioxin levels and Air Force's exposure index.

- Air Force decided to use serum dioxin levels on entire cohort for assessing exposure..
- Revisit of exposure indices on entire Ranch Hand cohort showed best exposure index (R^2=0.61) was from job classification (divided into four categories), the number of days of skin exposure, percent body fat during tour, and relative change in percent body fat. However, job classification alone had R^2=0.60. Initial exposure index was the poorest predictor of serum dioxin level. Highest 1987 serum dioxin level was 618 ppt.

Herbicide sprayers in New Zealand:[14]

- Good correlation (r=0.72, P=0.03) between duration (months) of spraying 2,4,5-T and serum dioxin levels, which ranged from 3 ppt to 131 ppt.

Residential exposure in Seveso, Italy:[15-17]

- Zone A (most contaminated zone) residents had highest serum dioxin levels- up to 56,000 ppt, median 447 ppt .
- Zone A residents with chloracne had higher levels on average than nonchloracne residents- however, there was overlap in levels between individuals in these two groups.
- Zone B residents showed no indication of continued dioxin exposure by living in this contaminated area post- July 10, 1976.
- In a large subset of women enrolled in Seveso Women's Health Study, about only 40% of women living in Zones A and B had elevated serum dioxin levels.

Discussion

Exposure indices may be of value for classifying exposure status of populations; however, the user of these indices must be aware that they may lead to a great deal of misclassification that may in turn lead to in general underestimation of any relationship determined between exposure and health outcomes. Especially when exposures are to chemicals with long biological half-lives, such as dioxin, the exposure index should be validated against the appropriate biomarker, such as serum dioxin levels. In the dioxin examples given here, the only exposure indices that highly correlated with the biomarker were those in which careful records of exposure were maintained and evaluated and when the exposure involved actual contact with the dioxin contaminated material and not with an environmental matrix containing the dioxin. We have also seen high correlations between eating dioxin-contaminated foods and serum dioxin levels.[18] However, it appears that there is a big leap in defining exposure in populations that may contact an environmental matrix that contains dioxin and the absorption and storage of dioxin in the body. This does not mean to imply that the use of biomarkers does not have some difficulties, such as individual differences in elimination rates and the occurrence of additional exposures after the last known exposure. However, we are acquiring additional information regarding understanding individual pharmacokinetic differences in eliminating dioxin, and although the elimination rate of dioxin has been shown to be slower as body mass index increases, the half-life is still lengthy, and thus the biomarker is still the best marker for classifying exposure status. It should be pointed out that the leap in defining exposure between populations eating dioxin-contaminated foods and serum dioxin levels may not be nearly as great.

In several studies of adult populations, dioxin levels that were measured many years after exposure ceased were used to estimate the cumulative levels following the last known exposure. This has generally been done in highly exposed populations using a 7-year half-life and first order kinetics. One of the particular problems in assessing exposure retrospectively is that in some populations because of relatively low initial serum levels and/or time since exposure, current serum dioxin levels may have decayed to near background levels. This does present some problems, but information on current serum

dioxin levels may still be relevant. For example, in a recent study of chemical corps veterans, those who sprayed herbicides in Vietnam had a statistically significant elevation in their mean current serum dioxin levels compared to non-Vietnam veterans without a spraying history while other 2,3,7,8-substituted dioxins levels were similar in the two groups.[19] This mean difference was possible to detect only because the background levels in the general population are decreasing. Also, because Agent Orange contained only 2,3,7,8-TCDD and not the other 2,3,7,8-substituted dioxins, we gain additional information when we ratio levels of 2,3,7,8-TCDD against other 2,3,7,8-substituted dioxins. In the case of the veterans who sprayed Agent Orange this ratio was higher than for those who did not- thus indicating that they had been exposed to a product, such as Agent Orange, that contained elevated levels of 2,3,7,8-TCDD relative to other 2,3,7,8-substituted dioxins; thus, serum dioxin levels may still be relevant for validating exposure to Agent Orange even after 35 years post-Vietnam service. Only through the use of highly precise and accurate high-resolution mass spectrometric measurements could we gather this information. Therefore, we still believe that serum dioxin measurements should still be used to attempt to validate exposures that may have occurred many years in the past.

References

1. Michalek JE and Tripathi RC. (1999) J Tox Environ Health. 57, 369.
2. Patterson Jr D, Hampton L, Lapeza C., Belser W., Green V., Alexander L., Needham L. (1987) Anal Chem. 59, 2000.
3. Patterson, Jr D, Hoffman R, Needham, L, Roberts D, Bagby J, Pirkle J, Falk H, Sampson E, Houk V. (1986) JAMA. 256, 2683.
4. Andrews J, Garrett W, Patterson D, Needham L, Roberts D, Bagby J, Anderson J, Hoffman R, Schramm W. (1989) Chemosphere 18, 499.
5. Needham L, Allen K, Patterson Jr D, Andrews J. (1990) Organohalogen Compounds. 1, 259.
6. Fingerhut M, Halperin W, Marlow D. (1991). N Engl J Med. 324, 212.
7. Sweeney MH, Fingerhut MA, Patterson Jr D, Connally L, Piacitelli J, Morris J, Greife R, Hornung R, Marlow D, Dugle J, Halperin W, Needham L. (1990) Chemosphere. 20, 993.
8. Destefano F, Devine O, Flanders W, Karon J, Needham L, Patterson D, Worth R. (1988) JAMA. 260, 1249.
9. Kahn PC, Gochfeld M, Nygren M. (1988) JAMA. 259, 1661.
10. Wolfe WH, Michalek JE, Miner JC. (1988) Mor Mortal Wkly Rep. 37, 309.
11. Michalek JE. ((1989) Appl Ind Hyg Special Issue. 68.
12. Michalek JE (1995) J Exp Anal Environ Epi. 5, 209.
13. Wolfe WH, Michalek JE, Miner JC. (1990) JAMA. 264, 1824.
14. Smith AH, Patterson Jr D, Warner ML. (1992) JNCI. 84, 104.
15. Mocarelli P, Needham LL, Marocchi A, et al. (1991) J Toxicol Environ Health. 32, 357.
16. Needham LL, Gerthoux P, Patterson Jr D, Brambilla P, Turner W, Beretta C, Pirkle J, Colombo E, Sampson E, Tramacere P, Signorini S, Meazza L, Carreri V, Jackson R, and Mocarelli P. (1997). Teratogenesis, Carcinogenesis, and Mutagenesis. 17, 225.
17. Eskenazi B, Mocarelli P, Warner M, Samuels S, Needham L, Patterson D, Brambilla P, Gerthoux P, Turner W, Casadini S, Cazzaniga M, Ce W-Y. (2001) Chemosphere. 43, 937.
18. Goldman LR, Harnly M, Flattery J, Patterson D, Needham L. (2000) Environ Health Perspect. 108, 13.
19. Kang HK, Dalager NA, Needham LL, Patterson D, Matanoski G, Kanchanaraksa S, Lees P. (2001) Chemosphere. 43, 943.

6768

New York Times
June 17, 2011
Pg. 10

Dioxin Traces Found Near U.S. Base In South Korea

By Mark McDonald

SEOUL, South Korea - Trace amounts of dioxin have been found in water samples taken near an American Army base in South Korea, according to a joint investigation into possible chemical dumping that analysts said could have repercussions for the alliance between South Korea and the United States.

The discovery of dioxin, a toxic chemical linked to an array of maladies, near Camp Carroll, in southeastern South Korea, was part of an initial report on water and soil tests being conducted by both countries.

The dioxin was found in three streams near Camp Carroll, investigators said Thursday, and all the samples were well within safe drinking standards set by the United States Environmental Protection Agency. Tests of three other streams and 10 wells were negative for dioxin.

Dioxin, a component of the powerful defoliant Agent Orange, has been linked to an array of maladies, including cancer, heart disease and birth defects. Agent Orange was widely used during the Vietnam War to expose the hiding places of enemy soldiers in jungles, swamps and forests.

A Pentagon official played down the initial findings of the investigation. "The trace of dioxin was negligible and appears to pose no health risk," the official said, adding that no indications of Agent Orange were found.

Military officials in Seoul said that Agent Orange also was sprayed along the heavily fortified border between North and South Korea in 1968. The spraying lasted about two months, they said, until local supplies of the herbicide were exhausted.

Political analysts said they had been encouraged by an unusually high level of cooperation between American and Korean military investigators, in part because the collaboration could defuse anger among those in South Korea who resent the American military presence here. About 28,500 American service members, primarily Army troops, are currently based in South Korea.

"There has been no delay in conducting investigations of the allegations and in extending full cooperation to the Korean government," said Evans Revere, the former No. 2 diplomat at the American Embassy in Seoul who is now a lecturer and diplomat in residence at Princeton University.

"Transparency is really important here," Mr. Revere said, "because of the need to deal with the inevitable conspiracy theories that will arise in the Korean media and among the political opposition."

But Mr. Revere, a longtime American diplomat in Asia, said the Agent Orange issue was a delicate one and had the "potential to have a significant impact on popular attitudes toward the U.S.-South Korea alliance."

Three former American soldiers - Steven House, Richard Cramer and Robert Travis - recently said they had helped to bury about 250 drums of waste at

Camp Carroll in 1978. Their allegations were first broadcast by KPHO, a television station in Phoenix.

The men said the disposal site was a deep trench near a helicopter pad at Camp Carroll. The ditch was about 100 yards long and wide enough to accommodate a dump truck, they said.

Mr. Travis said the 55-gallon drums were olive-drab green, marked with a stripe and labeled "chemical type - Agent Orange." He said some of the barrels were "dated 1967 for the Republic of Vietnam."

The United States Army has acknowledged that pesticides, herbicides and other toxic compounds were buried at Camp Carroll, but the chemicals and about 60 tons of contaminated soil were later dug up and removed. An American military spokesman in Seoul, Lt. Col. Jeffrey S. Buczkowski, said the Army was still searching its records to discover what became of the excavated chemicals and soil.

Investigators said Thursday that they could not link the discovery of the dioxin to the chemicals buried in 1978. Meanwhile, the South Korean military is conducting environmental tests at 85 former American bases that have been returned to South Korean control.

The commander of American forces in South Korea, Lt. Gen. John D. Johnson, held a meeting two weeks ago with South Korean residents who live or work near Camp Carroll.

"I pledge that I will do everything necessary to determine the truth," General Johnson said at the meeting. "My focus is to ensure there is no risk to the health of the people on Camp Carroll or off Camp Carroll. And if there is, I'll fix it."

Although the investigation looking into suspicions of chemical dumping is not yet complete, some analysts saw little chance that public anger here would reach the level that caused hundreds of thousands of Koreans to take to the streets in the summer of 2008 to protest - sometimes violently - the lifting of a ban on imports of American beef. The ban was first imposed in 2003 after a case of mad cow disease was detected in the United States.

The 2008 demonstrations, while ignited by the beef controversy, were also deeply tied to widespread frustrations over the early policies of President Lee Myung-bak, who took office in February 2008.

"The beef issue was more about Lee Myung-bak and his leadership style," Mr. Revere said, "and the beef scare provided a convenient pretext to bash him."

The fact that Camp Carroll is well to the southeast of Seoul may also dampen any nationwide outrage, said Lim Seong-ho, a professor of political science at Kyung Hee University in Seoul.

"The chemical danger is far away from most citizens," Mr. Lim said. "Certainly, some groups and people will try to reignite anti-American sentiment. But the chemical dumping is restricted to a small part of a remote area and does not bring a terrible sense of danger to the mind of the Korean public."

Some analysts saw possible comparisons between the Agent Orange issue and an

episode in 2002, when an American armored vehicle killed two 14-year-old Korean girls walking to a birthday party. The accident stirred local opposition to the 37,000 American service members then stationed in South Korea. The subsequent acquittal of two American sergeants by a United States military panel outraged Koreans.

At the time, Mr. Revere said, the South Korean government failed to "defend the alliance" against news media speculations and "well-organized anti-American elements who sought to exploit the tragedy for political ends."

Elisabeth Bumiller contributed reporting from Washington.

REVIEWS ON ENVIRONMENTAL HEALTH VOLUME 21, No. 2, 2006

Adverse Health Effects in Humans Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD)

Daniela Pelclová,[1] Pavel Urban,[1,2] Jan Preiss,[3] Edgar Lukáš,[1,2] Zdenka Fenclová,[1,2] Tomáš Navrátil,[4] Zora Dubská,[5] and Zdeňka Šenholdová[1]

[1]*Department of Occupational Medicine, 1st Medical Faculty, Charles University and General Faculty Hospital, 120 00 Prague, Czech Republic;* [2] *Centre of Occupational Medicine, National Institute of Public Health, Šrobárova 48, Prague, Czech Republic;* [3]*Department of Neurology, Na Homolce Hospital, Roentgenova 2, Prague, Czech Republic;* [4]*J. Heyrovský Institute of Physical Chemistry, Dolejškova 3, Prague, Czech Republic;* [5]*Department of Ophthalmology, 1st Medical Faculty, Charles University and General Faculty Hospital, Prague, Czech Republic*

ABSTRACT

The environmental contaminant 2,3,7,8-tetrachlordibenzo-*p*-dioxin (TCDD) belongs to the category of highly toxic, persistent organic pollutants that accumulate in animal fat and plant tissues. Today, background TCDD levels in human fat are showing a decreasing trend. The food chain is the main source of exposure in the human population. TCDD regulates the expression of a wide range of drug-metabolizing enzymes and has an impact on a large number of biological systems. The most pronounced effects have occurred in occupational settings following the uncontrolled formation of TCDD after industrial accidents, as well as in rare intentional intoxications. Although the acute effects of TCDD exposure are well described in the literature, the long-term consequences have been underevaluated. The most well-known symptoms of severe acute intoxication are chloracne, porphyria, transient hepatotoxicity, and peripheral and central neurotoxicity.

Because of the long-term persistence of TCDD in the human body, atherosclerosis, hypertension, diabetes, vascular ocular changes, and signs of neural system damage, including neuropsychological impairment, can be present several decades after massive exposure. Such chronic effects are nonspecific, multifactorial, and may be causally linked to TCDD only in heavily intoxicated subjects. This opinion is supported by the dose-dependent effect of TCDD found in exposed workers and by experimental animal studies.

KEYWORDS

chloracne, porphyria, diabetes, atherosclerosis, neurotoxicity, chronic effects

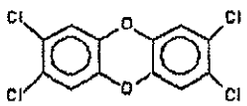
INTRODUCTION

Chemical Properties

The chlorinated dibenzo-*p*-dioxins (CDDs) are a family of 75 chemically related, extremely toxic compounds that are commonly referred to as chlorinated dioxins—colorless solids with varying harmful effects. Such compounds are divided into

Reprint requests to: Daniela Pelclová, Department of Occupational Medicine, 1st Medical Faculty, Charles University and General Faculty Hospital, D. Pelclová (✉), Na Bojišti 1, e-mail: daniela.pelclova@LF1.cuni.cz

eight groups of chemicals based on the number of chlorine atoms in the molecule. A CDD having four chlorine atoms at positions 2, 3, 7, and 8 is called 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (Fig. 1).



2,3,7,8-TCDD

Fig. 1: Structure of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)

This compound is one of the most toxic chemical substances known for animals but has an extreme range (by a factor of 1,000) in lethal effects among species /1/. Humans appear to be less sensitive than most other mammals to its effects /2/. The International Agency for Research on Cancer (IARC) has classified TCDD as a human carcinogen /4/.

Environmental Fate

The CDDs are produced in nature from the incomplete combustion of organic material by forest fires or volcanic activity. In the early 1880s, such compounds were found in samples of archived surface soils that were collected from locations around the world before their anthropogenic formation from industrial processes began /3/. Although such compounds are intentionally prepared in small quantities for research purposes only, they are formed as unwanted byproducts of the industrial, municipal, and domestic incineration of many materials containing chlorine (plastics, wood treated with pentachlorophenol, polychlorinated biphenyls, and pesticides, for example). Sunlight and atmospheric chemicals break down only a small portion of CDDs, with complete thermal degradation usually occurring only at temperatures >800 °C /4/.

In the environment, CDDs are transported through air, water, and by migratory species across international boundaries, where they are deposited far from their place of release, accumulating in terrestrial and aquatic ecosystems. These chemicals can settle to the bottom sediment in cultured fish ponds, where they enter fish and duck tissues and then humans. The CDDs tend to be associated with soil, ash, or any surface having a high organic content, such as plant tissues /5/. Soil used in pottery represents another source of recent PCDD environmental contamination /6/. At low concentrations, these pollutants have been detected in cigarette smoke and vehicle exhaust /7/.

SOURCES OF HUMAN EXPOSURE

Environmental Exposure

Polychlorinated dibenzo-*p*-dioxins, dibenzofurans, hexachlorobenzene, and polychlorinated biphenyls belong to a category of chemicals that have been classified by the Stockholm Convention[1] as persistent organic pollutants—namely, they endure in the environment, bioaccumulate through the food web, possess toxic properties, and resist degradation. Hence, such substances are of high environmental health concern /8/. In the general population, intake from food consumption accounts for well over 90% of the body burden of CDDs. Because such chemicals accumulate in animal fat, most non-occupational and non-accidental exposure human exposure to CDDs occurs through eating meat, milk, butter, eggs, fatty fish, and similar products /4–5, 9–10/.

In human tissue, mean background lipid levels of TCDD are presently in the range of about 2 pg/g body fat. Mean TCDD lipid levels have decreased by close to a factor of 10 since the late 1970s /11/,

[1] Stockholm Convention on Persistent Organic Pollutants, www.pops.int/documents/convtext/convtext_en.pdf

when the development of sensitive methods permitted the accurate measurement of extremely low levels /12/. In residents of highly Agent orange-contaminated environments in Vietnam, TCDD levels increased 135 orders of magnitude compared with non-polluted areas /13/. Besides blood, another preferred matrix for evaluating human background exposure is breast milk /14–15/. Regardless of whether they pose a significant human health risk at current levels of exposure, CDDs are of considerable interest to toxicologists.

Mechanism of Toxicity

Recent reports are consistent with the hypothesis that TCDD produces most of its toxic effects by binding to a gene regulatory protein called the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor /16/. The mechanistic model indicates that binding of TCDD to the AhR, followed by the dimerization of the AhR with a nuclear transport protein (AhR nuclear transport protein - Arnt) and the interaction of this complex with specific DNA sequences (dioxin-responsive elements, or DREs), leads to an inappropriate modulation of gene expression /17/. Exposure to TCDD induces the transcription of the cytochrome (CYP) CYP1A1 /18/ and 1B1 genes coordinately with dose-dependent and time-dependent increases in CYP450 protein levels /18–20/. Cytochrome P450 is a multigene family of enzymes involved in the oxidative metabolic activation and detoxification of many endogenous and exogenous compounds, including carcinogens.

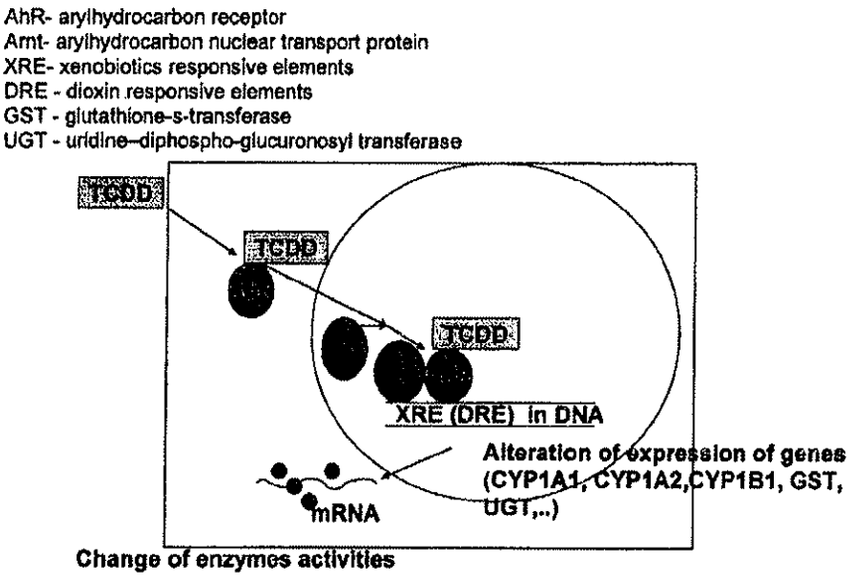


Fig. 2: Mechanism of the effect of TCDD

when the development of sensitive methods permitted the accurate measurement of extremely low levels /12/. In residents of highly Agent orange-contaminated environments in Vietnam, TCDD levels increased 135 orders of magnitude compared with non-polluted areas /13/. Besides blood, another preferred matrix for evaluating human background exposure is breast milk /14–15/. Regardless of whether they pose a significant human health risk at current levels of exposure, CDDs are of considerable interest to toxicologists.

Mechanism of Toxicity

Recent reports are consistent with the hypothesis that TCDD produces most of its toxic effects by binding to a gene regulatory protein called the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor /16/. The mechanistic model indicates that binding of TCDD to the AhR, followed by the dimerization of the AhR with a nuclear transport protein (AhR nuclear transport protein - Arnt) and the interaction of this complex with specific DNA sequences (dioxin-responsive elements, or DREs), leads to an inappropriate modulation of gene expression /17/. Exposure to TCDD induces the transcription of the cytochrome (CYP) CYP1A1 /18/ and 1B1 genes coordinately with dose-dependent and time-dependent increases in CYP450 protein levels /18–20/. Cytochrome P450 is a multigene family of enzymes involved in the oxidative metabolic activation and detoxification of many endogenous and exogenous compounds, including carcinogens.

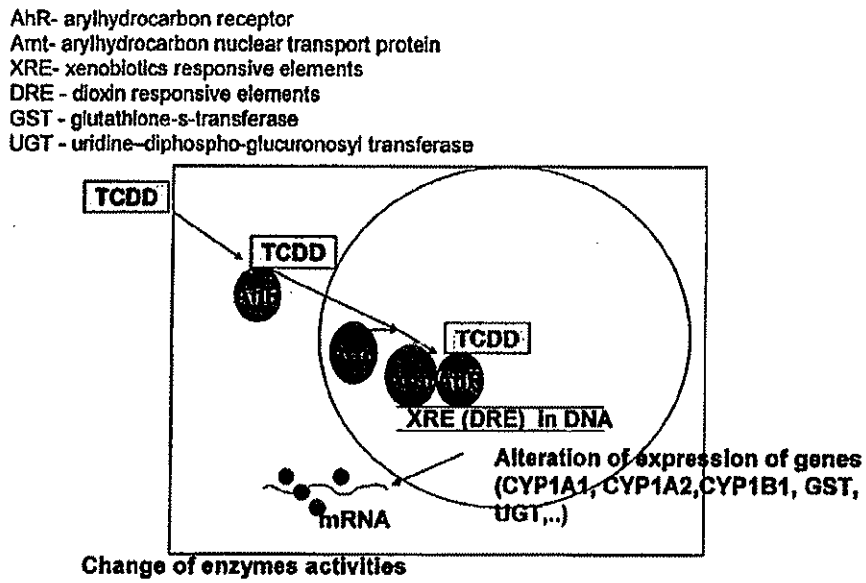


Fig. 2: Mechanism of the effect of TCDD

Through its interaction with AhR, TCDD regulates the expression of the genes encoding a wide range of xenobiotic metabolizing enzymes that participate in cell-cycle regulation and act as inflammatory mediators /17, 21–22/.

Verification of TCDD levels in Occupational and Accidental Exposure

Occupational or accidental exposures to TCDD have occurred during the production and use of various chemicals, including pesticides. During the years of highest industrial exposures, however, a method for the detection of CDDs in blood was not available. Therefore, such analyses could be performed only several decades later, thanks to the development of highly sensitive methods on the one hand (high-resolution gas chromatography/high resolution mass spectrometry) /23–24/ and to the long plasma half-life of TCDD on the other. The high price of the analysis, however, does not favor frequent TCDD measurement.

Absorption, Elimination, and Half-life of TCDD

In rodents, absorption from the gastrointestinal tract is in the range of 50% to 90%; pulmonary absorption is much more limited, and the rate of skin penetration of TCDD is very slow /25/. In all vertebrate studies so far, TCDD is retained in all tissue types, more so in those rich in fat. The highest distributions of TCDD were found in the liver and white fat, whereas those in the brain were extremely low /26/.

Because of the high toxicity and carcinogenicity of TCDD, limited data exist in humans to assign absorption by a specific route of exposure (oral, inhalation, dermal). In a male volunteer, absorption after ingestion of 105 ng TCDD reached > 87%. The unabsorbed TCDD was excreted in feces within 3 days, but the elimination of the absorbed dose by feces, the main route /27/, was very slow, amounting to only 0.03% /4/. In trials to enhance TCDD elimination in two patients during the first 3 years after their exposure to the compound, the non-digestible, non-absorbable dietary fat substitute Olestra increased elimination via the intestinal tract but had only a small effect on overall elimination /28/.

A single chemical analysis of blood or adipose tissue provides an approximate measure of past cumulative exposure to TCDDs /29–30/. A regression analysis of half-life measures and body weight data selected from the literature revealed the longest TCDD elimination half-lives ever reported for laboratory mammals and humans and seemed to be empirically correlated to organism body weight /31/. The estimates of TCDD half-life in humans based on measurements in serum samples taken tens of years post exposure were in the range of 7 to 10 years /32/. At low exposure levels, minimal enzymatic induction occurs, and the elimination of TCDD is very slow.

From 1965 to 1968, approximately 80 persons in the former Czechoslovakia became ill following occupational exposure to 2,3,7,8-TCDD. Thirty to thirty-five years after the exposure, the average half-life in four Czech TCDD-exposed chemical workers corresponded to about 8.0 years, which agrees with results of other studies (Table 1) /48/. Recent data on individuals exposed to very high concentrations have documented that the half-life soon after exposure is much shorter /28/. At high exposure levels, induction of CYP 450 1A2 approaches a maximum, and the elimination rate of TCDD is faster by an order of magnitude or more /29/.

Highest Exposures with Measured Plasma TCDD

Several occupational exposures to TCDD occurred during the production of trichlorophenol (TCP), 2,4,5-trichloroacetic acid (2,4,5-T) and pentachlorophenol (PCP). The physiologically based pharmacokinetic model for TCDD peak exposure assessment, which is not available for most studies, yielded higher results by one or more

orders of magnitude, depending on the time delay since the end of exposure. The following published back-calculated maximum levels of TCDD used a half-life of 7 to 10 years (Table 2). Military

TABLE 1

Repeated plasma 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) measurement (1996, 2001) and half-life 30–35 years after cessation of exposure in four previously exposed workers /48/

	Exposure (years)	Body Mass Index		TCDD (pg/g plasma lipids)		Half-life (years)
Year		1996	2001	1996	2001	
Case 1	1967–68	30.9	28.4	760	517	9.0
Case 2	1965–67	30.1	27.7	600	401	8.6
Case 3	1966–67	29.4	28.4	420	234	5.9
Case 4	1967–68	22.4	25.9	400	264	8.3

Note: Measurement in 4 controls in 2001 gave a value lower or equal to the quantitative limit of 7 pg/g of plasma lipids.

TABLE 2

Approximate exposures estimates in selected groups of subjects with the heaviest exposure, using a half-life of 7-10 years /4, 11, 32, 36, 39–41, 44-48, 103/

Place of exposure	Years	Max. mean back-calculated TCDD level in plasma to the date of exposure (pg/g fat)
USA, Veterans /4/	1962-1971	50
Vietnam – population /36/	1962-1971	120-260
New Zealand /40/	late 1960s	300
Seveso, Italy /41/	1976	390 zone A 78 zone B
BASF Ludwigshaven, Germany /39/	1953	400
Netherlands /4/	1963	1,434
USA, 12 chem. Companies /103/	1950s-1970s	2,000
Linz, Austria /32/	1973	2,682
Spolana, Czech Republic /44–48/	1965-68	6,100
Population level /11/	2000	2

6777

personnel in Vietnam who served in the U.S. armed forces in the years 1965 to 1971, when TCDD-contaminated Agent Orange was widely sprayed as an herbicide and defoliant (Operation Ranch Hand) had the back-calculated peak level of about 50 pg/g fat using a half-life of about 8 years /4/. The physiologically based model, however, brings levels that are about two orders higher /35/.

In 1991–1992, TCDD levels in the pooled blood samples of the population from South Vietnam, who lived in areas that had been heavily sprayed with Agent Orange during the war, were 15 to 33 pg/g fat. Back-calculation of levels to the time that war ended in 1971 yielded about ~120 to 260 pg/g fat /36/. As the TCDD exposure, however, might have originated partly from the food chain in the contaminated area later on, the back calculation does not correctly represent the peak level. The pooled samples of Korean veterans of the war in Vietnam have shown that the recent TCDD level is in the range of only 0.3 to 0.87 pg/g lipids /37/, placing them among low-level exposed subjects.

In 1953, an uncontrolled decomposition reaction occurred in BASF at Ludwigshaven, Germany. Back-calculation to the time of exposure revealed a peak blood TCDD concentration of ~400 pg/g lipid /38/. Another group of workers from a Boehringer-Ingelheim plant in Hamburg, Germany, which was manufacturing a range of herbicides, showed mean peak estimated TCDD plasma concentrations of ~140 pg/g fat /39/. In New Zealand in the late 1960s, pesticide applicators involved in ground-level spraying of the phenoxyherbicide 2,4,5-trichloro-phenoxyacetic acid (2,4,5-T) had a back-calculated mean peak TCDD level of ~300 pg/g fat /40/.

The accident involving the largest area occurred in 1976, caused by a blowout of a TCP production reactor in Seveso, Italy /41/. The chemical cloud probably contaminated the environment with several kilograms of TCDD. For the first time, TCDD blood levels were measured early after exposure, ranging between 1,770 and 56,000 pg/g fat in zone A, the most exposed. Yet, using blood drawn during 1992–1993 and a 7-year half-life, the respective average back-calculated levels in the population from zone A and zone B were only ~390 and ~78 pg/g fat /4, 41/. For a 1963 accident occurring in a chemical factory in the Netherlands, the back-calculated levels were 1,434 pg/g fat /4/.

In 1991, Fingerhut et al. /103/ published a 12-plant study of workers in the United States of America (U.S.) who produced chemicals contaminated with TCDD (15–37 years earlier), in which the back-extrapolated peak level was ~2,000 pg/g fat. Similarly, a study by Calvert et al. /42/ among workers exposed to PCDDs 15 years earlier in two U.S. chemical plants reported a back-calculated peak level of about 1,900 TCDD pg/g fat. Neuberger et al. reported a back-calculated mean blood level about 2,682 pg/g fat in 9 Austrian workers who had been exposed ~17 years earlier during the TCDD-contaminated production of 2,4,5-T. In another Austrian group of 50 chemical workers producing 2,4,5-T in 1971 to 1973, the mean blood concentration of TCDD reached 466 pg/g fat in 1996; the back-calculated level could be very high, more than 5,000, but is not given /43/.

Workers from Czechoslovakia belong to the highest exposed groups. In the years between 1965 and 1968, approximately 80 persons became ill due to the production of the butylester of 2,4,5-T in the Spolana plant. As a consequence of a higher temperature and pressure, TCDD originated as an intermediate product /44/. Early findings in this group have been described by Pazderová et al. /45/, and Pazderová-Vejlupková et al. /46–47/. Most workers have already died or were lost during the follow-up. In 1996, the blood analysis of TCDD in 13 workers was performed for the first time, with a further 3 men being tested in 2004. The back-calculated mean concentration of TCDD was estimated to be ~5,000 pg/g of plasma fat /48/, and for the total group of 16 subjects ~6,100 TCDD (in the range of 400 to 17,500) pg/g plasma fat.

TABLE 3

TCDD levels in 16 Czech patients 30 years after exposure /48/

Patient No	Born	Year of Exposure	TCDD (2004) (pg/g fat)
1	1945	1967-68	380*
2	1943	1965-67	300*
3	1943	1966-67	210*
4	1944	1967-68	200*
5	1938	1965	172*
6	1945	1966-67	128*
7	1944	1968	115*
8	1944	1968	110*
9	1946	1966-67	105*
10	1944	1969	85*
11	1948	1970	47*
12	1935	1964-67	40+
13	1940	1967	37*
14	1942	1966-68	20*
15	1944	1967	9*
16	1947	1965-66	7*

Note: TCDD level measured in 2004* or calculated from the 1966 measurement using an 8 years half-life.
+ Patient died in 2000.

Using the physiologically based pharmacokinetic model for TCDD peak exposure assessment, the mean level in the group of 16 workers was 74,000. The levels were in the range of 5,000 pg/g plasma fat (in patient No. 16, Table 3) to 211,000 pg/g of plasma fat (in patient No. 1). Similar to other countries, background TCDD levels in the Czech Republic usually do not exceed 2 pg/g fat /49/.

Among the highest directly measured levels in adults are values of 144,000 and 26,000 pg/g fat, seen in two Austrian women about half a year after presenting with the first symptoms of probable intentional poisonings /2/. According to the physiological pharmacokinetics model, their peak levels could have been as high as 507,000 and 87,000 pg/g fat /35/. Another well-known level was experienced in autumn 2004, with the alleged intentional poisoning of Ukrainian president Victor Yushchenko, who reportedly had a blood serum level of 100,000 pg/g fat /50/.

HEALTH EFFECTS IN HUMANS

Initial Symptoms

The outbreak of illness is usually a gradual onset of chloracne, fatigue, feeling of sickness, and weakness in the lower extremities, frequently with pain under the right costal arch[2], an indication of liver toxicity /45/.

Chloracne

Chloracne is a skin condition characterized by the presence of comedones[3], keratin[4] (epidermal) cysts, and inflamed papules (bumps) with hyperpigmentation. Chloracne usually appears within 2 days or weeks to 2 months after exposure to TCDD. Several studies have reported a positive association between chloracne and serum and adipose tissue levels of TCDD /38, 51/. The anatomical distribution, frequently involving the skin under the eyes, behind the ears, on the neck, back, and genital region, reflects skin contact with contaminated hands, which is probably more important than the serum level itself /32/. Therefore, a threshold level above which chloracne occurs can not be established. A patient showing only mild symptoms does

[2] Bridge of cartilage connecting ribs 7 through 10 with the lower portion of the breastbone
[3] Lesion caused by blockage of pores by dirt, debris, bacteria.
[4] Protein that makes up skin, hair, and nails

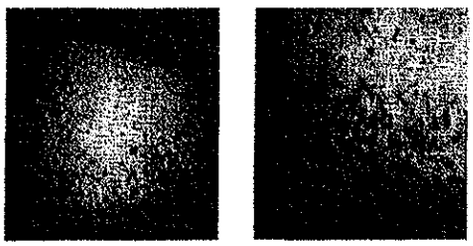


Fig. 3: Skin changes 35 years after exposure to TCDD in patient No. 5 (in descending order of TCDD level)

not preclude high TCDD serum levels /2/. In the Czech patients, 76 out of 80 symptomatic workers developed chloracne, and the skin involvement was generalized in five men.

Porphyria Cutanea Tarda

Reduced porphyrins (porphyrinogens) are intermediates in the biosynthesis of protoporphyrin, a compound that incorporates iron to form heme, the oxygen-binding portion of hemoglobin in red blood cells. Increased synthesis, accumulation in the liver, bone marrow, skin and other organs, and urinary excretion of the intermediate product uroporphyrin results in a condition called porphyria. Porphyria cutanea tarda covers a group of human genetic and acquired skin disorders with liver dysfunction caused by a deficiency of uroporphyrinogen decarboxylase, a heme synthetic enzyme. Halogenated aromatic hydrocarbons are among the most common chemicals causing uroporphyrinogen decarboxylase deficiency and the resulting overproduction and urinary excretion of uroporphyrin. Besides mediation through AhR genes, the location of non-Ahr genes responsible for porphyria and liver injury has recently been found /52/.

Several groups of exposed subjects have developed symptoms of acquired porphyria cutanea tarda—skin fragility, dark pigmentation, excess hair growth, liver enlargement, reddish-colored urine, and urinary excretion of porphyrins /4/. In Seveso residents, the impairment of porphyrin metabolism in most patients was only transient /53/. TCDD can induce a hepatic porphyria in mice that is similar to porphyria cutanea tarda in humans /109/. An underlying genetic abnormality of uroporphyrinogen decarboxylase might play a role in the severity of damage in patients exposed to dioxin. In persons suffering from the chronic hepatic form of porphyria with no overt porphyria cutanea tarda, no correlation between the TCDD level in adipose tissue and the level of uroporphyrin and coproporphyrin was found by Jung et al. /54/.

In 19 Czech patients, about 22% of patients with chloracne, Jirásek et al. /55/ described solar hypersensitivity and/or hyperpigmentation, which correlated with high porphyrinuria during the first years after the exposure, and hypertrichosis (excessive body hair) especially in the malar area of the cheeks. Fluorescence of the urine and of liver and bone marrow tissue was described in 7 subjects having both elevated and normal uroporphyrinuria up to 5 years after the exposure had stopped /45/. The skin symptoms disappeared within a few months or years /67/. Among the last 15 patients in 2004, tracked about 35 years after exposure, only mildly increased uroporphyrins were found in the urine (247 µg/24 h) of 2 subjects (13%)—patients No. 3 and No. 5 /56/. Patient No. 3 had suffered a mild porphyria cutanea tarda in the past and medium chloracne; patient No. 5 had severe porphyria cutanea tarda and persistent signs of generalized chloracne (Fig. 3).

Hepatic Effects

Santostefano et al. /57/ examined the effects of TCDD in isolated rat hepatocytes and found a

dose-dependent increase in the distribution of TCDD in centrilobular hepatocytes, which may be related to regional differences in P 450 induction. Although elevations of liver enzymes activity were found in Seveso children /58/ and chemical workers /43, 59/, none of the studies identified clinical evidence of liver disease in the study population. Elevated liver enzymes were seen predominantly in workers having a history of high alcohol consumption /60/ and they normalized within a few years. About one-third of the Czech chemical workers had a mild increase in liver test parameters during the first years after exposure. At that time, liver biopsy in five subjects showed only mild steatosis,[5] periportal fibrosis,[6] or the activation of Kupfer cells.[7] Thirty years after exposure, liver enzymes were not elevated /48/.

Body Weight Loss

Weight loss in humans corresponds to the "wasting syndrome" seen in animal studies /4/. Nausea, vomiting, epigastric pain, and loss of appetite in a patient with heavy TCDD intoxication prompted a weight loss of about 10 kg /2/. Transient weight loss was reported in two laboratory workers following an acute exposure to TCDD /61/. During a short period after exposure, weight loss was also noted in a group of our patients. About 30 years after the exposure ceased, however, the body mass index in the Czech patients was mostly in the overweight range /62/.

Lipid Levels

Atherosclerosis is a chronic progressive disease characterized by the accumulation of lipids and fibrous elements in the inner walls (intima) of the large arteries, including those feeding the heart and brain. As cholesterol cannot dissolve in blood, it is transported to and from cells by carriers called low-density lipoproteins (LDL) and high-density lipoproteins (HDL). High levels of LDL can combine with other substances to form thick, hard deposits (plaques) that clog arteries, increasing risk of heart attack and stroke. Conversely, HDL carries cholesterol away from the arteries; high levels appear to protect against atherosclerosis. A high level of triglyceride, another form of fat, is also associated with heart disease and diabetes.

Inflammation, the innate immune response to a first contact with a foreign substance, also plays a prominent role in the development of atherosclerosis. Following leukocyte[8] recruitment to the site of injury, the monocytes internalize modified lipoproteins, thereby acquiring the morphological characteristics of macrophages known as 'foam cells'.

Several experimental studies have supplied evidence supporting the hypothesis that TCDD exposure promotes atherosclerosis development. TCDD treatment in normal and hyperlipidemic mice resulted in the increased urinary excretion of vasoactive eicosanoids[9] and mean tail-cuff blood pressure, as well as increased serum triglycerides and cholesterol, but not HDL. The LDL level was increased only in the hyperlipidemic genotype. Dioxin distribution was highest in LDL particles, which might deliver TCDD to atherosclerotic plaques. In addition, subchronic dioxin treatment caused a trend toward an earlier onset and a greater severity of atherosclerotic lesions when compared with vehicle-treated mice /63/.

TCDD promotes the differentiation of macrophages into atherogenic foam cells /64/, suppresses the activity of lipoprotein lipase by downregulating hepatic PPARs (peroxisome proliferator-activated receptors), and raises the level of beneficial HDL

[5] Abnormally large quantities of intracellular fat
[6] Fibrous changes of the structure of tissues surrounding the portal vein that conducts blood from the digestive organs, spleen, pancreas, and gallbladder to the liver
[7] Specialized cells in the liver that destroy bacteria, foreign proteins, and worn-out blood cells

[8] Including lymphocytes, neutrophils, monocytes/macrophages
9 Compounds that play an important role in inflammation.

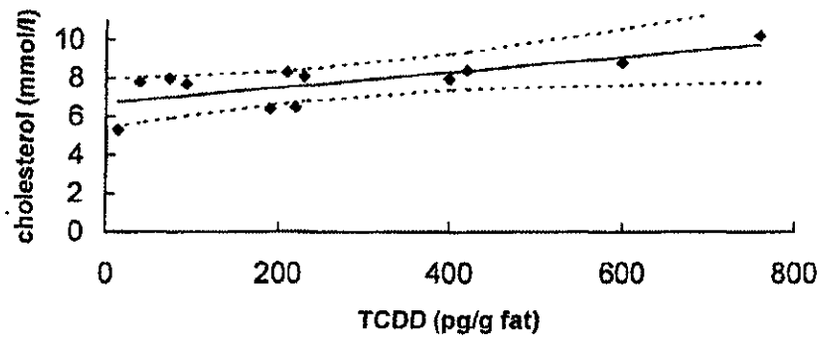


Fig. 4: Correlation of serum 2,3,7,8-TCDD and highest cholesterol measured in 12 subjects. r=0.74, p=0.01

in plasma /65/. Lipoprotein lipase is an enzyme that catalyzes the breakdown of fats, and PPARs are involved in both lipid metabolism and inflammation.

Blood lipids were not elevated in several human TCDD studies /4, 38, 43/, including those of the Seveso residents /58/. We should mention that several other factors, both endogenous and exogenous, could have played a role in normalizing lipid levels, including hypolipidemic treatment. Other epidemiological studies did report significant increases in total cholesterol and/or triglyceride levels among persons exposed to TCDD when compared with unexposed controls /59, 61/. In a follow-up study 15 years after TCDD exposure, weak associations between TCDD, increased triglycerides, and abnormally decreased HDL cholesterol concentrations were noted by Calvert et al. /66/ and by Sweeney et al. /67/.

Both cholesterol and triglyceride levels were elevated shortly after intoxication with TCDD in two young Austrian women with extremely high blood TCDD levels and chloracne /2/. The level of exposure might be very important, as it indicated the dose-dependant increase of cholesterol in the group of Czech patients /62/ shown in Fig. 4. In 1996 and 2004, hyperlipidemia was found in 92% and 87% of patients, respectively. After hypolipidemic treatment, both blood cholesterol and triglycerides, respectively, decreased during this interval, from a mean of 6.94 and 2.67 mmol/L to 5.24 and 2.46 mmol/L.

Cardiovascular Effects

Disorders of lipid metabolism are major risks factors for the development of coronary heart disease /68/. Most early data indicated that exposure to TCDD does not induce cardiovascular effects /7/. No evidence of an effect of TCDD on morbidity due to ischemic heart disease or on overall mortality or deaths due to circulatory disease was found in chemical workers at BASF, Germany /69/ or among Operation Ranch Hands Air Force veterans /70/, namely, groups having lower TCDD exposure. Calvert et al. /42/ found no

significant association between ischemic heart disease and TCDD; in any event, the statistical power of this study was too low to detect it.

According to Sweeney and Mocarelli /71/, mortality from cardiovascular diseases appeared to be elevated among cohorts of TCDD-exposed chemical workers and Seveso residents. An international study comprising 36 cohorts from 12 countries, with a total of 21,863 chemical workers, detected an increased risk for death from cardiovascular disease, especially ischemic heart disease, among TCDD-exposed workers /72/. Kim et al. /37/, found that among those with higher levels of exposure, Korean veterans of the war in Vietnam during the period 1995 to 1996 had an increased frequency of hypertension and of ischemic heart disease as well. In this study, however, pooled blood samples were examined with assessment of exposure based on questionnaires, which might represent a certain bias.

Among the 15 Czech subjects, 9 were treated for hypertension (60%), 5 fell ill with myocardial infarction (one twice), three with angina pectoris, and one with a stroke in the years 1995 to 1999 (30 years after exposure, but still with very high TCDD plasma levels). Echocardiography performed in 2004 showed abnormal relaxation and diastole filling of the left cardiac ventricle as the most frequent impairment in nine patients. A worker with the highest TCDD plasma level required surgery for severe stenosis (narrowing) of the carotid artery, which supplies blood to the head. In 2004, 73% of patients had atherosclerotic plaques in the carotids. Unlike in 2001, intima-media[10] thickness did not differ from that of the control group of the same age and body mass index, probably thanks to lipid-lowering therapy, which reverses the progression of early arteriosclerosis of the carotid artery /73/. Accordingly, no myocardial infarction was noted after 1999. In addition to that, a finding of endothelial dysfunction in our TCDD-exposed patients supports the hypothesis that oxidative stress is the main reason for this dysfunction, which can lead to pro-atherosclerotic events (Pelclová et al., submitted).

[10] The middle coat of the blood vessel wall

Ocular Effects

Experimental results support the hypothesis of a causal relationship between eye capillary changes and hypercholesterolemia /74–75, /. High levels of exposure to TCDD among Vietnam veterans were associated with increased frequency of retinopathy /37/. In 2001, 32 years after TCDD exposure, degenerative changes of the ocular fundus[11] were present in 67% of the Czech workers. In 2004, 35 years after the exposure ceased, retinal angiosclerosis[12] and chronic conjunctivitis[13] were present in all 15 workers /56, 62/.

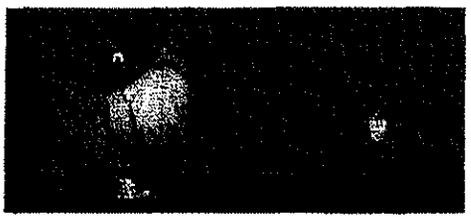


Fig. 5: Ocular changes 35 years after exposure in a Czech worker (patient No. 9). Left: chronic conjunctivitis with hyperemia and papillary hypertrophy in the lower tarsal conjunctiva. Right: change of the caliber of vessels in the eye fundus - constriction of arteries, dilatation of veins, and pathological arterio-venous crossings with compression of veins.

Neurological and Neuropsychological Effects

Despite its low molecular weight and highly lipophilic character, TCDD does not penetrate well into nervous tissue. Correspondingly, several authors

[11] The part of the eye opposite the pupil
[12] Thickening and hardening of blood vessel walls in the retina
[13] Eye infection, also known as 'pinkeye'

have expressed doubts that TCDD can cause any neurological damage /76–77, /. On the other hand, other authors suppose that exposure to TCDD might be associated with certain adverse neurological effects. This view applies especially to high levels of exposure. In experimental studies, rats exposed to TCDD developed polyneuropathy[14] in a dose-dependent manner /79–79, /. Klawans /80/ and Thömke et al. /81/ reported peripheral neuropathy in chemical workers, as did Michalek et al. /82/ in Operation Ranch Hand and Kim et al. /37/ in Korean veterans of the Vietnam War. According to Bertazzi et al. /83–84, /, peripheral neuropathy was an early and reversible effect in the Seveso accident victims. In our patients, the respective frequencies of a polyneuropathic pattern in nerve-conduction studies in the 1970s, 1996, and 2004 follow-ups were 38%, 23%, and 20% /109/. Severe neuropathy was confirmed by histology in one Czech patient with severe intoxication who died 2 years after the exposure stopped /45/.

Damage to the central nervous system is a more controversial issue. The hypothalamus and pituitary gland have been identified as potential sites of TCDD action, with corresponding alterations, especially to the dopaminergic system, which plays a crucial role in role in motor function and neurological and psychiatric disease processes. /85/. Further, TCDD can damage nervous tissue by inducing oxidative stress /86/, which has been associated with blood-brain barrier disruption /110–111/. In addition to direct neurotoxic effects, indirect damage to nervous tissue can be induced by vascular impairment /19/.

Neuberger et al. /43/ found sleep disturbances in 44%, headaches in 32%, and neuralgia (nerve pain) in 30% of 159 TCDD-exposed herbicide production workers. Recently, Ingel et al. /87/ noted a significant correlation between individual plasma TCDD levels and emotional stress in Russian women. On the other hand, findings in U.S. veterans of the Vietnam War with relatively low serum dioxin levels exhibited only small differences and of uncertain clinical significance, due to interference with post-traumatic stress disorder /88/.

In our patients, dysfunction of the central nervous system could be inferred from neuropsychological, neurological, and neurophysiological examinations. In 1996, impairment of cognitive performance (Memory Quotient, see Fig. 6, Verbal IQ, subtests Vocabulary, Arithmetic and Similarities, Benton Visual Retention Test) correlated with TCDD concentration and with an elevation of plasma cholesterol and triglyceride levels /48/. Neurasthenic syndrome and/or organic psychosyndrome were found in 85% patients. Eight years later, in 2004, about 38 years after exposure, neurasthenic syndrome was found in 47% of our patients; the EEG, VEP, and the Lanthony test were abnormal in 53%, 33%, and 47%, respectively. These findings can be interpreted as a manifestation of an incipient diffuse encephalopathy. In 2004, only few significant correlations were found between TCDD and neuropsychological variables (Category Test of the HRNB and percentage of Nonperseverative errors on the Wisconsin Card Sorting Test (Urban et al, submitted). Lowering the blood lipids in these patients might have improved the vascular dysfunction /89/.

All the findings described above were observed in highly exposed subjects but were etiologically non-specific. In our subjects, however, high alcohol consumption does not seem to interfere with the TCDD dose-dependent association with neuropsychological impairment. Only two subjects with lower TCDD levels admitted a higher daily intake of alcohol (patient No. 11 in descending order of plasma TCDD level, 1.5 liters of beer, and patient No. 15, 2 liters of beer). Four patients (No. 1, 5, 7, and 9) were moderate daily alcohol consumers (0.5 L beer), seven subjects admitted occasional alcohol intake only, and one man was abstinent. According to Stampfer et al. /90/, moderate consumption of as much as one drink per day may actually decrease

[14] The simultaneous malfunction of many peripheral nerves

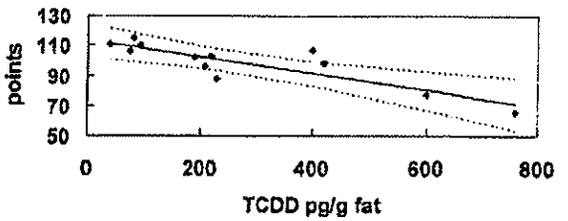


Fig. 6: Correlation of serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and Memory Quotient in 1996. r = -0.78, p =0.01

the risk of cognitive decline, which is plausible given the strong link between alcohol and decreased risk of cardiovascular disease.

Diabetes Mellitus

Several studies have found a possible link between TCDD and diabetes. The development of Type 2 diabetes mellitus usually begins with 'insulin resistance', meaning that the body does not respond properly to insulin, such that blood sugar levels are high even when insulin levels are high. The insulin resistant state increases the chances of developing diabetes and heart disease. Activators of PPAR, a key regulator of systemic insulin sensitivity, delay the onset of type 2 diabetes by lowering plasma, hepatic, and intramuscular triglycerides. One possibility for TCDD-mediated diabetes could be an inhibition of PPAR through the Ah receptor. A plausible molecular connection between dioxin-like compounds and Type 2 diabetes was proposed by Remillard and Bunce /91/, who suggested that dioxin exposure might be a risk factor for diabetes through an antagonism of PPAR functions.

Four decades after the BASF Ludwigshaven accident, mean fasting glucose levels in the exposed workers were elevated and associated with current levels of TCDD /92/. Korean veterans of the war in Vietnam had an increased frequency of diabetes /37/. On the other hand, no positive dose-response was found in the NIOSH population of 267 chemical workers /93/.

In Operation Ranch Hand veterans having a serum TCDD level above 33.3 pg/g fat, the adjusted relative risk for fasting serum glucose levels, diabetes prevalence, and the oral glucose tolerance test was significantly elevated /94/. According to Kern et al. /95/, high blood TCDD levels could promote an insulin-resistant state, but the magnitude of this effect appeared to be small. An 18-fold increase in blood TCDD resulted in only a 10% change in insulin sensitivity in 29 matched pairs. Twenty percent of Czech patients were diagnosed with Type 2 diabetes up to 2 years after exposure. Among the last 15 patients in 2004, 4 (27%) were diabetics, 2 of whom were treated with oral medications to control diabetes, and a further 2 were treated with a diabetic diet only /56/.

Other Hormonal Effects

Androgens and estrogens induce cell-cycle progression and regulate gene expression by very similar molecular mechanisms /96/. In vivo studies in experimental animals suggest a cross-talk between the signal transduction pathways of AhR and steroid hormone receptors, including estrogen,

androgen, and thyroid hormone receptors. The transcriptional activities of TCDD and AhR may be linked to estradiol and the estrogen receptor /97/.

Hormonal effects were not studied in most groups having high exposures, and no clinical effects have been described. Sweeney et al. /67/ found a relation among serum levels of TCDD, prolactin, luteinizing, follicle-stimulating hormone, triiodothyronine (T3), thyroid-stimulating hormone (TSH), testosterone, and glucagon levels. The mean serum TCDD concentration in exposed sprayers was between 2.6 and 8.1 pg/g fat. As such, TCDD levels are commonly found in the general population, suggesting that background levels of TCDD could pose a risk to human health /98/. A hypothesis has been put forth that in the developed world, TCDD exposure is associated with an increased incidence of endometriosis, an estrogen-dependent reproductive and endocrine disorder involving dysfunction of the immune system /99/.

Immunological Effects

In the BASF accident study, immunologic changes following TCDD exposure have been examined in only a few studies. Levels of immunoglobulins (Ig) IgA, IgG, IgM, and complement C4 and C3 were higher in exposed workers than in an unexposed control population /93/. In the NIOSH medical study of workers exposed to chemicals contaminated with TCDD, Sweeney et al. /67/ found a relation between serum TCDD levels and counts of helper T-lymphocytes.

Pulmonary Effects

In a study of TCDD-exposed persons with clinical evidence of chloracne as a late effect, Suskind and Hertzberg /100/ observed that pulmonary functions in exposed smokers were lower than in nonexposed smokers. This finding was not confirmed in other studies, including our patients.

Death

In experimental animals, TCDD-induced mortality does not occur immediately after exposure but rather only after several days or weeks. In all mammalian species tested so far, 'wasting syndrome', a progressive body weight loss and reduced food intake, was consistently observed. Other characteristic signs of toxicity were atrophy of the thymus, bone marrow, and testicles, gastrointestinal hemorrhage, hyperplasia or metaplasia of gastric, intestinal, urinary, and bile tract mucosa, liver lesions, and porphyria /4/. No human study reported an acute instance of death /7/.

Pazderova-Vejlupkova et al. /45/ described one case of probable TCDD-induced death. This 55-year-old healthy man was exposed for 9 months as a chemical worker; he died 2 years after the end of exposure. Pathological anatomy findings showed unusually severe atherosclerosis of the brain (diffuse status lacunaris, i.e., multiple small infarcts), liver, pancreas and kidneys, cardiac hypertrophy, porphyria with ultra-violet light fluorescence of liver, kidney, and bone marrow tissue, as well as peripheral neuropathy. The immediate cause of death was aspiration bronchopneumonia caused by an impaired swallowing mechanism. Death was attributed to TCDD and compensated as an occupational disease. Unfortunately, as TCDD-level measurement was not available in 1970, direct proof for this conclusion was unobtainable. Based on experimental data, however, lethal TCDD intoxication is plausible with the course and pathological findings of this case.

Cancer

The IARC /4/ evaluated TCDD in 1997 as a compound carcinogenic to humans, based on evidence that TCDD is a multi-site carcinogen in experimental animals through a mechanism involving the AhR, which functions in the same way as in humans. Similar tissue concentrations were

found in experimental animals and in heavily exposed human populations, in which an increased overall cancer risk was observed, as well as in animal bioassays. Certain studies, including the study on U.S. Vietnam War veterans /101/ and that of Bodner et al. /102/ on Dow Chemical Company workers, did not find a cancer association. Nevertheless, the four most important human studies for the evaluation of the carcinogenicity by the IARC were those on herbicide producers with relatively severe exposures—one in the U.S. /103/, one in the Netherlands /104/, and two in Germany /105–106/, in addition to one extensive international cohort /107/ and one case in the Seveso population in Italy /108/. An increased risk for lung cancer, soft-tissue sarcoma, and non-Hodgkin lymphoma was found. Overall, the strongest evidence for the carcinogenicity of TCDD was for all cancers combined /4/.

CONCLUSION

TCDD is an important chemical having high toxicity and long persistence, both in the environment and in the human body. In the past, the most serious intoxications came from industry. Recently, TCDD has also been used intentionally with harmful intent, the most well-known case being Ukrainian president Yushchenko. The acute effects of TCDD exposure are well described in the literature, yet the long-term consequences, except carcinogenicity, seem to be rather underevaluated.

Chloracne is one of the most obvious symptoms of acute intoxication, in addition to porphyria, transient hepatotoxicity, hypertension, hyperlipidemia, diabetes, and peripheral and central neurotoxicity. On the other hand, atherosclerosis, hypertension, diabetes, ocular vascular changes, and signs of neural-system damage, including neuropsychological impairment, can be present several decades after massive TCDD exposure because of its long-term persistence in the human body. Such chronic effects are nonspecific and multifactorial and may be causally linked only to severely intoxicated subjects. This opinion is supported by the dose-dependent effect of TCDD in experimental studies and in heavily exposed groups of subjects, such as Czech chemical workers. TCDD toxicity can be mitigated by symptomatic pharmacological treatment, including hypolipidemic drugs. As a specific remedy to decrease TCDD levels is not yet available, patients with severe exposures should be followed-up and treated symptomatically.

ACKNOWLEDGMENT

We would like to express thanks to the Ministry of Education MSM 0021620807 for the support of the research project, to the Axys Varilab laboratory in Czech Republic, and to Professor Steve Diskin for linguistic assistance.

REFERENCES

1. Institute of Medicine of the National Academics, Board on Health Promotion and Disease Prevention, Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides: Veterans and Agent Orange: update 2002. Washington, DC, USA: National Academy Press, 2003; 1–619.
2. Geusau A, Abraham K, Geissler K, Sator MO, Stingl G, Tschachler E. Severe 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) intoxication: clinical and laboratory effects. Environ Health Perspect 2001; 109: 865–869.
3. Green NJ, Hassanin A, Johnston AR, Jones KC. Observations on historical, contemporary, and natural PCDD/Fs. Environ Sci Technol 2004; 38: 715–723.
4. International Agency for Research on Cancer. Polychlorinated dibenzo-para-dioxins. In: Polychlorinated Dibenzo-para-dioxins and Polychlorinated dibenzofurans. Lyon, France: IARC Monographs 1997; 69: 33–343.
5. Dwernychuk LW, Cau HD, Hatfield CT, Boivin TG, Hung TM, Dung PT, et al. Dioxin reservoirs

in southern Viet Nam—a legacy of Agent Orange. Chemosphere 2002; 47: 117–137.
6. Ferrario J, Byrne C. Dibenzo-p-dioxins in the environment from ceramics and pottery produced from ball clay mined in the United States. Chemosphere 2002; 46: 1297–1301.
7. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Chlorinated Dibenzo-p-Dioxins. Atlanta, Georgia, USA: ATSDR, www.atsdr.cdc.gov/toxprofiles/tp104.html.
8. Renwick AG, Barlow SM, Hertz-Picciotto I, Boobis AR, Dybing E, Edler L, et al. Risk characterisation or chemicals in food and diet. Food Chem Toxicol 2003; 41: 1211–1271.
9. Fries GF: Transport of organic environmental contaminants to animal products. Rev Environ Contam Toxicol 1995; 141: 71–109
10. Weiss J, Päpke O, Bergman A. A worldwide survey of polychlorinated dibenzo-p-dioxins, dibenzofurans, and related contaminants in butter. Ambio 2005; 34: 589–597.
11. Aylward LL, Hays SM. Temporal trends in human TCDD body burden: Decreases over three decades and implications for exposure levels. J Exposure Anal Environ Epidemiol 2002; 12: 319–328.
12. Young AL. TCDD biomonitoring and exposure to Agent Orange: still the gold standard. Environ Sci Pollut Res 2004; 3: 143–146.
13. Schecter A, Cao D, Papke O, Prange J, Constable JD, Matsuda M, et al. Recent dioxin contamination from Agent Orange in residents of a Southern Vietnam city. JOEM 2001; 43: 435–443.
14. Hooper K, Chuvakova T, Kazbekova G, Hayward D, Tulenova A, Petreas MX, et al. Analysis of breast milk to assess exposure to chlorinated contaminants in Kazakhstan: sources of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposures in an agricultural region of southern Kazakhstan. Environ Health Perspect 1999; 107: 429–430.
15. Bencko V, Černá M, Jech L, Šmíd J: Exposure of breast-fed children in the Czech Republic to PCDDs, PCDFs, and dioxin-like PCBs. Environ Toxicol Pharmacol 2004; 18: 83–90.
16. Gu YZ., Hogenesch JB, Bradfield CA. The PAS superfamily: sensors of environmental and developmental signals. Annu Rev Pharmacol Toxicol 2000; 40: 519–561.
17. Nebert DW, Roe AL, Dieter MZ, Solis WA, Yang Y, Dalton TP. Role of the aromatic hydrocarbon receptor and [Ah] gene battery in the oxidative stress response, cell cycle control, and apoptosis. Biochem Pharmacol 2000; 59: 65–85.
18. Whitlock JP, Jr. Induction of cytochrome P450 1A1. Annu Rev Pharmacol Toxicol 1999; 39: 103–125.
19. Filbrandt CR, Wu Z, Zlokovic B, Opanashuk L, Gasiewicz TA. Presence and functional activity of the aryl hydrocarbon receptor in isolated murine cerebral vascular endothelial cells and astrocytes. Neurotoxicology 2004; 25: 605–616.
20. Hakkola J, Pasanen M, Pelkonen O, Hukkanen J, Evisalmi S, Anttila S, et al. Expression of CYP 1B1 in human adult and fetal tissues and differential inducibility of CYP1B1 and CYP 1A1 by Ah receptor ligands in human placenta and cultured cells. Carcinogenesis 1997; 18: 391–397.
21. Lai ZW, Pineau T, Esser C. Identification of dioxin-responsive elements (DREs) in the 5' regions of putative dioxin-inducible genes. Chem Biol Interact 1996; 100, 97–112.
22. Puga A, Xia Y, Elferink C. Role of the aryl hydrocarbon receptor in cell cycle regulation. Chem Biol Interact 2002; 141, 117–130.
23. Päpke O, Ball M, Lis ZA, Scheunert K. PCDD/PCDF in whole blood samples of unexposed persons. Chemosphere1989; 19: 941–8.
24. Rappe C, Nygren M, Marklund S, Keller LO, Berggvist PA, Hansson M. Assessment of human exposure to polychlorinated dibenzofurans and dioxins. Environ Health Perspect 1985; 60: 303–304.
25. Weber LW, Zesch A, Rozman K: Penetration, distribution and kinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in human skin in vitro. Arch Toxicol 1991; 65: 421–428.
26. Weber LW, Ernst SW, Stahl BU, Rozman K: Tissue distribution and toxicokinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats after intravenous injection. Fundam Appl Toxicol 1993; 21: 523–534.
27. Rohde S, Moser GA, Päpke O, McLachlan MS. Clearance of PCDD/Fs via the gastrointestinal tract in occupationally exposed persons. Chemosphere 1999; 38: 3397–3410.
28. Geusau A, Schmaldienst S, Derfler K, Papke O, Abraham K. Severe 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) intoxication: kinetics and trials to enhance elimination in two patients. Arch Toxicol 2002; 76: 316–325.
29. Aylward LL, Brunet RC, Carrier G, Hays SM, Cushing CA, Needham LL, et al. Concentration-dependent TCDD elimination kinetics in humans: toxicokinetic modeling for moderately to highly exposed adults from Seveso, Italy, and Vienna, Austria, and impact on dose estimates for the

6788

NIOSH cohort. J Exposure Anal Environ Epidemiol 2005; 15: 51–65.
30. Neuberger M, Rappe C, Bergek S, Cai H, Hansson M, Jager R, et al: Persistent health effects of dioxin contamination in herbicide production. Environ Res 81; 1999: 206–214.
31. Miniero R, De Felip E, Ferri F, di Domenico A: An overview of TCDD half-life in mammals and its correlation to body weight. Chemosphere 2001; 43: 839–844.
32. Neuberger M, Landvoigt W, Derntl F Blood levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in chemical workers after chloracne and in comparison groups. Int Arch Occup Environ Health 1991; 63: 325–327.
33. Michalek JE, Pirkle JL, Needham LL, Patterson DG Jr., Caudill SP, Tripathi RC, et al. Pharmacokinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Seveso adults and veterans of operation Ranch Hand. J Expo Anal Environ Epidemiol 2002; 12: 44–53.
34. Emond C, Michalek JE, Birnbaum LS, DeVito M. Comparison of the use of a physiologically based pharmacokinetic model and a classical pharmacokinetic model for dioxin exposure assessments. Environ Health Perspect 2005; 113: 1666–1668.
35. Emond C, Birnbaum LS, DeVito MJ, Physiologically based pharmacokinetic model for developmental exposures to TCDD in the rat. Toxicol Sci 2004; 80: 115–133.
36. Dai LC: Agent Orange in the Viet Nam War: History and Consequences. Hanoi, Vietnam: Vietnam Red Cross Society, 2000; 1–202.
37. Kim J-S, Lim H-S, Cho S-I, Cheong H-K, Lim M-K. Impact of Agent Orange exposure among Korean Vietnam veterans. Ind Health 2003; 41: 149–157.
38. Ott MG, Messerer P, Zober A. Assessment of past occupational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin using blood lipid analyses. Int Arch Occup Environ Health 1993; 65: 1–8.
39. Flesch-Janys D, Becher H, Gurn P, Jung D, Konietzko J, Manz A, et al. Elimination of polychlorinated dibenzo-p-dioxins and dibenzofurans in occupationally exposed persons. J Toxicol Environ Health 1996; 47: 363–378.
40. Smith AH, Patterson DG Jr, Warner ML, Mac Kenzie R, Needham LL. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels of New Zealand pesticide applicators and their implication for cancer hypotheses. J Natl Cancer Inst 1992; 84: 104–108.
41. Landi MT, Consonni D, Patterson DG Jr, Needham LL, Lucier G, Brambilla P. 2,3,7,8-tetrachlorodibenzo-p-dioxin plasma levels in Seveso 20 years after the accident. Environ Health Perspect 1998; 106: 273–277.
42. Calvert GM, Wall DK, Sweeney MH, Fingerhut MA Evaluation of cardiovascular outcomes among U.S. workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Environ Health Perspect 1998; 106 Suppl 2: 635–643.
43. Neuberger M, Rappe C, Bergek S, Cai H, Hansson M, Jager R, et al. Persistent health effects of dioxin contamination in herbicide production. Environ Res 1999; 81: 206–214.
44. Zemek A, Kočan A. 2,3,7,8-tetrachlorodibenzo-p-dioxin in soil samples from a trichlorophenol-producing plant. Chemosphere 1991; 23: 1769–1776.
45. Pazderová J, Lukáš E, Němcová M, Spáčilová M, Jirásek L, Kalenský J, et al. Chronic poisoning by chlorinated hydrocarbons, formed in the production of 2,4,5-sodium trichlorophenoxyacetate. Pracov Lék 1974; 26: 332–339. [in Czech, English abstract]
46. Pazderová-Vejlupková J, Lukáš E, Němcová M, Pícková J, Jirásek L. Chronic poisoning by 2,3,7,8-tetrachlordibenzo-p-dioxine. Pracov Lék 1980; 32: 204–209. [in Czech, English abstract]
47. Pazderová-Vejlupková J, Lukáš E, Němcová M, Pícková J, Jirásek L. The development and prognosis of chronic intoxication by 2,3,7,8-tetrachlordibenzo-p-dioxine in men. Arch Environ Health 1981; 36: 5–11.
48. Pelclová D, Fenclová Z, Dlasková Z, Urban P, Lukáš E, Procházka B, et al. Biochemical, neuropsychological, and neurological abnormalities following 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure. Arch Environ Health 2001; 56: 493–500.
49. Černá M, Bajgar L, Crhová Š, Grabic R, Kozák J, Kratěnová J, et al. Levels of PCDDs, PCDFs, and PCBs in the blood of the non-occupationally exposed residents living in the vicinity of a chemical plant, comparison with a background level for the Czech population. Organohalogen Compounds 2004; 66: 2637–2641.
50. Young AL Regens JL. Serum TCDD levels and health effects from elevated exposure: Medical and scientific evidence. Environ Sci Pollut Res 2005; 12: 1–4.
51. Mocarelli P, Needham LL, Marocchi A, Patterson DG Jr, Brambilla P, Gerthoux PM. Serum concentrations of 2,3,7,8-tetrachlorodibenzo-p-

dioxin and test results from selected residents of Seveso, Italy. J Toxicol Environ Health 1991; 32: 357–66.
52. Robinson WS, Clothier B, Akhtar RA, Yang AL, Latour I, van Ijperen C, et al. Non-Ahr gene susceptibility loci for porphyria and liver injury induced by the interaction of 'dioxin' with iron overload in mice. Molecul Pharmacol 2002; 61: 674–681.
53. Doss M, Sauer H, von Tiepermann R, Colombi AM. Development of chronic hepatic porphyria (porphyria cutanea tarda) with inherited uroporphyrinogen decarboxylase deficiency under exposure to dioxin. Int J Biochem 1984; 16: 369–373.
54. Jung D, Konietzko J, Reill-Konietzko G, Muttray A, Zimmermann-Holz HJ, Doss M, et al. Porphyrin studies in TCDD-exposed workers. Arch Toxicol 1994; 68: 595–598.
55. Jirásek L, Kalenský J, Kubec K, Pazderová J, Lukáš E. Chlorakne, Porphyria cutanea tarda und andere Intoxikationen durch Herbizide Hautartzt 1976; 27: 328–333. [In German, English abstract]
56. Pelclová D, Fenclová Z, Preiss J, Škrha J, Prázný M, Spáčil J, et al. Damage during chronic intoxication with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Abstracts of the conference "Framing the Future in Light of the Past: Living in a Chemical World", Bologna, Italy, 2005; 118.
57. Santostefano MJ, Richardson VM, Walker NJ, Blanton J, Lindros KO, Lucier GW, et al. Dose-dependent localization of TCDD in isolated centrilobular and periportal hepatocytes. Toxicol Sci 1999; 52: 9–19.
58. Mocarelli P, Marocchi A, Brambilla P, Gerthoux P, Young DS, Mantel N. Clinical laboratory manifestations of exposure to dioxin in children. A six-year study of the effects of an environmental disaster near Seveso, Italy. JAMA 1986; 256: 2687–2695.
59. Martin JV. Lipid abnormalities in workers exposed to dioxin. Br J Ind Med. 1984; 41: 254–256.
60. Calvert GM, Hornung RW, Sweeney MH, Fingerhut MA, Halperin WE Hepatic and gastrointestinal effects in an occupational cohort exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. JAMA 1992; 267: 2209–2214.
61. Oliver RM. Toxic effects of 2,3,7,8 tetrachlorodibenzo 1,4 dioxin in laboratory workers. Br J Ind Med 1975; 32: 49–53.
62. Pelclová D, Fenclová Z, Preiss J, Procházka B, Spáčil J, Dubská Z, et al. Lipid metabolism and neuropsychological follow-up study of workers exposed to 2,3,7,8-TCDD. Int Arch Occup Environ Health 2002; 75 Suppl: 60–66.
63. Dalton TP, Kerzee JK, Wang B, Miller M, Dieter MZ, Lorenz JN, et al.. Dioxin exposure is an environmental risk factor for ischaemic heart disease. Cardiovascul Toxicol 2001; 1: 285–298.
64. Vogel CFA, Sciullo E, Matsumura F Activation of inflammatory mediators and potential role of Ah-Receptor ligands into foam cell formation. Cardiovasc Toxicol 2004; 4: 363–373.
65. Shaban Z, El-Shazly S, Abdelhady S, Fattouh I, Muzandu K, Ishizuka M, et al. Down regulation of hepatic PPARα function by AhR ligand. J Vet Med Sci 2004; 66: 1377–1386.
66. Calvert GM, Willie KK, Sweeney MH, Fingerhut MA, Halperin WE. Evaluation of serum lipid concentrations among U.S. workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Arch Environ Health 1996; 51: 100–107.
67. Sweeney MH, Calvert GM, Egeland GA, Fingerhut MA, Halperin WE, Piacitelli LA. Review and update of the results of the NIOSH medical study of workers exposed to chemicals contaminated with 2,3,7,8-tetrachlorodibenzo-dioxin. Teratog Carcinog Mutagen 1997/98; 17: 241–247.
68. Dobiášová M. AIP—atherogenic index of plasma like significant predictor of cardiovascular risk: from research to practice. Vnitr Lek 2006; 52: 64–71. [In Czech, English Abstract]
69. Zober A, Messerer P, Ott MG: BASF studies: Epidemiological and clinical investigations on dioxin-exposed chemical workers. Teratog Carcinog Mutagen 1997/98; 17: 249–256.
70. Wolfe WH, Michalek JE, Miner JC, Rahe A, Silva J, Thomas WF, et al. Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. I. Physical health. JAMA. 1990; 264: 1824–1831.
71. Sweeney MH, Mocarelli P. Human health effects after exposure to 2,3,7,8-TCDD. Food Addit Contam 2000; 17: 303–316.
72. Vena J, Boffetta P, Becher H, Benn T, Bueno-de-Mesquita HB, Coggon D, et al. Exposure to dioxin and nonneoplastic mortality in the expanded IARC international cohort study of phenoxy herbicide and chlorophenol production workers and sprayers. Environ Health Perspect 1998; 106 Suppl 2: 645–653.
73. Spáčil J, Češka R, Petrášek, Šobra J. The effect of four-year hypolipidaemic treatment on the intimal thickness of the common carotid artery in patients with familiar hyperlipidaemia. Int

6790

Angiol 1999; 18: 313–319
74. Zenker HJ, Beer EM. Early changes of the vascular system of the eye in hyperlipoproteinemia. Klin Monatsbl Augenheilkd. 1989; 195: 7–13. [In German, English abstract]
75. Yamakawa K, Bhutto IA, Lu Z, Watanabe Y, Amemiya T. Retinal vascular changes in rats with inherited hypercholesterolemia—corrosion cast demonstration. Curr Eye Res 2001; 22: 258–265.
76. Assennato G, Cervino D, Emmett EA, Longo G, Merlo F. Follow-up of subjects who developed chloracne following TCDD exposure at Seveso. Am J Ind Med 1989; 16: 119–125.
77. Sweeney MH, Fingerhut MA, Arezzo JC, Hornung RW, Connally BL. Peripheral neuropathy after occupational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Am J Ind Med 1993; 23: 845–858.
78. Grahmann F, Claus D, Grehl H, Neundorfer B. Electrophysiologic evidence for a toxic polyneuropathy in rats after exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). J Neurol Sci 1993; 115: 71–5.
79. Grehl H, Grahmann F, Claus D, Neundorfer B. Histologic evidence for a toxic polyneuropathy due to exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in rats. Acta Neurol Scand 1993; 889: 354–357.
80. Klawans, H.L.: Dystonia and tremor following exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Mow Disord 1987; 2: 255–261.
81. Thömke F, Jung D, Besser R, Röder R, Konietzko J, Hopf HC. Increased risk of sensory neuropathy in workers with chloracne after exposure to 2,3,7,8-polychlorinated dioxins and furans. Acta Neurol Scand 1999; 100: 1–5.
82. Michalek JE, Akhtar FZ, Arezzo JC, Garabrant DH, Albers JW. Serum dioxin and peripheral neuropathy in veterans of Operation Ranch Hand. Neurotoxicology 2001; 22: 479–90.
83. Bertazzi, P.A.: Long-term effects of chemical disasters. Lessons and results from Seveso. Sci Total Environ 1991; 106: 5–20.
84. Bertazzi, PA, Bernucci I., Brambilla G, Consonni D, Pesatori AC. The Seveso studies on early and long-term effects of dioxin exposure: a review. Environ. Health Perspect 1998; 106 Suppl 2: 625–633.
85. Russell DH, Buckley AR, Shah GN, Sipes IG, Blask DE, Benson B. Hypothalamic site of action of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicol Appl Pharmacol 1988; 94: 496–502.
86. Hassoun EA, Al-Ghafri M, Abushaban A. The role of antioxidant enzymes in TCDD-induced oxidative stress in various brain regions of rats after subchronic exposure. Free Radicals Biol Med 2003; 35: 1028–1036.
87. Ingel F, Platonova V, Katosova L. Human emotional stress, dioxin blood contents and genetic damage in Chapaevsk town. Chemosphere 2001; 43: 989–998.
88. Barrett DH, Morris RD, Akhtar FZ, Michalek JE Serum dioxin and cognitive functioning among veterans of Operation Ranch Hand. Neurotoxicology. 2001; 22: 491–502.
89. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005; 64: 277–281.
90. Stampfer MJ, Kang JH, Chen J, Cherry R, Grodstein F. Effects of moderate alcohol consumption on cognitive function in women. N Engl J Med 2005; 352: 245–253.
91. Remillard RBJ, Bunce NJ. Linking dioxins to diabetes: Epidemiology and biological plausibility. Environ Health Perspect 2002; 110: 853–858.
92. Ott MG, Zober A, Germann C. Laboratory results for selected target organs in 138 individuals occupationally exposed to TCDD. Chemosphere 1994; 29: 2423–2437.
93. Steenland K, Calvert G, Ketchum N, Michalek J. Dioxin and diabetes mellitus. An analysis of the combined NIOSH and Ranch Hand Data. Occup Environ Med 2001; 58: 641–648.
94. Henriksen GL, Ketchum NS, Michalek JE, Swaby JA. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. Epidemiology 1997; 8: 252–258.
95. Kern PA, Said S, Jackson WR Jr, Michalek JE: Insulin sensitivity following Agent Orange exposure in Vietnam veterans with high blood levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Clin Endocrinol Metab 2004; 89: 4665–72.
96. Barnes-Ellerbe S, Knudsen KE, Puga A. 2,3,7,8-Tetrachlorodibenzo-p-dioxin blocks androgen-dependent cell proliferation of LNCaP cells through modulation of pRB phosphorylation Mol Pharmacol 2004; 66: 502–511.
97. Matthews J, Wilhen B, Thomsen J, Gustaffson JA. Aryl hydrocarbon receptor-mediated transcription: ligand-dependent recruitment of estrogen receptor alpha to 2,3,7,8-tetrachlorodibenzo-p-dioxin–responsive promoters. Mol Cell Biol 2005; 25: 5317–5328.
98. Johnson E, Shorter C, Bestervelt L, Patterson D,

6791

Needham L, Piper W, et al. Serum hormone levels in humans with low serum concentrations of 2,3,7,8-TCDD. Toxicol Ind Health 2001; 17: 105–112.
99. Birnbaum LS, Cummings AM: Dioxins and endometriosis: A plausible hypothesis. Environ Health Perspect 2002; 110: 15–21.
100. Suskind RR, Hertzberg VS. Human health effects of 2,4,5-T and its toxic contaminants. JAMA 1984; 251: 2372–2380.
101. Mahan CM, Bullman TA, Kang HK, Selvin S. A case-control study of lung cancer among Vietnam veterans. JOEM 1997; 39: 740–747.
102. Bodner KM, Collins JJ, Bloemen LJ, Carson ML. Cancer risk for chemical workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Occup Environ Med 2003; 60: 672–675.
103. Fingerhut MA, Halperin WE, Marlow WE, Piacitelli LA, Honchar PA, Sweeney MH, et al. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. New Engl J Med 1991; 324: 212–218.
104. Bueno de Mesquita HB, Doombos G, van der Kuip DAM, Kogevinas M, Winkelmann R. Occupational exposure to phenoxy herbicides and chlorophenols and cancer mortality in the Netherlands. Am J Ind Med 1993; 23 : 289–300.
105. Ott MG, Zober A. Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after a 1953 reactor accident. Occup Environ Med 1996; 53: 606–616.
106. Becher H, Flesch-Janys D, Kauppinen T, Kogevinas M, Steindorf K, Manz A, et al. Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins. Cancer Causes Control 1996; 7: 312–321.
107. Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P, Bueno de Mesquita HB, et al. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols and dioxins: An expanded and updated international cohort study. Am J Epidemiol 1997; 145: 1061–1075.
108. Bertazzi PA, Pesatori AC, Consonni D, Tironi A, Landi MT, Zocchetti C. Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. Epidemiology 1993; 4: 398–406.
109. Haorah J, Knipe B, Leibhart J, Ghorpade A, Persidsky Y. Alcohol-induced oxidative stress in brain endothelial cells causes blood-brain barrier dysfunction. J Leukoc Biol 2005; 78: 1223–1232.
110. Lukáš E, Urban P, Pelclová D, Fenclová Z, Rappe C. Neurological and neurophysiological follow-up on workers exposed to 2,3,7,8-TCDD, J Neurol Sci, 2001; 187 Suppl 1: 291.
111. Kim GW, Lewen A, Copin J, Watson BD, Chan PH. The cytosolic antioxidant, copper/zinc superoxide dismutase, attenuates blood-brain barrier disruption and oxidative cellular injury after photothrombotic cortical ischemia in mice. Neuroscience 2001; 105: 1007–1018.
112. De Matteis F. Porphyria cutanea tarda of the toxic and sporadic varieties. Clin Dermatol 1998; 16: 265–267.

Available online at www.sciencedirect.com
ScienceDirect
Crop Protection 26 (2007) 266–269
Crop Protection
www.elsevier.com/locate/cropro

Regulatory progress, toxicology, and public concerns with 2,4-D: Where do we stand after two decades?

James S. Bus[a,*], Larry E. Hammond[b]

[a]*The Dow Chemical Company, Toxicology and Environmental Research and Consulting, 1803 Building, Midland, MI 48674, USA*
[b]*Industry Task Force II on 2,4-D Research Data, Carmel, IN 46033, USA*

Received 10 January 2005; accepted 14 June 2005

Abstract

2,4-D is member of the phenoxy family of herbicides and has major uses in agriculture, forestry, turf, non-crop and aquatic weeds. Since its introduction in 1946, the toxicology of 2,4-D has been studied extensively and repeatedly. Beginning in 1980, regulatory agencies in North America and Europe initiated re-registration/re-evaluation activities for 2,4-D, which resulted in the formation of the Industry Task Force II on 2,4-D Research Data, and has resulted in the submission of 60 toxicology studies conducted to GLP standards using 2,4-D acid and its dimethylamine salt and 2-ethylhexyl ester forms. The various forms of 2,4-D were toxicologically equivalent. 2,4-D in all three forms has low-to-moderate acute oral toxicity (rat LD_{50} 699–896 mg/kg) and is not well absorbed through skin. In rat and mouse subchronic and chronic studies, overall dietary no-observed-adverse-effect-levels (NOAEL) were 15 and 5 mg/kg/day, respectively. 2,4-D was not carcinogenic in either rodent species, consistent with a lack of genotoxicity in in vitro and in vivo test systems. Mild kidney toxicity was the primary toxic effect in these studies. 2,4-D was not a developmental toxicant in rat (overall NOAEL 25 mg/kg/day) and rabbit (overall NOAEL 75 mg/kg/day) studies, had a low potential for multi-generation reproductive toxicity and neurotoxicity (NOAELs 5 mg/kg/day, respectively). When compared to estimated human exposure levels, the overall toxicology NOAEL of 5 mg/kg/day represents a margin of exposure (MOE) of 1700 for commercial applicators and 50,000 for home and garden users. Thus, coupled with the extensive toxicology data, 2,4-D meets safety standards for all countries where it is registered. Additional 2,4-D information is available on the Industry Task Force II on 2,4-D Research Data website www.24d.org.

Keywords: 2,4-D; 2,4-Dichlorophenoxyacetic acid; Toxicology; Epidemiology; Cancer

1. Introduction

2,4-Dichlorophenoxyacetic acid (2,4-D) is member of the phenoxy family of herbicides and has major uses in agriculture crops, forestry, turf, non-crop and aquatic weeds. Since its introduction in 1946, the toxicology of 2,4-D has been studied extensively and repeatedly. Beginning in 1980, regulatory agencies in North America and Europe initiated re-registration/re-evaluation activities for 2,4-D which resulted in the formation of the Industry Task Force II on 2,4-D Research Data, and has also resulted in submission of 60 toxicology studies conducted to good laboratory practice (GLP) standards using 2,4-D acid and its dimethylamine salt and 2-ethylhexyl ester forms.

The toxicology and human health effects of 2,4-D have been extensively reviewed (Munro et al., 1992; Bus and Leber, 2001; Gingell et al., 2001; Kennepohl and Munro, 2001; Garabrant and Philbert, 2002). Although there are thousands of studies describing the potential toxicity and health effects of 2,4-D, the purpose of this review is to overview the findings of animal and human health studies primarily conducted or sponsored by the Industry Task Force II on 2,4-D Research Data (2,4-D Task Force) with the three forms of 2,4-D (acid, dimethylamine salts, and 2-ethylhexyl ester). These studies serve as key data elements used by regulatory agencies to assess the potential human health risks associated with the use of 2,4-D.

*Corresponding author. Tel.: +1 989 636 4557; fax: +1 989 638 9863.
E-mail addresses: jbus@dow.com (J.S. Bus), lhammond@indy.rr.com (L.E. Hammond).

0261-2194/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.cropro.2005.06.010

2. Acute toxicology

The acute oral toxicity of 2,4-D in rats is represented by LD_{50} values of 699, 949 and 896 mg/kg, respectively, for the acid, salt and ester forms (Munro et al., 1992; Bus and Leber, 2001; Gingell et al., 2001). At these high dose levels clinical signs include ataxia and myotonia. In rabbits, LD_{50} values of all three forms of 2,4-D following dermal application were all greater than 2000 mg/kg (Munro et al., 1992), and are consistent with a reported low skin absorption of less than six percent (Kennepohl and Munro, 2001, Maibach and Feldmann, 1974; EPA, 2004). Lethality also is not seen in rats following acute inhalation exposures, with LC_{50} values greater than 1.8, 3.5 and 5.4 mg/L for the respective forms of 2,4-D (Munro et al., 1992).

All forms of 2,4-D are slight to minimal skin irritants in standard rabbit skin irritation tests. In addition, 2,4-D is not reported as a skin sensitizer in guinea pig sensitization studies (Kennepohl and Munro, 2001; EPA, 2004).

Both the acid and dimethylamine salts are severe eye irritants while the ester form is a minimal eye irritant (Munro et al., 1992; Gingell et al., 2001; Kennepohl and Munro, 2001; EPA, 2004).

3. Subchronic and chronic toxicity including carcinogenicity

The subchronic and chronic toxicity of 2,4-D has been characterized in rats, mice and dogs. All studies included evaluation of an extensive series of test parameters during and at termination of the studies. Parameters studied included: clinical observations, body weights, food consumption, ophthalmoscopic examinations, hematology and clinical chemistries, gross necropsies, organ weights, and complete organ histopathology evaluations.

In 90-day subchronic studies, rats were administered either 2,4-D acid and its salt and ester forms daily in the diet at 0, 1, 15, 100 or 300 mg/kg/day, salt and ester forms given as acid equivalents to 2,4-D (Charles et al., 1996a). Minimal histological alterations in kidney, liver, testes, and adrenals were mostly observed at the top dose level, a dose clearly that exceeded a maximum tolerated dose (MTD) as represented by body weight gain depressions of 37–88 percent of control values. Retinal degeneration was noted only in female rats treated with 300 mg/kg/day. Based on minimal histological alterations and minimal changes in hematology and clinical chemistry responses (red blood cell mass; thyroxin T_3 and T_4 values, platelet counts), the overall no observed adverse effect level (NOAEL) dose for these studies was 15 mg/kg/day. Importantly, comparable toxicity was observed for all three forms of 2,4-D. The slight effects on thyroid hormone levels, which were limited to high - doses of 2,4-D, suggest 2,4-D has only minimal potential to alter thyroid endocrine function.

In chronic toxicity/carcinogenicity studies, rodents were administered the 2,4-D acid form only daily in the diet, female and male rats at 0, 5, 75 and 150 mg/kg/day, and female and male mice at respective dose levels of 0, 5, 150 and 300 mg/kg/day and 0, 5, 62.5 and 125 mg/kg/day (Charles et al., 1996b). Paralleling observations in the subchronic toxicity studies, 2,4-D exhibited a low potential for chronic toxicity, with minimal effects noted in rats in kidney, liver, thyroid, and eyes that were limited to the high-dose levels. Both the rat and mice studies found no evidence of carcinogenicity, even though the top dose groups of both studies achieved MTD dose definitions. The overall NOAEL value for the combined rat/mouse studies was 5 mg/kg/day. Mild effects in kidneys were common to both species.

The findings of the carcinogenicity studies reported above have been evaluated by several regulatory and international agencies. The United States Environmental Protection Agency (EPA) concluded "2,4-D acid was not carcinogenic in male or female Fischer 344 rats...(and) was not carcinogenic in male and female B6C3F1 mice." (EPA, 1996). Both the World Health Organization (WHO) and the European Union Commission Health and Consumer Protection Directorate (EU) stated "There was no evidence of carcinogenicity ...in mice...(and) in rats." (WHO, 1996; EU, 2001).

In genotoxicity assays, all of the various 2,4-D forms tested negative in genotoxicity assays including an in vivo mouse micronucleus assay (Charles et al., 1999a), Salmonella (Ames) reverse mutation assays both with and without metabolic activation (Charles et al., 1999b), and a rat hepatocyte unscheduled DNA synthesis assay (Charles et al., 1999b). In additon, 2,4-D did not produce chromosomal aberrations in primary cultures of rat lymphocytes, or forward mutations at the hypoxanthine guanine phosphoribosyl transferase (HGPRT) locus of Chinese hamster ovary cells (Gollapudi et al., 1999). The lack of carcinogenicity of 2,4-D in chronic animal toxicity studies is consistent with the overall lack of genotoxicity for 2,4-D and its salt and ester forms.

In a number of epidemiologic studies, conducted during its lengthy and extensive use in agriculture, 2,4-D has been evaluated for potential carcinogenicity in humans. Despite early associations of 2,4-D use with non-Hodgkin's lymphoma, a comprehensive review and evaluation of the epidemiologic literature concluded: "Epidemiologic studies provide scant evidence that exposure to 2,4-D is associated with soft tissue sarcoma, non-Hodgkin's lymphoma, Hodgkins disease, or any other cancer." (Garabrant and Philbert, 2002). This conclusion is consistent with a recent study conducted by the United States National Cancer Institute (NCI), in which a large case control study of farmworkers in the American Midwest potentially exposed to 2,4-D found no evidence of an association between non-Hodgkin's lymphoma and "ever having used 2,4-D" (DeRoos et al., 2003).

Hayes and coworkers at the US NCI described a case control study claiming a link of residential use of 2,4-D to malignant lymphomas outcomes in pet dogs with access to treated areas (Hayes et al., 1991). However, a re-evaluation

6794

of the raw data from this study did not confirm either a dose–response relationship or actual association between 2,4-D use and occurrence of canine malignant lymphoma (Kaneene and Miller, 1999).

Knowledge of the dose and species-dependent pharmacokinetic behavior of 2,4-D significantly enhances the understanding of the relevance of toxicity findings of 2,4-D in rodents, and particularly in dogs, to predicting potential human health risks. Once absorbed, 2,4-D is rapidly and completely excreted in urine by both rats and humans, but not dogs (Van Ravenzwaay et al., 2003; Timchalk, 2004). In rodents and human, renal excretion of 2,4-D is facilitated by a saturable organic anion active transporter located in the renal tubules (Timchalk, 2004). The transporter does not effectively function in dogs. Studies in rats indicate the renal clearance of 2,4-D is clearly saturated at oral dose levels of 50 mg/kg, resulting in non-linear increases in 2,4-D blood concentrations at this dose and above (Gorzinski et al., 1987; Van Ravenzwaay et al., 2003). Given this non-linear behavior, saturation of 2,4-D renal clearance at 50 mg/kg suggests that animal toxicity findings observed at this dose level and higher overestimate potential human risks. In the case of dogs, both subchronic and chronic studies indicate this species, with an overall NOAEL of 1 mg/kg/day (Charles et al., 1996c), is more sensitive to 2,4-D-induced toxicity than rodents, with an overall NOAEL of 5 mg/kg/day (Charles et al., 1996b). Since the dog is lacking an effective renal organic anion clearance mechanism, this differential species response has been attributed to an inability of the dog to effectively clear 2,4-D from the body, resulting in significantly higher 2,4-D blood concentrations in dog relative to rats and humans at an equivalent oral dose of 5 mg/kg (Van Ravenzwaay et al., 2003; Timchalk, 2004). Recently, the EPA has concluded, that the rat represents a better predictor of potential toxicity in man than the dog (EPA, 2004).

4. Teratogenicity, reproductive toxicity and neurotoxicity

The potential for 2,4-D to produce birth defects and alter reproductive and neurological function also has been assessed in a series of GLP-quality studies. The teratogenicity of 2,4-D and its various salt and ester forms has been evaluated in both rats and rabbits (Charles et al., 2001). Mild fetal developmental toxicity was observed only at doses which also produced evidence of maternal toxicity, indicating developing rats and rabbits fetus are not uniquely sensitive to 2,4-D toxicity. The overall NOAEL for developmental toxicity in these studies was 25 mg/kg/day.

The potential 2,4-D reproductive toxicity has been assessed in a two-generation reproduction study in rats (oral dietary doses of 0, 5, 20 and 80 mg/kg/day; summarized in Munro et al., 1992; Bus and Leber, 2001; Gingell et al., 2001). The top dose resulted in excessive toxicity in the offspring and was not further evaluated. Minimal decreases in pup body weights in an absence of effects on fertility were reported at the mid-dose level, resulting in an overall reproductive toxicity NOAEL of 5 mg/kg.

The neurotoxicity potential of 2,4-D has been evaluated in both a single-dose acute and a 1-year chronic dietary study in rats (Mattsson et al., 1997). These studies included assessments of a functional observational battery, motor activity, and comprehensive neurohistopathology of perfused tissues. In the acute neurotoxicity study, 2,4-D acid was administered at nominal dose levels 0, 15, 75 and 250 mg/kg (0, 13, 67 and 227 actual). The top dose of 227 mg/kg caused slight transient alterations in gait and coordination and decreased motor activity 1-day after treatment that was fully reversible by day 8 post-treatment. The overall acute NOAEL was established as 67 mg/kg based on a mild locomotor response noted in a single animal at the mid-dose of 67 mg/kg. In the chronic dietary assessment the study NOAEL was 75 mg/kg/day based on retinal degeneration in high -dose, 150 mg/kg/day female rats.

5. Margins of exposure (MOE) between animal toxicity findings and human exposures

Characterization of the potential human risks to pesticide exposures can be estimated by calculation of MOEs, the ratio of NOAEL values obtained from animal toxicity studies to estimated human exposures. As shown in the information above, the overall lowest NOAEL from animal toxicity studies is 5 mg/kg/day based on the findings from chronic rat and mouse studies. Since 2,4-D is completely and rapidly excreted in urine in humans, collection of total 24-h urine samples provides reasonable estimates of immediate 2,4-D exposures. For professional workers employed as commercial yard sprayers, total 2,4-D exposure has been estimated as 0.003 mg/kg/day, resulting in a calculated MOE of 1700 (Yeary, 1986). For non-professional home and garden 2,4-D users, exposure is estimated at 0.0001 mg/kg, resulting in an MOE of 50,000 (Solomon et al., 1993). In both cases the large MOE between a dose causing no toxic effects in animals and actual estimates of human exposures under real-world use conditions suggest a high margin of safety for approved uses of 2,4-D.

6. Summary

Studies conducted or sponsored by the Industry Task Force II on 2,4-D Research Data provide a package of GLP-quality toxicity studies that characterize the range of toxicity potential of 2,4-D as required by the United States and European regulatory authorities. Details of these studies and others can be obtained at the 2,4-D Task Force website, www.24d.org. Overall, these studies indicate that 2,4-D has only low-to-moderate toxicity. Chronic and other toxicity responses are generally limited to high doses, well above those known to result in non-linear

6795

pharmacokinetic behavior. 2,4-D is not an animal carcinogen or genotoxicant, does not cause birth defects, and has low potential for reproductive toxicity and neurotoxicity. The various acid, salt and ester forms of 2,4-D show toxicologic equivalence. Thus, 2,4-D meets safety standards for all countries in which it is registered.

References

Bus, J.S., Leber, A.P., 2001. Miscellaneous chlorinated hydrocarbon pesticides. In: Bingham, E., Cohrssen, B., Powell, C.H. (Eds.), Patty's Toxicology, fifth ed., vol. 4, Wiley, New York, NY, pp. 673–679.

Charles, J.M., Cunny, H.C., Wilson, R.D., Bus, J.S., 1996a. Comparative subchronic studies on 2,4-dichlorophenoxyacetic acid, amine and ester in rats. Fund. Appl. Toxicol. 33, 161–165.

Charles, J.M., Bond, D.M., Jeffries, T.K., Yano, B.L., Stott, W.T., Johnson, K.A., Cunny, H.C., Wilson, R.D., Bus, J.S., 1996b. Chronic dietary toxicity/oncogenicity studies on 2,4-dichlorophenoxyacetic acid in rodents. Fund. Appl. Toxicol. 33, 166–172.

Charles, J.M., Dalgard, D.W., Cunny, H.C., Wilson, R.D., Bus, J.S., 1996c. Comparative subchronic and chronic dietary toxicity studies on 2,4-dichlorophenoxyacetic acid, amine, and ester in the dog. Fund. Appl. Toxicol. 29, 78–85.

Charles, J.M., Cunny, H.C., Wilson, R.D., Ivett, J.L., Murli, H., Bus, J.S., Gollapudi, B., 1999a. In vivo micronucleus assays on 2,4-dichlorophenoxyacetic acid and its derivatives. Mutat. Res. 444, 227–234.

Charles, J.M., Cunny, H.C., Wilson, R.D., Bus, J.S., Lawlor, T.E., Cifone, M.A., Fellows, M., Gollapudi, B., 1999b. Ames assays and unscheduled DNA synthesis assays on 2,4-dichlorophenoxyacetic acid and its derivatives. Mutat. Res. 444, 207–216.

Charles, J.M., Hanley, T.R., Wilson, R.D., van Ravenzwaay, B., Bus, J.S., 2001. Developmental toxicity studies in rats and rabbits on 2,4-dichlorophenoxyacetic acid and its forms. Toxicol. Sci. 60, 121–131.

DeRoos, A.J., Zahm, S.H., Cantor, K.P., Weisenburger, D.D., Holmes, F.F., Burmeister, L.F., Blair, A., 2003. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup. Environ. Med. 60, 1–9.

Environmental Protection Agency, 1996. 2,4-Dichlorophenoxyacetic acid: review of a chronic toxicity/carcinogenicity study in rats, a carcinogenicity study in mice, and a re-review of a developmental toxicity study in rats. EPA Memorandum dated May 23, 1996 from Rowland, J. to Dumas, R., Bloom, J.

Environmental Protection Agency, 2004. 2,4-Dichlorophenoxyacetic acid; Availability of risk assessment. US Federal Register Notice June 23, 2004, vol. 69, pp. 35019–35021. ⟨http://www.epa.gov/edocket/⟩, edocket ID number OPP–2004–0167.

European Commission Health and Consumer Protection Directorate, October 1, 2001. Review report for the active substance 2,4-D. Appendix II. Endpoints and related information, 1. Toxicology and metabolism. 7599/VI/97-final.

Garabrant, D.H., Philbert, M.A., 2002. Review of 2,4-dichlorophenoxyacetic acid (2,4-D) epidemiology and toxicology. Crit. Rev. Toxicol. 32 (4), 233–257.

Gingell, R., Hammond, L.E., O'Donoghue, J., Staab, R.J., Daly, I.W., Bernard, B.K., Ranpuria, A., Wilkinson, J., Woltering, D., Johns, P.A., Montgomery, S.B., Leng, M.L., 2001. Phenol and Phenolics. In: Bingham, E., Cohrssen, B., Powell, C.H. (Eds.), Patty's Toxicology, fifth ed., vol. 4 Wiley, New York, NY, pp. 489–500.

Gollapudi, B.B., Charles, J.M., Linscombe, V.A., Day, S.J., Bus, J.S., 1999. Evaluation of the genotoxicity of 2,4-dichlorophenoxyacetic acid and its derivatives in mammalian cell cultures. Mut. Res. 444, 217–225.

Gorzinski, S.J., Kociba, R.J., Campbell, R.A., Smith, F.A., Nolan, R.J., Eisenbrandt, D.L., 1987. Acute pharmacokinetic and subchronic toxicological studies of 2,4-dichlorophenoxyacetic acid. Fund. Appl. Toxicol. 9, 423–435.

Hayes, H.M., Tarone, R.E., Cantor, K.P., Jessen, C.R., McCurnin, D.M., Richardson, R.C., 1991. Case-control study of canine malignant lymphoma: positive association with dog owner's use of 2,4-dichlorophenoxyacetic acid herbicides. J. Natl Cancer 83 (17), 1226–1231.

Kaneene, J.B., Miller, R., 1999. Re-analysis of 2,4-D use and the occurence of canine malignant lymphoma. Vet. Hum. Toxicol. 41 (2), 164–170.

Kennepohl, E., Munro, I.C., 2001. Phenoxy herbicides (2,4-D). In: Handbook of Pesticide Toxicology, vol. 2, (Chapter 72.6), Agents and Toxic Actions. Academic Press, New York, NY, pp. 1623–1638.

Maibach, H.I., Feldmann, R.J., 1974. Systemic absorption of pesticides through the skin of man. Occupational Exposure to Pesticides: Report to the Federal Working Group on Pest Management from the Task Group on Occupational Exposure to Pesticides, Appendix B US Government Printing Office, Washington, DC, pp. 120–127.

Mattsson, J.L., Charles, J.M., Yano, B.L., Cunny, H.C., Wilson, R.D., Bus, J.S., 1997. Single-dose and chronic dietary neurotoxicity screening studies on 2,4-dichlorophenoxyacetic acid in rats. Fund. Appl. Toxicol. 40, 111–119.

Munro, I.C., Carlo, G.L., Orr, J.C., Sund, K.G., Wilson, R.M., Kennepohl, E., Lynch, B.S., Jablinske, M., Lee, N.L., 1992. A comprehensive, integrated review and evaluation of the scientific evidence relating to the safety of the herbicide 2,4-D. J. Am. Coll. Toxicol. 11, 559–664.

Solomon, K.R., Harris, S.A., Stephenson, G.R., 1993. Applicator and bystander exposure to home garden and landscape pesticides. In: Racke, R., Leslie, A. (Eds.), Pesticides in Urban Environments. American Chemical Society, Washington, DC, pp. 102–122.

Timchalk, C., 2004. Comparative inter-species pharmacokinetics of phenoxy acid herbicides and related organic acids: evidence that the dog is not a relevant species for evaluation human health risk. Crit. Rev. Toxicol. 200, 1–19.

Van Ravenzwaay, B., Hardwick, T.D., Needham, D., Pethen, S., Lappin, G.J., 2003. Comparative metabolism of 2,4-dichlorophenoxyacetic acid (2,4-D) in rat and dog. Xenobiotica 33, 805–821.

World Health Organization, 1996. Pesticide Residues in Food. Toxicological Evaluations, Part II., FAO Plant Production and Protection Paper 140: 31–38 and WHO/PCS/97.1: 45–96.

Yeary, R.A., 1986. Urinary excretion of 2,4-D in commercial lawn specialists. Appl. Ind. Hyg. 3, 119–121.

6796

REPORTS

Serum 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Levels of New Zealand Pesticide Applicators and Their Implication for Cancer Hypotheses

Allan H. Smith, Donald G. Patterson, Jr., Marcella L. Warner, Ron MacKenzie, Larry L. Needham*

Background: The phenoxyherbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) has been widely used by professional pesticide applicators in New Zealand since before 1950. Epidemiologic studies of the risk of cancer and birth defects have been conducted in this group of workers, but little is known about the extent of their exposure to the 2,4,5-T contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a potent carcinogen in animals. *Purpose:* The objective of this study was to determine whether the blood serum levels of TCDD in a group of professional 2,4,5-T applicators in New Zealand were greater than those of a matched control group not involved in 2,4,5-T spraying. *Methods:* Of 548 men employed as professional pesticide applicators in New Zealand from 1979 through 1982, nine were selected who had sprayed pesticides, although not necessarily 2,4,5-T, for at least 180 months. These applicators had sprayed 2,4,5-T for a range of 83-372 months. We measured the blood serum levels of polychlorinated dibenzo-*p*-dioxins and dibenzofurans, which were substituted with chlorine at the 2,3,7,8 position, in the nine pesticide applicators and in a matched group of nine control subjects. *Results:* The average serum level of TCDD for applicators was almost 10 times that for the matched control subjects, while the average levels of all other congeners and isomers measured in the two groups did not differ substantially. TCDD levels in eight of the nine applicators were higher than those in the control subjects (mean difference, 47.7 parts per trillion). The variation in TCDD levels among the applicators was related to their duration of work exposure to 2,4,5-T. *Conclusions:* On the basis of our findings in these subjects in New Zealand, we conclude that increased risks of cancer from brief exposure to phenoxyherbicides reported in other countries are probably not attributable to the TCDD that contaminates 2,4,5-T. We cannot determine from these results, however, whether TCDD exposure from prolonged use of 2,4,5-T poses significant health risks. [J Natl Cancer Inst 84:104–108, 1992]

The results of epidemiologic studies in Sweden have indicated that exposure to phenoxyherbicides and their contaminants may induce soft-tissue sarcoma (*1-5*) and malignant lymphoma (*6*), although conflicting evidence from Sweden has also been presented (*7-9*). The results of studies in New Zealand have not shown an association between these cancers and exposure to phenoxyherbicides (*10-14*). Epidemiologic studies in other countries have produced mixed results (*15-21*). The main weakness in these studies has been exposure assessment involving subjects attempting to recall short periods of herbicide use many years previous to the time of the study (*22*).

The phenoxyherbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) has been widely used in New Zealand since before 1950. During its manufacture, 2,4,5-T becomes contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a potent carcinogen for some animal species. Since 1970, the levels of TCDD in 2,4,5-T manufactured in New Zealand have been steadily decreasing from approximately 1 part per million (ppm) in 1971 to approximately 0.005 ppm in 1985 (*10*). No measurements of the level of contamination were available for 2,4,5-T produced before 1971.

Professional pesticide applicators involved in ground-level spraying of 2,4,5-T in New Zealand are perhaps the group most heavily exposed to agricultural use of 2,4,5-T in the world. Many of the applicators spray for more than 6 months per year, and some have been spraying for more than 20 years. Various epidemiologic studies of cancer and birth defects and use of 2,4,5-T in New Zealand have been conducted (*10-14,23,24*), but little is known about the actual extent of human exposure to TCDD.

The objective of this study was to compare blood serum levels of TCDD between a group of professional 2,4,5-T applicators in New Zealand and a matched control group not involved in 2,4,5-T spraying. To determine whether TCDD levels were elevated in the applicators, we measured, in both groups,

Received April 8, 1991; revised October 10, 1991; accepted October 16, 1991.

Support provided to M. L. Warner by the University of California Toxic Substances Program.

A. H. Smith, M. L. Warner, School of Public Health, Department of Biomedical and Environmental Health Sciences, University of California, Berkeley.

D. G. Patterson, Jr., L. L. Needham, Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services, Atlanta, Ga.

R. MacKenzie, Department of Laboratory Services, Wellington Hospital, Wellington, New Zealand.

We thank Dr. Neil Pearce for his assistance.

**Correspondence to:* Allan H. Smith, M.D., Ph.D., Department of Biomedical and Environmental Health Sciences, School of Public Health, University of California, Berkeley, CA 94720.

the serum levels of all polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), which were substituted with chlorine at the 2,3,7,8 position. Here, we present the findings as they relate to TCDD exposure levels and use this information to interpret earlier epidemiologic findings regarding 2,4,5-T use and the hypothesis that TCDD causes cancer in humans.

Study Design and Methods

Study Subjects

From a file of 548 men actively employed as professional pesticide applicators in New Zealand at any time from 1979 through 1982 (*23,24*), we identified 11 men aged 65 years or less with the greatest number of years and months per year of pesticide application experience. The file was originally established for studies of reproductive outcomes and is composed of all chemical applicators registered with the Agricultural Chemicals Board in 1979 and who were able to be located (*23*). Data in this file were based on exposure to pesticides in general and were not specific for the use of 2,4,5-T.

All 11 applicators identified had started spraying pesticides, although not necessarily 2,4,5-T, before 1960; were still spraying in 1984; and had sprayed pesticides for at least 180 months. A current address was located for nine of the 11 applicators. All nine applicators were invited in writing and by telephone to participate in the study, and all responded and signed a consent form agreeing to participate. Applicators were interviewed by telephone about their work histories, which included questions concerning lifetime use of 2,4,5-T in terms of years, months per year, and days per week. The applicators then donated one unit (500 mL) of blood at the blood bank nearest their homes. The blood was drawn by qualified New Zealand blood bank technicians.

The individually matched control group was composed of nine New Zealand men selected according to the following criteria: voluntary blood donation at the same blood bank where an applicator's blood had been drawn, age within 5 years of that applicator's age, no previous employment as a farm worker, no previous spraying of 2,4,5-T or any other agricultural chemical, and written permission for use of the blood drawn for research purposes, after a letter describing the study was read. These criteria ensured that the control group was similar in sex, age, and geographic distribution to the applicator group and that identical procedures were used to collect blood from both groups. Blood samples were processed and sent to the Centers for Disease Control in Atlanta, Ga., where researchers in a blinded evaluation measured levels of PCDDs and PCDFs in serum.

Laboratory Analysis

Centers for Disease Control researchers measured levels of PCDDs and PCDFs in serum, using the Centers for Disease Control serum method, which has been previously described for TCDD (*25*) and validated for the other PCDDs and PCDFs (*26*). A mixture of carbon 13-labeled PCDDs and PCDFs was added to the serum, and the mixture was allowed to equilibrate at room temperature for 30 minutes. The serum was next extracted with a mixture of saturated ammonium sulfate, ethanol, and hexane, and the hexane layer was separated.

The aqueous phase was further extracted with fresh hexane, and the combined hexane layers were then treated with concentrated sulfuric acid. The hexane extract was then washed with water, dried, and applied to column 1 of a five-column cleanup procedure developed by Smith et al. (*27*) and modified by the Centers for Disease Control (*28,29*) for human samples. The total lipid content was calculated by summing the analytically determined concentrations of the individual lipids (total cholesterol, free cholesterol, phospholipids, and triglycerides) (*30*).

The same mixture of carbon 13-labeled standards was added to each sample, which was then analyzed with two blank samples, two unknown samples, and one quality control sample. The samples were analyzed by high-resolution gas chromatography (model 5890; Hewlett-Packard Co., Palo Alto, Calif.) and by high-resolution mass spectrometry (model 70S; Fisons Instruments, Manchester, England) by the same operator. Concentrations were calculated, using the standard curves developed for each congener by the isotope-dilution mass spectrometry technique (*25*).

Results

In 1988, the average age of the nine applicators was 53 years (range, 45-62 years), which was similar to that of the control subjects (average age, 53 years; range, 44-64 years). Results of the analyses for PCDDs and PCDFs in serum for the applicators and the matched control subjects are summarized in Table 1. Average concentrations are expressed as parts per trillion (ppt), on a lipid-adjusted basis, and standard error of each congener and isomer measured is presented for each group. "Lipid-adjusted basis" means that the level of each congener or isomer is expressed as grams of congener or isomer per gram of total lipids in serum. The ratio of the averages for applicators to those for matched control subjects for each congener and isomer measured is also presented in Table 1. The average level of TCDD measured among the nine applicators was greater than that measured among the matched control subjects by a factor of 9.5. The average levels of the other congeners and isomers measured among the two groups did not differ by more than a factor of 1.4.

Serum levels of TCDD for applicators and matched control subjects are presented in Table 2. For purposes of identification, each applicator was assigned a letter (A through I), according to decreasing concentration of TCDD in the serum. As indicated in Table 2, the levels of TCDD in the serum of eight of the nine applicators were higher than those of the matched control subjects. The mean difference for all nine pairs was 47.7 ppt ($P<.01$).

In Table 3, TCDD levels for the applicators are presented with the duration of work exposure to 2,4,5-T. Initial applicator selection for the study was based on exposure to pesticides in general, since information for 2,4,5-T use was unavailable. As indicated in Table 3, some applicators did not start spraying 2,4,5-T until after 1960, and they reported a wide variation in total months of spraying.

Fig. 1 depicts the relationship between TCDD level in the serum of the applicators and their total duration of work exposure to 2,4,5-T. In general, serum

6798

Table 1. Levels on a lipid-adjusted basis of PCDDs and PCDFs in serum of nine 2,4,5-T applicators and nine matched control subjects

Congener*	Average level, ppt ± SE†		Ratio‡
	Applicator	Matched control	
Dibenzodioxins			
TCDD	53.3 ± 16.1	5.6 ± 1.1	9.5
1,2,3,7,8-PnCDD	12.4 ± 1.1	8.8 ± 0.7	1.4
1,2,3,4,7,8-HxCDD	6.8 ± 0.5	5.7 ± 0.4	1.2
1,2,3,6,7,8-HxCDD	28.6 ± 5.1	23.3 ± 4.9	1.2
1,2,3,7,8,9-HxCDD	9.9 ± 0.9	8.2 ± 0.6	1.2
1,2,3,4,6,7,8-HpCDD	121.9 ± 28.5	119.4 ± 18.4	1.0
OCDD	788.6 ± 82.3	758.7 ± 92.8	1.0
Dibenzofurans			
2,3,7,8-TCDF	1.6 ± 0.3	1.7 ± 0.3	0.9
1,2,3,7,8-PnCDF	<2.1§ ± 0.2	<2.0§ ± 0.2	1.1
2,3,4,7,8-PnCDF	8.0 ± 0.9	7.4 ± 0.8	1.1
1,2,3,4,7,8-HxCDF	5.4 ± 0.3	5.1 ± 0.5	1.1
1,2,3,6,7,8-HxCDF	5.5 ± 0.4	5.6 ± 0.6	1.0
1,2,3,7,8,9-HxCDF	<0.8§ ± 0.1	<0.8§ ± 0.1	1.0
2,3,4,6,7,8-HxCDF‖	<1.1§ ± 0.4	<1.7§ ± 0.2	1.1
1,2,3,4,6,7,8-HpCDF	14.2 ± 0.7	16.0 ± 2.3	0.9
1,2,3,4,7,8,9-HpCDF‖	<1.6§ ± 0.1	<1.9§ ± 0.3	0.8

*1,2,3,7,8-PnCDD = 1,2,3,7,8-pentachlorodibenzodioxin; 1,2,3,4,7,8-HxCDD = 1,2,3,4,7,8-hexachlorodibenzodioxin; 1,2,3,6,7,8-HxCDD = 1,2,3,6,7,8-hexachlorodibenzodioxin; 1,2,3,7,8,9-HxCDD = 1,2,3,7,8,9-hexachlorodibenzodioxin; 1,2,3,4,6,7,8-HpCDD = 1,2,3,4,6,7,8-heptachlorodibenzodioxin; OCDD = octachlorodibenzodioxin; 2,3,7,8-TCDF = 2,3,7,8-tetrachlorodibenzofuran; 1,2,3,7,8-PnCDF = 1,2,3,7,8-pentachlorodibenzofuran; 2,3,4,7,8-PnCDF = 2,3,4,7,8-pentachlorodibenzofuran; 1,2,3,4,7,8-HxCDF = 1,2,3,4,7,8-hexachlorodibenzofuran; 1,2,3,6,7,8-HxCDF = 1,2,3,6,7,8-hexachlorodibenzofuran; 1,2,3,7,8,9-HxCDF = 1,2,3,7,8,9-hexachlorodibenzofuran; 2,3,4,6,7,8-HxCDF = 2,3,4,6,7,8-hexachlorodibenzofuran; 1,2,3,4,6,7,8-HpCDF = 1,2,3,4,6,7,8-hepatochlorodibenzofuran; 1,2,3,4,7,8,9-HpCDF = 1,2,3,4,7,8,9-heptachlorodibenzofuran.

†Values are adjusted for total lipids in serum.

‡Ratio = average for applicators/average for matched control subjects.

§Not detected. Values are detection limits.

‖A number of positive signals were below limit of quantification.

Table 2. Levels of TCDD in serum of nine 2,4,5-T applicators and nine matched control subjects

Applicator designation	TCDD level in serum, ppt*		Absolute difference
	Applicator	Matched control	
A	131.0	8.8	122.2
B	113.0	2.9	110.1
C	94.8	3.6	91.2
D	55.5	5.2	50.3
E	37.6	9.3	28.3
F	21.8	3.1	18.7
G	14.1	3.6	10.5
H	8.5	2.4	6.1
I	3.0	11.3	−8.3
Mean	53.3	5.6	47.7

*Values are adjusted for total lipids in serum.

levels of TCDD in applicators increased linearly with total duration of exposure to 2,4,5-T (r = .72, P = .03, and slope = 0.39). We do not know why the level for applicator B is elevated more than expected—113 ppt after 137 months of exposure.

Discussion

The levels of TCDD measured in the applicators in our study were clearly elevated, although they were lower than those reported for other subjects with known exposure. In a U.S. study, 2,4,5-T production workers with heavy exposure to TCDD had an average lipid-adjusted serum level of about 250 ppt, measured 15-37 years after exposure had ceased (*31-33*). Based on a 7-year half-life, the mean level at last occupational exposure for the production workers was estimated at about 2240 ppt (*33*). Vietnam war veterans involved with Operation Ranch Hand had a median level of about 12 ppt (range, 0-618 ppt) at least 15 years after the last exposure of each (*34*). Although most of the applicators in our study were still spraying 2,4,5-T at the time of the blood donations, the levels measured are predominantly from exposures occurring prior to 1970 when TCDD contamination was more than 200 times the present level. Based on a 7-year half-life, the serum TCDD levels of these applicators may have averaged about 300 ppt 18 years ago.

The levels of TCDD in our control group were similar to those found in most population studies (*31*). The means and ranges of the levels of other PCDDs and PCDFs for the applicators and matched control subjects were somewhat lower, however, than those reported for the general population in other industrial countries (*31*).

The variation in levels of TCDD in the serum of professional applicators was related to the duration of work exposure of each to 2,4,5-T. Fingerhut et al. (*32*) and Sweeney et al. (*33*) also correlated the duration of workplace exposure with the serum levels of TCDD in U.S. workers who produced 2,4,5-T and 2,4,5-trichlorophenol.

Our findings have important implications concerning the hypotheses that exposure to TCDD through use of phenoxyherbicides results in various cancers such as soft-tissue sarcoma and non-Hodgkin's lymphoma. Our results indicate that the use of 2,4,5-T over many years in New Zealand resulted in substantial exposure to TCDD.

In this study, applicators had average serum TCDD levels 47.7 ppt higher than control subjects (Table 2), resulting from an average of 193 months of spraying 2,4,5-T (Table 3). Thus, on average, each 4 months of spraying resulted in a 1-ppt increase of TCDD in the blood of the applicators, up to 35 years later. On the basis of these figures, we can infer that after 1 year of spraying, the applicators' TCDD levels would increase by just 3 ppt, still below the 5.6-ppt average found in the control subjects. The increase would be greater if the extrapolation incorporated a half-life estimate for TCDD in humans, back to the time when the applicators had their heaviest exposures. Even so, since the half-life for TCDD is 5-10 years (*35*), these results suggest that the increase in serum TCDD would be modest among workers who sprayed for only 1 year. Thus, if exposure to 2,4,5-T containing TCDD causes cancer in humans, the epidemiologic evidence would likely come only from individuals with exposure occurring over many years.

6799

Table 3. Levels of TCDD in serum of nine professional applicators with history of work exposure to 2,4,5-T*

Applicator designation	TCDD level in serum, ppt	Years sprayed 2,4,5-T		Total mo sprayed 2,4,5-T
		Started	Stopped†	
A	131.0	1953	1988	372
B	113.0	1954	1988	137
C	94.8	1960	1988	278
D	55.5	1960	1985	232
E	37.6	1951	1987	165
F	21.8	1958	1987	165
G	14.1	1959	1988	180
H	8.5	1959	1988	121
I	3.0	1961	1988	83

*Values are adjusted for total lipids in serum.
†1988 indicates applicator was still spraying at the time of study.

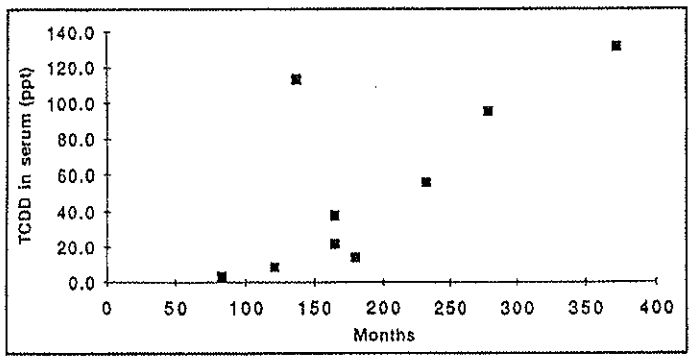


Fig. 1. Concentration of TCDD in serum of applicators in relation to total months spent spraying 2,4,5-T. Level of TCDD is adjusted for total level of lipids in serum.

Evidence that exposure to TCDD causes human cancer, however, is largely based on studies of subjects with astonishingly short exposure. Swedish case-control studies have involved very short durations of exposure. (*a*) In one case-control study (*1*), only two of 13 persons with soft-tissue sarcoma were exposed to phenoxyherbicides for more than 1 year, producing a relative risk estimate of 5.3. (*b*) In another study of soft-tissue sarcoma (*2*), a relative risk estimate of 5.7 was reported for persons with less than 30 days of exposure. (*c*) In the most recent case-control study (*4*), the relative risk estimate was 2.1 for persons with the longest duration of exposure—more than 8 weeks. (*d*) The Swedish case-control study of malignant lymphoma (*6*) yielded a relative risk estimate of 4.3 for persons with fewer than 90 days of exposure. On the basis of our present findings, it seems unlikely that exposures of such short duration would substantially increase serum levels of TCDD beyond background levels.

Our conclusions are supported by at least two other research efforts. First, Norstrom et al. (*36*) found no evidence that the 2,4,5-T used in Sweden had higher levels of TCDD contamination than that used in New Zealand. The levels of TCDD contamination in Sweden were measured at 1.1 ppm in 1952 and 0.4 ppm in 1960, compared with 1 ppm in 1971 in New Zealand (*10*). Second, a little-cited Swedish study (*37*) of dioxin and furan levels in human adipose tissue reported no difference between the mean level of TCDD in patients with cancers attributed to phenoxyherbicide exposure (2 ppt) and that in other cancer patients (3 ppt).

Case-control studies conducted in New Zealand did not identify any professional pesticide applicators with soft-tissue sarcoma or malignant lymphoma, although brief exposure to 2,4,5-T was reported in some case subjects and control subjects. The overall relative risk estimate for soft-tissue sarcoma with any exposure to phenoxyherbicides was 1.1 (90% confidence limits, 0.7-1.8) (*10*), and no evidence of an increased risk associated with duration of exposure was found. The corresponding relative risk estimate for non-Hodgkin's lymphoma was 1.3 (90% confidence limits, 0.7-2.3) (*13*). The results of this study indicate that the subjects in these earlier case-control studies probably had not experienced substantial exposure to TCDD.

If TCDD causes human cancer, epidemiologic associations should be sought in persons with substantial occupational exposures. Although some Operation Ranch Hand personnel have experienced substantial exposures, only the cohort of chemical plant workers in the National Institute of Occupational Safety and Health (NIOSH) study (*38*) is known to have had substantial exposures to TCDD as well as increased cancer risks. When measured several years after exposure had ceased, average levels of TCDD were high—about 250 ppt.

Fingerhut et al. (*39*) previously reported a cluster of soft-tissue sarcoma cases in the NIOSH cohort. Their recent report (*38*) confirmed an increased risk of soft-tissue sarcoma with an estimated relative risk of 9.22 (95% confidence limits, 1.90-27.0) for more than 1 year of exposure. The average duration of work in processes involving exposure to TCDD contamination was 6.8 years. The results of the Swedish case-control studies (*1,2,4*) are inconsistent with these findings with respect to the hypothesis that TCDD causes cancer in humans. The Swedish studies reported relative risk estimates between 2 and 6 for exposures to TCDD that were trivial compared with those of the chemical production workers.

The NIOSH cohort study (*38*) did not reveal an increased risk of other cancers that have been postulated to be related to TCDD exposure (*3,15*), including cancers of the lymphatic and hematopoietic tissues. The possibility, however, that persons with TCDD exposure have an increased risk of cancers at a variety of sites, e.g., the lung, raises an important hypothesis. Results that could support this hypothesis were reported in a study of German workers exposed to TCDD after a 2,4,5-trichlorophenol reactor accident in 1953 (*40*). For a subset of workers who had developed chloracne and had at least a 20-year latent period, a relative risk of

6 800