ENVIRONMENTAL PROTECTION AGENCY
SECURITY AND INSPECTION DIVISION

INSPECTION BRANCH REPORT

PROPOSAL TO USE HUMANS FOR PESTICIDE TESTING

INV-462-HQ

JUNE 30, 1977

Submitted by: Arnold J. Schneider
Inspector

Kenneth J. Wilk
Inspector

Approved by: Francis B. Dukes
Chief
Inspection Branch

TABLE OF CONTENTS

	Page
Exhibits	ii
Predication	1
Summary	1
Details	2
Interviews:	
James Michael Conlon	2
Fitzhugh Green	2
Lamar B. Dale, Jr.	3
Jean Pulliam	4
Mrs. Leonard Axelrod	4
Kenneth O. Olsen	5
Edwin L. Johnson	5
Irwin Baumel	6
Robert Zener	6
Jeffery Howard	6
Lee Schroer	7
Pam Symonds	8
Jane Stieber	8
Mary Rusnak	8
William Vernon Hartwell	8
Wayland Hayes	9
Eli Swisher	10
Compilation of EPA Agency Policy and DHEW Regulations involving testing on Human Subjects	10

EXHIBITS

A. Copies of Newspaper Articles from the Washington Post of May 11, 1977 and the New York Times of May 12, 1977

B. Congressional Inquiry from Senators Warren Magnuson and Adlai Stevenson dated May 11, 1977

C. Proposal for a sole source contract to test thyroid effects of selected EBDC fungicides and their Metabolites in Humans

D. EPA Order 4540.1, Clearance of Foreign Grant and Contract Awards

E. Memorandum dated March 5, 1973 from Dr. H. Fairchild, Special Pesticide Review Group to Dr. H. Korp, Deputy Assistant Administrator, Office of Pesticide Programs

F. Memorandum dated March 12, 1974 from Dr. W. Roessler Deputy Director of Criteria and Evaluation Division to DAA for Pesticide Programs

G. The Vanderbilt University proposal submitted by Dr. W. Hayes on September 20, 1974.

H. Memorandum dated October 2, 1974, from Dr. L. Dale to Director, Criteria and Evaluation Division

I. Memorandum dated October 9, 1974, from Dr. Axelrod to the DAA for Pesticide Programs

J. Memorandum dated November 7, 1974, from Dr. Axelrod to the DAA for Pesticide Programs

K. Handwritten note dated December 18, 1974, from Edwin L. Johnson to Dr. Axelrod

L. Internal review dated February 1975 of Ethylene Bisdithiocarbamate Fungicides and their Residues dated February 1975

M. 1975 FOI Request from the Environmental Defense Fund; Health Research Group; a citizen; and the answers

N. Disapproval of the proposal for the sole source contract to test thyroid effects of selected EBDC fungicides and their metabolites in Man

O. Memorandum dated April 29, 1975 from Lee Schroer, Attorney to Jeffery H. Howard, Associate General Counsel.

P. C&P Telephone printout of Long Distance Telephone Service

Q. Compilation of EPA Agency Policy and DHEW Regulations involving testing on Human Subjects

PREDICATION

This investigation is predicated upon an oral request from James M. Conlon, Associate Deputy Assistant Administrator for Pesticide Programs to investigate the facts surrounding the proposal to test the fungicide, EBDC, and its metabolite, ETU, on human subjects in Mexico in order to be familiar with and responsive to the report on this proposal that appeared in the Washington Post on May 11, 1977 (Exhibit A).

Subsequently, a request for an investigation into this matter was received from Senators Warren Magnuson and Adlai Stevenson (Exhibit B).

SUMMARY

Ethylene bisdithiocarbamate (EBDC) is a widely used fungicide which degrades into ethylene thiourea (ETU) and appears as a residue in food and feed crops. High levels of ETU in diets of experimental animals result in hyperplasia and adenocarcinoma of the thyroid gland. While tolerance levels exist for the EBDC fungicide, no tolerance levels have been established for ETU. With this problem and the fact that EBDC is on the list of fungicides to be re-registered under the Pesticide Act, the Criteria and Evaluation Division attempted to find a way to set the tolerance levels. From 1974 to April 1975 memoranda, reports, and proposals were made concerning the testing for tolerance levels of EBDC and ETU, including testing in humans.

In April 1975, a proposal was prepared by Dr. Axelrod, Director of the Criteria and Evaluation Division, requesting a contract be awarded to a researcher in a Mexico City hospital to conduct human testing involving EBDC and ETU in Mexico City.

Since 1972, EPA has incorporated Department of Health, Education and Welfare (DHEW) regulations concerning any testing involving human subjects. EPA also has a procedure which must be followed in all foreign contracts and grants. As the proposal in question involved both of these elements, it would have been subjected to these provisions. Modifications would, necessarily, have to have been made and various approval outside of the Office of Pesticides were needed, including that of the Department of State.

There is no evidence that the proposal was written by anyone other than Dr. Axelrod; and approvals appearing on the proposal were routine approvals within Pesticide Programs. The proposal was disapproved by the Deputy Assistant Administrator for Pesticide Programs and never reached the formal contract stage where outside approvals would have been needed.

DETAILS

Interview of James Michael Conlon

Mr. Conlon, Associate Deputy Assistant Administrator for Pesticide Programs was interviewed on May 14, 1977. According to Conlon, a contract proposal was written by the Criteria and Evaluation Division (Exhibit C). It proposed that a sole-source contract be entered into with a hospital in Mexico City for the purpose of studying the effects of selected EBDC fungicides on humans. The proposal was disapproved by Dr. Edwin L. Johnson, Deputy Assistant Administrator (DAA) for Pesticide Programs.

Interview of Fitzhugh Green

Mr. Green, who in 1975 was the Director of the Office of International Activities for EPA, was interviewed on May 23, 1977. He said that he received a telephone call from someone in Dr. Axelrod's office who made an inquiry about giving a contract to a researcher in Mexico. Green described this inquiry as a trial balloon. He was not sure of the identity of the caller but did remember that the proposal was explained and that the reason given for going to Mexico was to avoid the DHEW "prohibition" on testing humans. Green said he responded to the caller that this was a "bum idea." The caller said, "How could you make up your mind without seeing the proposal?" Green said he told the person to bring the proposal to his office. He added that was the last he heard of it.

He said the next time he saw Johnson, Green asked about the proposal. Johnson said that he "canned it." Green said that any indication that he approved the proposal, as reported in the newspaper, is a "total lie."

NOTE: EPA Order 4540.1, dated December 29, 1972, requires the formal and signed approval of the Office of International Activities and the concurrence of the Department of State on all proposals for awarding foreign grants and contracts (Exhibit D). This proposal had not reached the stage where this procedure would have taken place. Consequently, formal, signed approval of the Office of International Activities or concurrence of the Department of State was never obtained. The procedure based on this order is for the program to request clearance of foreign research award from International Activities. International Activities sends the scope of work on the proposal with a request to the Department of State for its concurrence. The Department of State notifies the U. S. Embassy in the country where the contractor or researcher is located. The U. S. Embassy then verifies the reputation of the researcher and the affiliated company or

university. After the concurrence and the award of the contract, EPA advises the State Department and the U. S. Embassy of the status of the project.

Interview of Dr. Lamar B. Dale, Jr.

Dr. Dale was interviewed on May 25, 1977. He stated that he told the newspaper reporter that the proposal was Dr. Axelrod's idea. The concept of testing on humans to determine tolerances for EBDC and ETU began with a memorandum (Exhibit E) dated March 5, 1973, from Mr. Homer Fairchild, Acting Coordinator, Special Pesticide Review Group, to Dr. Henry J. Korp, Deputy Assistant Administrator, Office of Pesticide Programs (OPP).

Dr. Dale said any contract for human testing would have to be given to a qualified clinician who would have to go before a DHEW panel for permission to do the study. After permission is given, the contract study could begin.

Dr. Dale stated that the idea of human testing continued to be entertained, and the need for a contract was discussed in a memorandum from William Roessler, Deputy Director, Criteria and Evaluation Division, to the DAA of Pesticide Programs (Exhibit F).

In September 1974, according to Dr. Dale, an unsolicited proposal was received from Dr. Wayland J. Hayes, Jr. of Vanderbilt University to test dithiocarbamate fungicides (EBDC) on humans (Exhibit G).

Dr. Dale said Dr. Axelrod did not think the proposal was acceptable because it did not include a study of ETU. Dr. Dale also expressed the opinion that he thought even Dr. Hayes wasn't confident that the proposal would be approved.

Dr. Dale wrote Dr. Axelrod on October 2, 1974, he considered the Vanderbilt proposal to be excellent, and with minor alterations, would provide the data needed for a decision on EBDC (Exhibit H). Dr. Axelrod then wrote the DAA for Pesticide Programs supporting the proposal stating, "...As you know, the previous studies and analyses of animal experimentation have yielded equivocal data, and we would have the privilege of an ethical and acceptable human experimentation..." (Exhibit I).

Dr. Dale drafted a memorandum on November 7, 1974, for Dr. Axelrod's signature to the DAA for Pesticide Programs criticizing the Vanderbilt proposal and suggesting the addition of "short term studies in humans with ETU to establish a level which has no adverse effect on thyroid function" (Exhibit J).

Dr. Johnson, DAA for Pesticide Programs, replied on December 18, 1974, to Dr. Axelrod's memorandum of November 7, 1974 with a handwritten note expressing doubt for the need of the Vanderbilt study, but leaving it up to Dr. Axelrod to decide whether to proceed with the study (Exhibit K).

Dr. Dale said he felt any human study should be done by industry, but Dr. Axelrod felt EPA should do it as the public would not trust the results from industry.

Nothing came of the Vanderbilt study. In February 1975, an internal review was completed on EBDC, which, among other issues identified the need to study EBDC and ETU in humans (Exhibit L title page and pertinent pages only).

Dr. Dale said that he was told by Dr. Axelrod that he (Dr. Axelrod) was "going to Mexico" on a proposal for EBDC. Dr. Axelrod also told Dr. Dale, that he (Dr. Axelrod) had talked with Fitzhugh Green of International Activities concerning a contract in Mexico. Dr. Dale said the next thing he knew was that the contract proposal was on Johnson's desk and a Freedom of Information (FOI) request had been received from the Environmental Defense Fund (EDF) regarding the proposal. Dr. Dale added that Dr. Irwin Baumel, a toxicologist who formerly worked for him, may have worked on the contract proposal since Baumel was the Branch's "EBDC man."

Interview of Jean Pulliam

Jean Pulliam, Research Progress Coordinator, OPP, was interviewed on May 26, 1977. She worked for Dr. Axelrod as a branch chief during the period in question, and she was an associate of his when both were employed by Southwest Research Institute in San Antonio, Texas. She denied any involvement in the planning of the "Mexican proposal" and did not know who else may have been involved besides Dr. Axelrod. Pulliam considered herself to be a close personal friend of Dr. Axelrod and because of their friendship, she took responsibility for removing Dr. Axelrod's personal effects from his office after his death in August 1975 and giving them to Mrs. Axelrod.

Interview of Mrs. Leonard Axelrod

On June 3, 1977, Mrs. Axelrod was contacted telephonically to arrange for an interview. Mrs. Axelrod advised she had no information to offer regarding this investigation. She also stated that the boxes of her husband's personal effects, which had been returned to her by Jean Pulliam, did not contain any office files. Since the boxes only contained personal effects, Mrs. Axelrod said she would object to EPA investigators looking through them.

Interview of Kenneth O. Olsen

Kenneth O. Olsen, Supervisor of Information and Management Group, Office of Toxic Substances, was interviewed on May 27 and May 31, 1977. During the period in question he was a program manager for Dr. Axelrod. Olsen maintained that he had an administrative function within the group and had no action involving the proposal other than seeing that funds were available. Olsen said that one of his duties was to write status reports of projects and that is why his name appears on office memoranda. He denied any involvement in the proposal or any knowledge of how it was prepared.

Interview of Edwin L. Johnson

Edwin L. Johnson, Deputy Assistant Administrator for Pesticide Programs, was interviewed on June 1, 1977. Johnson said he was Acting DAA during 1972 and most of 1973, and occupied a staff position in the DAA's immediate office during the latter part of 1973 and most of 1974. In November 1974, he became Acting DAA; and in April 1975, he was appointed DAA.

He stated he hadn't seen the proposal until it arrived on his desk. as he was responsible for signing sole-source justifications. After his approval, the proposal would have gone to contracts. He said he didn't like the Vanderbilt proposal and the suggestions of human testing in several prior documents. Johnson said he didn't know if the proposal was legal or what regulations were governing human testing so he sent it to Robert Zener, EPA's General Counsel. Zener telephoned Johnson to say the proposal was given to Jeffery Howard, an attorney on the staff.

Johnson further stated that Howard telephoned him to say the proposal was "atrocious" and told Johnson to expect a telephone call from Ms. Hinkle of EDF. Howard told Johnson that EDF would file an FOI request for the proposal. Johnson asked whether EDF should get a copy of the proposal, and Howard said to give it to them because they already had a copy. From this conversation, Johnson inferred that Howard had notified EDF of the proposal and gave them a copy.

NOTE: On April 29, 1975, EDF representative Maureen Hinkle requested the proposal under the Freedom of Information Act (Exhibit M). Besides the EDF request this exhibit includes: EDF's reaction dated May 5, 1975, written by William Butler, Washington counsel for EDF; Dr. Talley's answer to the Butler letter; a copy of the FOI request from the Health Research Group dated June 3, 1975; and copies of two other private FOI requests.

Mr. Johnson said that he told Dr. Axelrod that he planned to disapprove the proposal unless Dr. Axelrod could give a better reason

for testing on human subjects and particularly why it should be conducted in Mexico. Then, on May 1, 1975, Johnson notified Dr. Axelrod of the disapproval (Exhibit N).

Interview of Irwin Baumel

Dr. Baumel was interviewed on June 7, 1977. He was with EPA from January 1975 to August 1975 and during that time, he worked for Dr. Axelrod. According to Dr. Baumel, Dr. Axelrod pushed for human experimentation, not Dr. Dale. Dr. Baumel stated that Dr. Axelrod worked very closely with Kenneth Olsen and when Dr. Axelrod was not in the division it was Olsen who ran the division. Though Dr. Baumel was the person usually in charge of the EBDC projects, Dr. Axelrod informed Dr. Baumel that he, Dr. Axelrod, would be the project officer on the proposal. Dr. Axelrod went on to say the proposal he had in mind was going to be conducted in Mexico. Later Dr. Baumel overheard Dr. Axelrod tell Olsen "We got the Mexican deal" and Dr. Axelrod seemed very happy. In Dr. Baumel's opinion, Dr. Axelrod thought this "study was really needed."

Interview of Robert Zener

Mr. Zener was the General Counsel for the Agency during the time of the proposal. When interviewed on June 7, 1977, he said he vaguely remembers the circumstances but does recall he was "appalled" and there was "general shock or outrage" concerning the human testing features of the proposal. He said he gave the proposal to Jeffery Howard to handle and he felt it was obvious the proposal would be disapproved. Zener said he wasn't surprised the proposal was "leaked" to the EDF, but denied he did it and had no idea whether Howard did it.

Zener said he did not research the matter and was not familiar with regulations governing human testing.

Interview of Jeffery Howard

Mr. Howard had been a member of the staff of the General Counsel during the period in question and was interviewed on June 9, 1977. He said he first became aware of the proposal when he received it from Johnson as a package (originals and copies) with a routing slip from Johnson asking, "Is this legal?" Howard said his first reaction was that he was "flabbergasted" at the idea of human testing. Howard gave some background concerning the relationship between Pesticide Programs and Office of General Counsel; a part of this relationship was an understanding whereby contracts involving pesticides would be reviewed by Office of General Counsel.

Howard said he had a telephone call from Dr. Axelrod concerning the proposal. Howard questioned the term "knowing consent" in the contract and he told Dr. Axelrod that DHEW had a moratorium on human testing until its regulation could be written. According to Howard, this information about the moratorium came from a memorandum prepared by Lee Schroer of the staff of OGC.

Howard quoted Dr. Axelrod as saying that the researcher mentioned in the proposal was an old friend and that Dr. Axelrod was concerned that there was no standard for ETU. Dr. Axelrod, according to Howard, felt animal studies could not provide a standard and human studies were needed.

Howard said he became concerned that nothing would be done to stop the proposal from becoming a contract. He said he wrote a memorandum to Mr. Train, who was then Administrator of EPA, telling him about the proposal and citing reasons for stopping it.

Howard said he talked with Mr. Butler of EDF about the proposal and told him what to put in the FOI request and then Howard telephoned Johnson. Howard said he was "horrified" that the FOI was sent to Dr. Talley to answer instead of OGC where Howard would have had a chance to reply to the request.

Howard denied he was responsible for the 1977 newspaper article. He said that when he left EPA, he took his own files and records which included the original proposal in question and several copies. All of these records were stored in his garage until six months ago when he threw them out. Howard did say that when he left the agency he gave copies of the proposal to Congressional investigators and in particular members of the Kennedy committee.

NOTE: A search of the files of OGC was made to find a copy of the memoranda referred to by Howard. Of particular interest was the memorandum written by Lee Schroer (Exhibit C) and the memorandum written to Mr. Train. The Train memorandum was never found.

Interview of Lee Schroer

Mr. Schroer, Attorney Office of General Counsel, was interviewed on June 14, 1977. He said he vaguely remembers a contract which concerned testing of skin tissue on aborted fetuses. Based on a request from Howard, Schroer wrote a memorandum (Exhibit C) dated April 29, 1975 discussing the fetus contract and the DHEW prohibition on fetus study (this memorandum does not address itself to the "Mexican proposal"). Schroer doesn't remember seeing the "Mexican proposal" and doubts that he wrote a memorandum concerning it. He expressed the opinion that Howard may have confused the aborted fetus contract with the "Mexican proposal."

Interview of Pam Symonds

Ms. Symonds was Dr. Axelrod's secretary and she has since left EPA. Several telephone interviews were conducted. Symonds does not remember typing the proposal. She read the recent newspaper articles (Exhibit A) and said she thought it concerned the aborted fetus contract and not the EBDC proposal. She said the person who could answer most of the questions about the EBDC proposal would be Kenneth Olsen as he was the person closest to Dr. Axelrod. Symonds does remember placing a long distance telephone call to Mexico City for Dr. Axelrod (Exhibit P). She said the phone number would be in the telephone directory she kept in the office.

NOTE: The following name, phone number, and address were found in that directory:

Dr. Emanuel Macheo
(905) 536-7500 (Area code 905 is Mexico City)
Head Pathology,
Hospital of Gynecology and Obstetrics,
Gabriel Marcera #222, Mexico City.

Interview of Jane Stieber

Ms. Stieber, an Environmental Protection Specialist, was Olsen's secretary. She said she talked with Ms. Symonds about the newspaper articles. Ms. Stieber does not remember typing the proposal; however, she said that Olsen would be able to answer any questions on the proposal.

Interview of Mary Rusnak

Ms. Rusnak, a secretary in Technical Transfer, was the secretary to Dr. Dale. She also said she didn't remember the proposal but also said that Mr. Olsen had all the needed information.

Interview of William Vernon Hartwell

Mr. Hartwell was interviewed on June 23, 1977, via telephone (377-2388). He is presently employed by the U. S. Department of Interior and in 1974 was employed by EPA. His branch chief was Dr. Axelrod. One of Mr. Hartwell's functions at EPA was to head a review team concerning an examination of the literature and the needs concerning testing of EBDC fungicides. Hartwell said he left EPA in July 1974 to join Interior and during the interim he took a vacation. Dr. Axelrod requested Hartwell to deliver a package to Dr. Hayes at Vanderbilt University during this vacation period. Hartwell said he wasn't sure what was in the package, but he suspects it was the background literature he had prepared for Axelrod

on EBDC. Hartwell thought Axelrod was giving the package to Hayes because he was an expert in this field and any testing would be cleared through the University Clinical Review Board. Hartwell said he had worked for Dr. Hayes when they were both with the Public Health Service. Dr. Hayes was in charge of the Toxicology Section of the Technology Branch in Atlanta, Georgia and Hartwell was a member of the group stationed in Phoenix, Arizona.

Interview of Wayland Hayes

Two telephonic interviews were conducted with Wayland Hayes (Area Code 615-322-2262) on June 23 and 24, 1977. According to Dr. Hayes, Mr. Hartwell came with a "great pile of paper" which was information on EBDC. Hayes made a proposal to study the drug disulfivam on alcoholics at a V.A. hospital and the EBDC fungicide, maneb on prisoners at a State prison. Dr. Neal was going to assist in the study and do his study on animals. One of the problems involved in the study was how to get sensitive measurements of the drug's (disulfivam) effect in the body. Disulfivam is chemically similar to EBDC.

Dr. Hayes said the study would have to be approved by the University Clinical Review Board and he saw no problem as this drug was already being given to humans.

Dr. Hayes came to EPA and met with Dr. Axelrod concerning the proposal. Axelrod told Hayes the study should include ETU. Hayes said no and "the chances of an ETU study being approved by the board were exactly zero." Dr. Hayes said he came to discuss maneb part of the proposal and Axelrod wanted to substitute ETU and the meeting ended without an agreement. Hayes said he wasn't interested in testing ETU's.

As far as Hayes is concerned, nothing happened with the proposal and the proposal was never presented to the Review Board. In response to the question concerning Dr. Neal's statement in the newspaper stating that the Board disapproved the study, Hayes said Neal is mistaken, the proposal never went to the Board.

Dr. Hayes was questioned whether he had any connection with Rohm and Hass, a chemical firm concerning this proposal. He said there was no relationship between him and the company.

Dr. Hayes explained the procedures on how the Review Board functions. He said when the committees were first organized, they were "very constructive" but have become "very conservative." A proposal involving human testing is given to the Board for review and it may suggest or recommend procedure changes. If approval is granted, the committee monitors the study. At the end of the study when the report is written, a statement is usually included concerning subjects' rights and the procedures used.

Interview of Eli Swisher

Dr. Eli Swisher is the manager of agricultural chemical standards for Rohm and Haas Company, Philadelphia, Pennsylvania, and was interviewed on June 29, 1977. He stated except as noted below his company has no contracts or proposals with EPA.

In 1973, Rohm and Haas (R&H) was asked for suggestions for testing EBDC. This request was made by Dr. Axelrod. EPA had told R&H that tests were needed but the agency would contract for the study and it would not be conducted by R&H or the chemical industry.

According to Dr. Swisher, nothing developed which involved R&H in 1974; however, he learned that there had been a problem between an agency sponsored study and a university. After this happened, Dr. Axelrod had asked for a proposal from R&H.

In February 1975, R&H submitted what Dr. Swisher refers to as a protocol to test EBDC. Included in this protocol was what Dr. Swisher characterized as a toxicologist's view of how such a study could be made. There was the suggestion that medical students be used as subjects because they would better understand the purpose of the study, be able to articulate any side effects, and there would be no question as to knowing consent.

Dr. Swisher was asked about the confidential memorandum referred to in a newspaper article. He said the memorandum was marked "Company Confidential" because it came from R&H research division and was attached to the front of the protocol which was sent to EPA.

Compilation of EPA Agency Policy and DHEW Regulations involving testing on Human Subjects (Exhibit Q)

1. A memorandum from Contracts Management dated March 7, 1972, to all Directors of Contracts notifying them of the DHEW publication (NIH) 72-102 dated December 1, 1971, regarding policy on Protection of Human Subjects and a December 20, 1971 memorandum entitled "Human Experimentation Under EPA Contracts."

2. A copy of the May 15, 1973, Federal Register, Volume 38, Number 93, page 12784-12787: Publicizes the EPA regulations on Human Testing financed by Research and Demonstration Grants.

3. A copy of page 30962 from the Federal Register, Volume 39, Number 167, dated August 27, 1974, declaring a moratorium on fetus research.

4. A copy of the Federal Register, Volume 40, Number 50, dated March 13, 1975, pages 11854 to 11858, concerning Protection of Human Subjects.

5. A copy of 40 CFR, Part 40 codifying the new regulations for Research and Demonstration Grants involving human subjects in 40.135-2 as amended in May 8, 1975.

6. A copy of a memorandum dated May 22, 1975 from Mr. Train to each of his Assistant Administrators that all human testing must observe the DHEW regulations and the Office of Research and Development is responsible for human testing information and clearances.

7. A copy of 45 CFR, Part 46 codifying the DHEW regulations on fetus research in 46.201 dated August 8, 1975.

8. A copy of the standard phrase added to all contracts involving human testing dated November 21, 1975.

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

JUL 1 1977

OFFICE OF THE ADMINISTRATOR

OCT 2 / 1977

Honorable Warren G. Magnuson
Chairman, Committee on Commerce, Science
and Transportation
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

As Mr. Costle promised in his letter of May 18, 1977, I am enclosing a full report of our inquiry into the proposed, but disapproved, study on feeding the fungicide, ethylene bisdithiocarbamate, (EBDC) to human subjects in Mexico (hereinafter called the Mexico proposal). This report provides a factual chronology, as best we can determine, of the events surrounding the proposal and includes all of the documents that we have been able to locate pertaining to this matter. This report also covers a proposed, but never funded, study submitted by researchers at Vanderbilt University (hereinafter called the Vanderbilt proposal) to test one of the EBDC pesticides on volunteer inmates from the Tennessee State prison as well as test a chemically-related drug on patients from a Veterans Administration hospital. This proposal was part of the chronology leading to the proposal to conduct tests in Mexico City.

This inquiry involved the full-time efforts of two professional investigators for three full weeks and considerable additional time by Mr. Dietrich, Director, Program and Management Operations for the Office of Water and Hazardous Materials. These people were not affiliated with the Office of Pesticide Programs and were not aware of this matter before it was reported in the Washington Post on May 11, 1977. I am confident of the completeness and integrity of this inquiry.

While the enclosed report provides the full details of our findings, I would like to summarize and comment on what, in my judgment, are the principal findings:

1. Over a two-year period, prior to the Mexican proposal, there was considerable professional scientific debate within EPA on the adequacy of the data available to elucidate the health effects of the EBDC and ethylene thiourea (ETU). Animals tested with ETU,

an impurity in manufactured EBDC products as well as a decomposition and metabolic product of EBDC, showed adverse effects on the thyroid, including cancer or cancer-like effects. Some scientists, including Dr. Axelrod and Dr. Dale, felt that there were undetermined threshold levels for EBDC and ETU which, if exceeded, would cause, in man, the adverse effects observed in animals. They believed that the only way to determine those threshold levels for man was to test both EBDC and ETU in the human system. They did not believe that such threshold levels could be extrapolated from animal studies or that such extrapolated results from animal studies could be used to make defensible regulatory decisions on EBDC or ETU. They firmly believed that human studies were necessary to establish safe tolerance levels for residues of EBDC and ETU on food products to sufficiently protect all human beings.

2. In September 1974, Dr. Hayes of Vanderbilt University submitted to EPA a proposal (1) to first test disulfuram (a drug which is chemically similar to EBDC) on patients at a nearby Veterans Administration hospital who were already receiving this drug for the treatment of alcoholism, and (2) to then test one of the six manufactured EBDC fungicides on inmates at the Tennessee State Prison. Our evidence indicates that Dr. Axelrod had informally discussed the EBDC problem with Dr. Hayes and invited him to submit a proposal. Our evidence does not indicate that Dr. Axelrod had worked in cooperation with a major manufacturer of EBDC in developing the Vanderbilt proposal as alleged in an article in the Washington Post on June 23, 1977. However, Dr. Axelrod, apparently, had informally and professionally discussed the testing of EBDC with Dr. Swisher of the Rohm and Haas Company, one of the manufacturers of EBDC. Such professional discussions with representatives of registrants is not unusual and, in fact, is a necessary aspect of EPA's pesticide regulatory activities. The Vanderbilt proposal clearly indicated that the details of the human testing were quite tentative and had to be further worked out. More importantly, the proposal clearly delineated that testing would be conducted under the "full and continuing consent and in conformity with...procedures established by the Vanderbilt University Clinical Investigation Committee." This meant that the testing would have been carried out in a fully ethical manner, with legally effective consent on the part of the participants being tested and in full conformity with prevailing HEW guidelines on human testing.

3. After reviewing the proposal, Dr. Axelrod recommended that it be modified to also include the human testing of ETU. Apparently, Dr. Axelrod suggested this modification to Dr. Hayes who rejected the modification because it would have involved the testing of a suspected carcinogen on humans and therefore would not have

been approved by the University's Clinical Investigation Committee. In addition, Mr. Johnson, Deputy Assistant Administrator, expressed severe reservations about the proposal because, in his opinion, he did not feel that EPA needed to supplement existing animal studies data on EBDC and ETU with human data to make a regulatory decision. (Mr. Johnson did authorize Dr. Axelrod to proceed with the proposal if he felt he must, but this tentative approval was based on the submitted proposal that excluded the testing of ETU.) As a result of both events, the Vanderbilt proposal was not further considered. Thus it did not proceed into formal processing within EPA, which would have required Mr. Johnson's formal approval by signature on a special form, nor did it proceed further at Vanderbilt University where it would have had to be approved by the Vanderbilt University Clinical Investigation Committee.

4. In February 1975, Dr. Swisher of the Rohm and Haas Company apparently submitted to Dr. Axelrod a suggested protocol for testing EBDC in which he suggested conducting the tests on medical students. We are still trying to locate this submission in our files. Our current evidence indicates, however, that this proposal was never seriously considered; certainly, it was not entered into any formal processing which would be necessary to carry it to a point of funding.

5. In April 1975, a proposal was developed for a sole source contract to be awarded to the Hospital de Gineco-Obstretricia in Mexico City. Our evidence strongly suggests that this proposal was conceptualized, articulated and written solely by Dr. Leonard R. Axelrod, former Director of the Criteria and Evaluation Division of the Office of Pesticide Programs. Our evidence also indicates, circumstantially, that Dr. Axelrod discussed this proposal with someone at the Mexico City hospital. We cannot, of course, verify these inferences because Dr. Axelrod died shortly after the proposal was written. However, we have not been able to find any evidence, circumstantial or otherwise, of co-authors, cooperators or participants in the development of the Mexican proposal.

6. Pursuant to routine Agency procedures, the Mexican proposal would have had to go through several reviews before the Contract Management Division of EPA could have negotiated and awarded a contract to the Hospital de Gineco-Obstretricia. The first required review was that of the Deputy Assistant Administrator for Pesticide Programs. That review was accomplished and resulted in a disapproval of the proposal by Mr. Edwin L. Johnson, the Deputy Assistant Administrator. This disapproval was based on Mr. Johnson's own dislike for human testing and on the advice of Mr. Jeffery H. Howard, Associate General Counsel. The proposal did not proceed into subsequent steps of routine processing after this disapproval and was not again reproposed or reconsidered. I should point out, at this point, that the Washington Post article

was incorrect in implying that the proposal was fashioned in a way to avoid the routine review by the Deputy Assistant Administrator and other offices and was in error in stating that the rejection of the proposal was the result of an "administrative fluke."

7. If the Mexican proposal had proceeded into subsequent steps, it would have had to pass two critical reviews which I believe would have resulted in its rejection or its modification to provide for ethical human testing adhering to, or equivalent to, the HEW regulation on Protection of Human Subjects. The first review would have been that of the Contracts Management Division which, among other things, would have reviewed the proposal for consistency with HEW policy on human testing. The second review would have been that of EPA's Office of International Activities and the Department of State which I believe would have resulted in a review by the United States Embassy in Mexico. Although our evidence reveals that Dr. Axelrod discussed this proposal with Mr. Fitzhugh Green, Director of the Office of International Activities, those discussions were informal and preliminary and did not result in Mr. Green's approval.

8. At the time that both the Vanderbilt and Mexican proposals were developed, parts of EPA had, or were developing, policy and procedures governing human testing. However, during that period the Office of Pesticide Programs had no policy or procedures on human testing. In this context, although I can fault Dr. Axelrod for his lack of good judgment in developing a proposal that failed to explicitly require ethical human testing, I cannot conclude that he, or any other persons, who might have been aware of the Mexican proposal, violated EPA regulations or any Federal statue.

I believe the above summary and comments respond to your first question.

In overall comment, I would conclude that there was a sincere and strongly held scientific belief, on the part of Dr. Axelrod, that human testing was essential to make a difficult regulatory decision on tolerances for EBDC and ETU residues on food crops. I cannot, however, conclude, in his absence, that there was deliberate attempt on his part to sponsor unethical human testing. I suspect that he gave little attention to the ethical protocols that would have to be followed in human testing, and preferred to leave those aspects to the institution performing the tests. I do not agree with this passive approach. I believe we have an obligation to positively assure ethical testing or, and in some cases, reject human testing.

Relative to your second question, there is no evidence that officials within the Department of Health, Education and Welfare or other agencies, such as the Department of State, were consulted in the development of the proposal. This, in part, was because the Mexican proposal (also the Vanderbilt proposal) did not get beyond its early stage of development and into formal processing. In remaining part, it was because there was no legal requirement and little or no programmatic need to consult with the Department of Health, Education and Welfare.

In response to your third question, let me first make the following points:

1. On May 15, 1973, EPA promulgated regulations governing EPA-funded research and demonstration grants. These regulations specifically required compliance with HEW guidelines on human testing.

2. We have procedures within our Contracts Management Division which require review of proposals involving human testing.

3. On May 22, 1975, shortly after the disapproval of the proposal, Mr. Russel E. Train, former Administrator of EPA, reinforced Agency policy on human testing by issuing a directive to all offices of the Agency requiring compliance with the HEW regulation on Protection of Human Subjects. That directive is included in the enclosures of the enclosed report and is still in effect.

4. We conduct and sponsor (through grants and contracts) and have conducted and sponsored since the establishment of EPA, the clinical testing of air pollutants on human subjects at, or through, our Health Effects Research Laboratory at Research Triangle Park, North Carolina. This testing is strictly controlled and managed, and strictly adheres to all current Federal statutes, regulations and guidelines on human testing. In the nearly seven years of testing under EPA, and in prior years of testing under the National Air Pollution Control Administration, we have never experienced any abnormal or adverse incidents. I am not including any details on this program because I understand that your current interest is restricted to the proposals discussed above, but I will be most happy to provide you with any information on this program that you may desire.

5. Human testing is not banned by any Federal statute or any HEW regulation but is strictly limited to ethical testing by Federal statutes and regulations. The HEW regulation on Protection of Human Subjects, to which I have referred at several points in this response, allows human testing but only under several strict conditions. The two principal conditions are (a) that "legally effective informed consent" is obtained from the human subjects

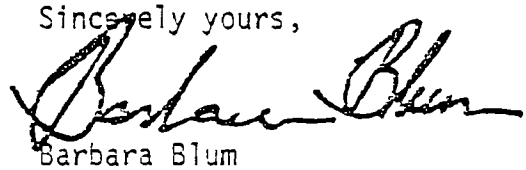
on which testing is performed and (b) that an "Institutional Board" composed of qualified, mature and experienced experts must be established to review and approve proposals for, and continuously monitor, the conduct of human testing programs to assure "safeguarding of the rights and welfare of human subjects."

As indicated above, EPA's current policy requires compliance with the HEW regulation on Protection of Human Subjects. I have directed that this policy be reviewed and strengthened, and implemented through the establishment of very strict procedures issued through an EPA Order to make certain that all EPA testing meets the most rigid legal and ethical standards. I expect to issue such an Order within three weeks.

Relative to your last question, and in addition to issuing an EPA Order, I have called for a full accounting of all human testing, past and current, within EPA and intend to carefully evaluate the findings.

I hope that I have been fully responsive to your questions and your concerns on this matter. I regret the occurrence of this incident, but am gratified that EPA management had the good judgment to reject the Mexican proposal. If I can provide you with any additional information, I shall be happy to do so.

Sincerely yours,



Barbara Blum
Deputy Administrator

Enclosure