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

008432

JUL 2 1991

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: EPA ID # S385024; ^{14}C Mancozeb - Review of "The Disposition of ^{14}C-Mancozeb in the Mouse" (MRID #416563-01)

Tox. Chem. Number: 913-A, 539, 930, 585, 41A, and 443AA
Project Number: 1-0039
Submission Number: S384798

From: Paul Chin, PhD
Section 2
Toxicology Branch I
Health Effects Division (H7509C)

Paul Chin 6/19/91

To: Kathy Martin/Janet Auerbach, PM 60
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Thru: Joycelyn Stewart, Ph.D.
Acting Section Head
Section 2, Toxicology Branch I
Health Effects Division (H7509C)

6/20/91

KB 6/24/91

I. CONCLUSIONS:

The Toxicology Branch I has reviewed "The Disposition of ^{14}C-Mancozeb in the Mouse" listed in Section II. ACTION REQUESTED. Data evaluation record is attached.

STUDY

The Disposition of ^{14}C-Mancozeb in the Mouse (MRID 416563-01, Iveresk Research International Project No. 137823, February 6, 1990)

CLASSIFICATION (Core-Grade): Supplementary
This study was conducted in an adequate manner to generate valid results. It was not intended to satisfy the toxicology data requirement for metabolism (85-1). The 3 major metabolites constituted significant portion (86-100%) of the urinary radioactivity (see last column, Table 10). The study would have provided more useful information if the metabolites of mancozeb in the mouse had been identified.

NOTE: There is a satisfactory rat metabolism study in which

metabolites were identified, therefore, the toxicology data requirement for metabolism (85-1) has been satisfied. The registrant stated that this study is not a required submission. The registrant is proposing to use these data to support their surrogate data case for their maneb worker reentry data requirement.

STUDY SUMMARY:

The absorption, distribution, biotransformation, and excretion of mancozeb was studied after oral administration to mice. Male and female mice were dosed with ^{14}C-ethylene-U-labeled mancozeb (^{14}C-mancozeb) at single oral doses of 2.5 and 150 mg/kg and at repeated doses (14 daily doses) of unlabeled mancozeb at 2.5 mg/kg followed by administration of a single oral dose of labeled mancozeb at 2.5 mg/kg. Mancozeb was rapidly absorbed, extensively metabolized, and rapidly excreted. Over a 7-day period, most (97-103 percent) of the test compound administered was excreted from the animals. The radioactivity recovered in the urine, feces, CO_2, and CS_2 in the exhaled air was 26-44, 48-64, 0.4-4.2, and at the limit of detection to 3.9 percent of the administered dose, respectively. A mean of less than 1.4% of the dose remained in carcass and tissues after 7 days. Peak tissue (including plasma) concentration of radioactivity occurred 1 and 2 hours after the administration of the test compound. One of four major metabolites of mancozeb in the urine was identified to be ethylenethiourea (ETU). The amount of this metabolite represents less than 5 percent of the administered dose. The remaining 3 major metabolites which constitute significant portion (86-98%) of the urinary radioactivity (see last column, Table 10) were not identified. Elimination of absorbed radioactivity via bile was insignificant (less than 0.2% of the dose) following single oral administrations of mancozeb to male and female mice at 2.5 mg/kg.

II. ACTION REQUESTED:

Review the following study:

The Disposition of ^{14}C-Mancozeb in the Mouse (MRID 416563-01, Iveresk Research International Project No. 137823, February 6, 1990)

III. **BACKGROUND:**

<u>There is a satisfactory rat metabolism study in which metabolites were identified</u>, therefore, the toxicology data requirement for metabolism (85-1) has been satisfied.

This study is additional data in support of the EBDC Task Force response to the PD 2/3, and is also submitted in support of maneb. Because the Q^* was calculated using the mouse tumor incidence, the registrants believe that the conversion rate of mancozeb to ETU in the mouse should be used to determine the risk of exposure by various routes. (For the Agency reply, see a memo from Judith Hauswirth, HED to Valerie Bael, RD dated July 15, 1988).

cc: Larry Dorsey, SACB, H7509C

Primary Reviewer: Paul Chin, Ph.D. 6/19/91
Section 2, Toxicology Branch I (H7509C)
Secondary Reviewer: Joycelyn Stewart, Ph.D.
Section 2, Toxicology Branch I (H7509C)

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DATA EVALUATION REPORT

STUDY TYPE: Metabolism - Mouse (85-1)
Tox Chem No: 913A
MRID No: 416563-01
TB Project No: 1-0089

TEST MATERIAL: Manganese ethylenebis(dithiocarbamate) (polymeric) complex with zinc salt

SYNONYMS: Mancozeb, Penncoceb and Vondozeb plus

SPONSOR: Pennwalt Corporation, Agrochemicals Division, Philadelphia, PA

TESTING FACILITY: Inveresk Research International
Musselburgh, EH21 7UB, Scotland

STUDY NO.: IRI Project No. 137823

REPORT TITLE: The Disposition of [14C]-mancozeb in the Mouse
Report No. 4909

AUTHORS: B. D. Cameron, B. Speirs, and K. Clydesdale

REPORT ISSUED: February 6, 1990

CONCLUSIONS:

The absorption, distribution, biotransformation, and excretion of mancozeb was studied after oral administration to mice. Male and female mice were dosed with ^{14}C-ethylene-U-labeled mancozeb (^{14}C-mancozeb) at single oral doses of 2.5 and 150 mg/kg and at repeated doses (14 daily doses) of unlabeled mancozeb at 2.5 mg/kg followed by administration of a single oral dose of labeled mancozeb at 2.5 mg/kg. Mancozeb was rapidly absorbed, extensively metabolized, and rapidly excreted. Over a 7-day period, most (97-103 percent) of the test compound administered was excreted from the animals. The radioactivity recovered in the urine, feces, CO_2, and CS_2 in the exhaled air was 26-44, 48-64, 0.4-4.2, and at the limit of detection to 3.9 percent of the administered dose, respectively. A mean of less than 1.4% of the dose remained in carcass and tissues after 7 days. Peak tissue (including plasma) concentration of radioactivity occurred 1 and 2 hours after the administration of the test compound. One of four major metabolites of mancozeb in the urine was identified to be ethylenethiourea (ETU). The amount of this metabolite represents less than 5 percent of the administered dose. The remaining 3 major metabolites which constitute significant

portion (86-98%) of the urinary radioactivity (see last column, Table 10) were not identified. Elimination of absorbed radioactivity via bile was insignificant (less than 0.2% of the dose) following single oral administrations of mancozeb to male and female mice at 2.5 mg/kg.

CLASSIFICATION (Core-Grade): Supplementary
This study was conducted in an adequate manner to generate valid results. It was not intended to satisfy the toxicology data requirement for metabolism (85-1).

NOTE: There is a satisfactory rat metabolism study in which metabolites were identified, therefore, the toxicology data requirement for metabolism (85-1) has been satisfied.

STUDY DESIGN:
The study was designed to determine the absorption, distribution, biotransformation, and elimination of [14C]-mancozeb when administered by oral gavage to mice after single high and low doses and repeated low doses. Summary of doses for the test groups used in the study are given in the following table.

Group*	Target Dose (mg/kg)	Route	No. Animals M	No. Animals F	Actual Dose (mg/kg)
Pretrial	2.5	single oral	5	-	2.68
Group A	2.5	single oral	-	5	2.82
Group B	2.5	repeated oral**	5	5	
	2.5	single oral			2.68
Group C	150	single oral	5	5	190.34
Group D	2.5	single oral	14	-	1.97
			-	14	2.48
Group E	2.5	single oral	12	-	2.14
			-	12	2.82
Group F	2.5	single oral	4	4	2.76
Group G	2.5	single oral	2	2	2.50
Group H	150	single oral	2	2	179.70

* All animals from Pretrial, Groups A, B and C were sacrificed 7 days after treatment.

** The animals in Group B received repeat oral doses of non-radiolabeled mancozeb by gavage for 14 days. On day 15 of the study, the animals were administered radiolabeled mancozeb as a single oral dose.

MATERIALS AND METHODS:

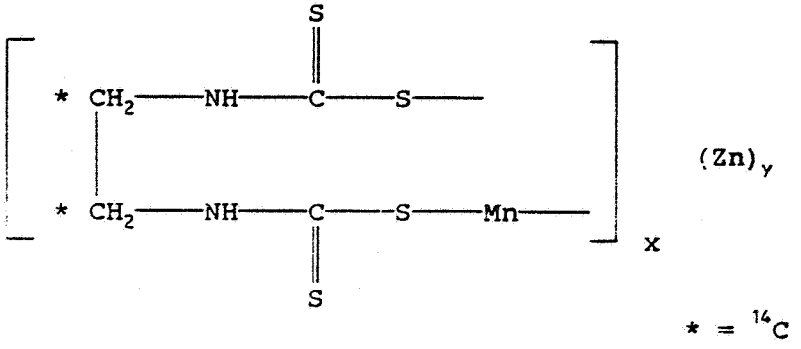
1. Animals

Male and female Charles River CD-1 strain mice, supplied by Charles River (UK) Limited, Margate, Kent, were used throughout this study. Animals used were in the weight range 24-36 g. Daily temperature and humidity were 16-23 °C and 15-96%, respectively. Food and tap water were available ad libitum.

Following dosing, animals in dosing groups Pretrial, A, B and C were placed into glass metabolism cages. Animals in dosing groups D, E, F, G and H were placed into individual polycarbonate and stainless steel cages.

2. Test Material

The radiochemical purity (98 - 99%) of [ethylene-U-14C]-mancozeb ([14C]-mancozeb) was confirmed by thin layer chromatography. The specific activity of the supplied material was 43.2 uCi/mg. This material was used to formulate low (2.5 mg/kg) and high (150 mg/kg) dose levels with technical mancozeb (unlabeled, purity unspecified). The structure and radiolabeled position (*) of [14C]-mancozeb are shown below:



3. Preparation of dosing solutions

Dose suspensions were prepared immediately prior to administration by weighing [14C]-mancozeb into a volumetric flask and suspending in 1% aqueous sodium carboxymethylcellulose. Radioactive doses administered were calculated by determining the amount of radioactivity associated with 'mock doses' taken at the time of dosing. Doses were administered using an olive bulbed oropharyngeal needle and a glass (Hamilton) syringe.
Male and female Charles River CD-1 strain mice, supplied by Charles River (UK) Limited, Margate, Kent, were used throughout this study. Animals used were in the weight range 24-36 g. Daily temperature and humidity were 16-23 °C and 15-96%,

respectively. Food and tap water were available ad libitum.

Following dosing, animals in dosing groups Pretrial, A, B and C were placed into glass metabolism cages. Animals in dosing groups D, E, F, G and H were placed into individual polycarbonate and stainless steel cages.

4. Animal experiments

Nine groups of mice were used in this study (Pretrial and Groups A-H).

Pretrial Group and Dosing Group A - Excretion Kinetics Following Single Oral Administration of [14C]-Mancozeb. (Target Dose Level 2.5 mg/kg, Uci/mouse = 3.04-3.1)

The Pretrial Group and Dosing Group A consisted of 5 male and 5 female mice, respectively. The animals received a single oral dose of [14C]-mancozeb and were placed in Jencon's all-glass metabolism cages specially designed for the separate collection of urine and faeces. One metabowl was set up for CO_2 and CS_2 collection. Urine and feces were collected frozen at the following times post dose: 0-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 h. Expired CO_2 and CS_2 were collected for the periods 0-8 and 8-24 h post dose from one animal.

At 7 days post dose the mice were sacrificed by CO_2 asphyxiation and total radioactivity in the following body fluids/tissues were measured:

Bone mineral	Liver
Bone marrow	Skeletal muscle
Brain	Adrenal
Fat	Thyroid
Heart	Thymus
Testes (ovaries)	Whole blood
Spleen	Plasma
Lungs	GI tract
Kidneys	Residual carcass

Dosing Group B - Excretion Kinetics Following Multiple Oral Administrations of Non-radiolabeled Mancozeb on Days 1-14 and [14C]-Mancozeb on Day 15. (Target Dose Level 2.5 mg/kg, uCi/mouse=3.18)

Dosing Group B consisted of 5 male and 5 female mice. The animals received a single oral administration of non-labelled mancozeb for 14 consecutive days. On Day 15 of the study the mice received a single oral administration of [14C]-mancozeb and were transferred to metabolism cages for collection of excreta. One male and one female mouse were placed into metabowls designed for the collection of CO_2 and CS_2. Samples were collected for

analysis of total radioactivity as described in the Pretrial Dosing Group.

Dosing Group C - Excretion Kinetics Following Single Oral Administration of [14C]-Mancozeb. (Target Dose Level 150 mg/kg, uCi/mouse=7.70)

Dosing Group C consisted of 5 male and 5 female mice. The animals received a single oral administration of [14C]-mancozeb and were placed into metabolism cages for collection of excreta. One male and one female mouse were placed into metabowls designed for the collection of CO_2 and CS_2. Samples were collected for analysis of total radioactivity as outlined in the Pretrial Dosing Group. In addition expired carbon dioxide, lead acetate traps and Cullens reagent traps were also collected at the 24-48 h and 48-72 h time points.

Dosing Group D - Blood Kinetics Following Single Oral Administration of [14C]-Mancozeb. (Target Dose Level 2.5 mg/kg, uCi/males=2.74, uCi/females=2.83)

Dosing Group D consisted of 14 male and 14 female mice. All animals received a single oral administration of [14C]-mancozeb and were then housed singly in polycarbonate cages. Two male and 2 female mice were sacrificed and blood samples were removed from the heart into heparinized tubes at each of the following times post dose: 0.25, 0.5, 1, 2, 4, 8 and 24 h. Levels of radioactivity in whole blood were determined.

Dosing Group E - Tissue Distribution by Quantitative Analysis Following Single Oral Administration of [14C]-Mancozeb. (Target Dose Level 2.5 mg/kg, uCi/males=3.18, uCi/females=3.07)

Dosing Group E consisted of 12 male and 12 female mice. The animals received a single oral administration of [14C]-mancozeb and were housed as in Dosing Group D. Three male and 3 female mice were sacrificed at each of the following times post dose:

1 h (time of peak blood concentration)*
8 h (time of half peak blood concentration)*
24 h and 48 h

(* = as determined in Dosing Group D)

At sacrifice levels of radioactivity were determined in the body fluids/tissues as outlined in the Pretrial Group.

Dosing Group F - Excretion of Total Radioactivity in Bile Following Single Oral Administration of [14C]-Mancozeb. (Target Dose Level 2.5 mg/kg, uCi/mouse=3.31)

Dosing Group F consisted of 4 male and 4 female mice. The

animals received a single oral administration of [14C]-mancozeb and were housed as in Dosing Group D. One male and one female animal was sacrificed at 1, 8, 24 and 48 h post dose. Immediately following sacrifice the entire gall bladder was removed. Excreta were collected at sacrifice or every 24 h. Gastrointestinal tract was analyzed separately from the residual carcass.

Dosing Group G - Tissue Distribution by Whole Body Autoradiography Following Single Oral Administration of [14C]-Mancozeb. (Target Dose Level 2.5 mg/kg, uCi/mouse=2.85)

Dosing Group G consisted of 2 male and 2 female mice. The animals received a single oral administration of [14C]-mancozeb and were housed as in Dosing Group D. One male and one female animal were sacrificed at 1 and 48 h post dose. Following sacrifice the animals were immediately prepared for whole body autoradiography.

Dosing Group H - Tissue Distribution by Whole Body Autoradiography Following Single Oral Administration of [14C]-Mancozeb. (Target Dose Level 150 mg/kg, uCi/mouse=7.12)

Dosing Group H consisted of 2 male and 2 female mice. The animals received a single oral administration of [14C]-mancozeb and were housed as in Dosing Group D. One male and one female animal were sacrificed at 1 and 48 h post dose. Following sacrifice the animals were immediately prepared for whole body autoradiography.

5. Quantitation of ethylenethiourea by metabolite profiling of urine

Metabolite profiling of pooled urine (20% by volume, 0-8 and 8-24 h) was undertaken to determine the extent of [14C]-mancozeb metabolism and to quantify the bioconversion of [14C]-mancozeb to [14C]-ethylenethiourea (ETU). A 2 dimensional thin layer chromatography (TLC) system was used to determine the % conversion dose to ETU in urine:

Solvent System 1: Chloroform: methanol: aqueous ammonia: water, 68:28:2:2 (v/v/v/v)

Solvent System 2: Ethyl acetate: ethanol : aqueous ammonia: water, 40:40:4:20 (v/v/v/v)

6. Quantitation of radioactivity

All samples were analyzed for 5 min by liquid scintillation counting technique. A limit of reliable detection of 30 dpm above background was used throughout the experiments.

7. Preparation of samples for analysis

Carbon Disulfide

Expired CS_2 was serially trapped through 10% v/v aqueous lead acetate (to remove H_2S) then through 2 Cullens reagent traps. Cullens reagent was prepared by pipetting 5 ml of copper-(II)-acetate solution into a 250 ml volumetric flask, adding 25 g of diethanolamine and making up to volume (250 ml) with ethanol.

$^{14}CO_2$

$^{14}CO_2$ production was measured in traps containing ethanolamine: 2-ethoxyethanol, 1:4 (v/v) solution.

Aqueous samples (Plasma, Urine, Cage Washing or Bile)

Duplicate aliquot of aqueous samples were made up to 1 ml with distilled water where necessary and mixed with 10 ml scintillation cocktail for counting.

Tissues, Gastrointestinal Tract, Whole Blood, Residual Carcass, and Feces

Aliquot of solid samples were weighed out and combusted using a Model 306 Tricarb automatic sample oxidizer (Packard).

QUALITY ASSURANCE:

A signed Statement of Confidentiality Claim was provided.
A signed Statement of compliance with EPA GLP's was provided.
A signed Quality Assurance Statement was provided.

RESULTS:

The excretion of radioactivity into urine (26-44% of the dose) and feces (48-64% of the dose) was rapid and complete, and tissue residues were very low. Over a 7-day period, most (86-104 percent) of the test compound administered was excreted from the animals. The excretion of radioactive carbon dioxide and carbon disulfide in expired air was 0.4-4.2% and 0-3.9% of the administered dose, respectively. The total levels of radioactivity in tissues including carcass ranged from 0.3 to 1.3% of the administered dose (Table 1).

Pretrial Group and Dosing Group A- Excretion Kinetics Following Single Oral Administration of [14C]-Mancozeb to Mice. (Target Dose Level 2.5 mg/kg) (Tables 2, 3 and 8)

Following single oral administration of [14C]-mancozeb at the low dose level to mice the majority (92-95%) of the administered dose

was excreted within 24 h. Over a 7-day-period, most (98%) of the administered dose had been excreted from the animals. The radioactivity recovered in the feces and urine was 59-64% and 31-35% of the dose, respectively. Expired CO_2 was a minor route of elimination (0.4% of the dose over 24 h) in both sexes.

At 7 days post dose, 0.28-0.30% of the administered dose was accounted for in the carcass and tissues. The highest mean level of total radioactivity was observed in the thyroid (0.31-0.33 ppm, less than 0.01% of the administered dose). The levels of total radioactivity in plasma and in whole blood were at the limit of detection and 0.01 ppm, respectively. The liver and kidneys both contained a mean of 0.02-0.03 ppm.

Dosing Group B - Excretion Kinetics Following Multiple Oral Administration of Non-radiolabeled Mancozeb on Days 1-14 and [14C]-Mancozeb on Day 15. (Target Dose Level 2.5 mg/kg) (Tables 4, 5 and 8)

In the preconditioned oral gavage group, the total radioactivity excreted in 24 h was 90 and 77% of the administered dose in males and females, respectively. Over a 7-day period, 96 and 85% of the dose was excreted in males and females, respectively. Fecal elimination accounted for 53-54% and urinary excretion accounted for 26-35% of the administered dose over 7 days. Expired CO_2 was a minor route of elimination (1.0% of the dose over 24 h). Mouse No.13 (male, 16% in urine, 56% in feces) and mouse No.16 (female, 1% in urine, 57% in feces) had an unusual excretory pattern.

At 7 days post dose 0.23-0.92% of the administered dose was accounted for in the carcass and tissues. The highest mean level of total radioactivity was observed in the thyroid (0.29 and 0.50 ppm in males and females, respectively). The levels of total radioactivity in plasma and whole blood were close to or at the limit of detection and 0.01-0.03 ppm, respectively. The liver and kidneys both contained less than 0.04 ppm.

Dosing Group C - Excretion Kinetics Following Single Oral Administration of [14C]-Mancozeb. (Target Dose Level 150 mg/kg) (Tables 6, 7 and 8)

In the high dose group, the majority (89-94%) of the radioactive dose was excreted in 24 h. Over a 7-day period, 96-99% of the administered dose was excreted in animals. Fecal elimination accounted for 48% (males) and 54% (females) and urinary excretion accounted for 43% (males) and 32% (females) of the administered dose over 7 days. Mouse No.23 (male) had an unusual excretory pattern where 67 and 30% of the administered dose was recovered in urine and 30% of the dose recovered in feces, respectively. Expired CO_2 accounted for 3-4% of the dose over 72 h.

At 7 days post dose, levels of total radioactivity, the carcass

and tissues only accounted for 0.81-1.95% of the administered dose. The highest mean level of total radioactivity was observed in the thyroid (37.51-48.47 ppm). The levels of total radioactivity in whole blood (2.83-2.97 ppm) were greater than those in plasma. The liver and kidneys contained 6.31-7.48 and 4.99-5.78 ppm, respectively.

Dosing Group D - Blood Kinetics Following Single Oral Administration of [14C]-Mancozeb. (Target Dose Level 2.5 mg/kg)

Following single oral administration of [14C]-mancozeb at the low dose level to mice, the levels of radioactivity in whole blood rose to a mean peak concentration of 0.19 ppm at 1 h post dose in males and 0.31 ppm at 2 h post dose in females and fell to 0.03-0.04 ppm at 24 h post dose.

Dosing Group E - Tissue Distribution by Quantitative Analysis Following Single Oral Administration of [14C]-Mancozeb. (Target Dose Level 2.5 mg/kg)

At 1 h following a single oral administration of [14C]-mancozeb at the low dose level to mice, the levels of total radioactivity in plasma, whole blood, organs and tissues were at their highest. The GI tract contained a mean of 17.71-19.53 ppm. The levels of total radioactivity in the liver and kidneys at 1 h post dose were 1.26-1.61 and 1.44-1.72 ppm, respectively.

Dosing Group F - Excretion of Total Radioactivity in Bile Following Single Oral Administration of [14C]-Mancozeb. (Target Dose Level 2.5 mg/kg)

Elimination of absorbed radioactivity via bile was not significant (less than 0.2% of the dose) following single oral administration of [14C]-mancozeb at the low dose level to mice. Peak concentrations of total radioactivity in the gall bladder were observed at 1 h post dose (0.06-0.15% of the dose or 3.21-10.02 ppm) and thereafter declined to 0.01-0.04 ppm at 48 h post dose.
At 24 h post dose fecal and urinary elimination accounted for 58 and 37% of the administered dose, respectively with 0.4% of the dose associated with the GI tract. The mean total radioactivity recovered at 48 h pose dose was 101-103% of the administered dose.

Dosing Groups G and H - Tissue Distribution by Whole Body Autoradiography Following Single Oral Administration of [14C]-Mancozeb. (Target Dose Level 2.5 and 150 mg/kg)

At 1 h following single oral administration of [14C]-mancozeb to mice at the low and high dose levels, radioactivity was present in all tissues. Highest concentrations of radioactivity were associated with the GI tract and the major excretory organs. At

48 h post dose the levels of radioactivity in all tissues were low.

Quantitation of Ethylenethiourea by Metabolite Profiling of Urine (Table 10)

Following single oral administration of [14C]-mancozeb at the low dose level to Pretrial Group and Group A, the total % conversion of dose to ETU in urine over 24 h was 1.12 (males) and 4.61% (females), respectively.

Following an oral dose of [14C]-mancozeb on Day 15 of a multiple low dose regime to mice (Group B) the total % conversion of dose to ETU in urine over 24 h was 0.79 (males) and 1.69% (females).

Following single oral administration of [14C]-mancozeb at the high dose level to mice (Group C) the total % conversion of dose to ETU in urine over 24 h was 1.07 (males) and 1.05% (females), respectively.

In the TLC chromatograms obtained after running in the first dimension at least 3 other major components were observed in these dosing groups. **These 3 major metabolites which constitute significant portion (86-100%) of the urinary radioactivity (see last column, Table 10) were not identified.**

Carbon Disulfide

Conversion of mancozeb to carbon disulfide over a 24-hour period was at the limit of detection in males and females following single (Pretrial and Group A) and multiple (Group B) oral administrations of [14C]-mancozeb at the low dose level. However, following single oral administration of [14C]-mancozeb at the high dose level (Group C), 3.9% (equivalent to 99 ug of CS_2) of the administered dose was accounted for as CS_2 over 72 h in both males and females.

DISCUSSION

This study appears to have been conducted in an adequate manner to generate valid results related to absorption, distribution, and excretion of mancozeb in mice following administration of single oral doses of 2.5 and 150 mg/kg and repeated doses of mancozeb at 2.5 mg/kg followed by administration of a single oral dose of mancozeb at 2.5 mg/kg.

The data demonstrates that less than 5% of an administered dose was converted to ETU in urine over a 24-hour period following various dose regimens in mice. This study was considered supplementary because the 3 major metabolites which constitute significant portion (86-100%) of the urinary radioactivity (see last column, Table 10) were not identified. The study would have

provided more useful information if the metabolites of mancozeb in the mouse had been identified.

There is a satisfactory rat metabolism study in which metabolites were identified, therefore, the toxicology data requirement for metabolism (85-1) has been satisfied.

This study is additional data in support of the EBDC Task Force response to the PD 2/3, and is also submitted in support of maneb. Because the Q_1^* was calculated using the mouse tumor incidence, the registrants believe that the conversion rate of mancozeb to ETU in the mouse should be used to determine the risk of exposure by various routes. (For the Agency reply, see a memo from Judith Hauswirth, HED to Valerie Zael, RD dated July 15, 1988).

Table 1. Radioactivity in the Urine, Feces, Expired CO_2, Cage Wash, CS_2, and Tissues (including carcass) as Percent (%) of Dose From Mice 7 Days Following a Single Oral Administration of ^{14}C-Mancozeb.

	Recovery, as % of Dose[a]		
	Dose Level		
	2.5 mg/kg (low)	150 mg/kg (high)	2.5 mg/kg (repeated)
Male			
Urine[b]	30.5	43.5	35.1
Feces	63.8	47.8	55.1
CO_2	0.4	4.2	1.0
Cage wash	3.7	3.3	5.5
CS_2	--[b]	3.9	--
Tissues	0.3	1.3	0.6
Total	98.7	104.0	97.3
Female			
Urine	34.6	31.8	25.9
Feces	58.7	54.2	52.6
CO_2	0.4	3.4	0.4
Cage wash	4.6	6.9	6.3
CS_2	--	3.9	--
Tissues	0.3	1.3	0.4
Total	98.6	101.5	85.6 (103.6)[c]

[a] Values are cumulative average of 5 male and 5 female mice. Data excerpted from Tables 1-12 from the Study Report.

[b] -- = At the limit of detection

[c] Include mean of radioactivity (18% of the administered dose) found in cage debris from two animals.

Table 2. Excretion of Radioactivity Following a Single Oral Administration of [14C]-Mancozeb to Male Mice. Pretrial Group - Dose level 2.5 mg/kg. Data excerpted from Table 1 of the Study Report. Values are average of 5 animals.

Sampling Time (hours)	% Administered dose (Mean)				
	Urine	Feces	Cage Wash	CO_2	Total
0-8	20.92	31.19	---[a]	0.18[b]	52.29
8-24	7.87	28.36	3.00	0.19[b]	39.42
24-48	1.21	3.33	0.35	---	4.89
48-72	0.38	0.54	0.13	---	1.05
72-96	0.09	0.15	0.04	---	0.28
96-120	0.00	0.11	0.02	---	0.13
120-144	0.03	0.04	0.03	---	0.10
144-168	0.02	0.05	0.09	---	0.16
Total	30.52	63.77	3.66	0.37[b]	98.32

[a] --- = Not determined.
[b] Radioactivity recovered from only one animal.

Table 3. Excretion of Radioactivity Following a Single Oral Administration of [14C]-Mancozeb to Female Mice. Group A - Dose level 2.5 mg/kg. Data excerpted from Table 4 of the Study Report. Values are average of 5 animals.

Sampling Time (hours)	% Administered dose (Mean)				
	Urine	Feces	Cage Wash	CO_2	Total
0-8	17.28	17.53	---[a]	0.20[b]	35.01
8-24	16.00	40.20	3.87	0.22[b]	60.29
24-48	0.87	0.66	0.41	---	1.94
48-72	0.20	0.24	0.09	---	0.53
72-96	0.08	0.07	0.02	---	0.17
96-120	0.04	0.02	0.05	---	0.11
120-144	0.04	0.01	0.04	---	0.09
144-168	0.03	0.01	0.06	---	0.10
Total	34.54	58.74	4.54	0.42[b]	98.24

[a] --- = Not determined.
[b] Radioactivity recovered from only one animal.

Table 4. Excretion of Radioactivity Following 14 Daily Administration of Unlabeled Mancozeb Followed by a Single Oral Administration of [14C]-Mancozeb to Male Mice. Group B - Dose level 2.5 mg/kg. Data excerpted from Table 7 of the Study Report. Values are average of 5 animals.

Sampling Time (hours)	% Administered dose (Mean)				
	Urine	Feces	Cage Wash	CO_2	Total
0-8	23.15	15.92	---[a]	0.62[b]	39.69
8-24	10.02	35.99	4.12	0.40[b]	50.53
24-48	1.37	1.66	0.41	---	3.44
48-72	0.29	0.26	0.15	---	0.70
72-96	0.10	0.13	0.06	---	0.29
96-120	0.05	0.04	0.10	---	0.19
120-144	0.05	0.01	0.16	---	0.22
144-168	0.02	0.04	0.45	---	0.51
Total	35.05	54.05	5.45	1.02[b]	95.57

[a] --- = Not determined.
[b] Radioactivity recovered from only one animal.

Table 5. Excretion of Radioactivity Following 14 Daily Administration of Unlabeled Mancozeb Followed by a Single Oral Administration of [14C]-Mancozeb to Female Mice. Group B - Dose level 2.5 mg/kg. Data excerpted from Table 7 of the Study Report. Values are average of 5 animals.

Sampling Time (hours)	% Administered dose (Mean)				
	Urine	Feces	Cage Wash	CO_2	Total
0-8	19.02	31.65	---[a]	0.13[b]	50.80
8-24	4.80	17.89	3.84	0.31[b]	26.84
24-48	1.10	2.26	0.59	---	3.95
48-72	0.26	0.37	0.49	---	1.12
72-96	0.07	0.09	0.17	---	0.33
96-120	0.32	0.06	0.68	---	1.06
120-144	0.05	0.02	0.06	---	0.13
144-168	0.27	0.31	0.50	---	1.08
Total	25.89	52.65	6.33	0.44[b]	85.31

[a] --- = Not determined.
[b] Radioactivity recovered from only one animal.

Table 6. Excretion of Radioactivity Following a Single Oral Administration of [14C]-Mancozeb to Male Mice. Group C - Dose level 150 mg/kg. Data excerpted from Table 10 of the Study Report. Values are average of 5 animals.

Sampling Time (hours)	% Administered dose (Mean)				
	Urine	Feces	Cage Wash	CO_2	Total
0-8	26.13	17.80	----[a]	1.31[b]	45.24
8-24	15.74	28.57	2.71	1.86[b]	48.88
24-48	1.13	0.94	0.29	0.58[b]	2.94
48-72	0.29	0.13	0.08	0.43[b]	0.93
72-96	0.07	0.13	0.05	---	0.25
96-120	0.04	0.07	0.02	---	0.13
120-144	0.03	0.05	0.03	---	0.11
144-168	0.02	0.06	0.11	---	0.19
Total	43.45	47.75	3.29	4.18[b]	98.67

[a] --- = Not determined.
[b] Radioactivity recovered from only one animal.

Table 7. Excretion of Radioactivity Following a Single Oral Administration of [14C]-Mancozeb to Female Mice. Group C - Dose level 150 mg/kg. Data excerpted from Table 10 of the Study Report. Values are average of 5 animals.

Sampling Time (hours)	% Administered dose (Mean)				
	Urine	Feces	Cage Wash	CO_2	Total
0-8	16.37	24.28	---[a]	1.05[b]	41.70
8-24	12.78	28.01	5.32	1.62[b]	47.73
24-48	1.83	1.19	0.64	0.40[b]	4.06
48-72	0.49	0.27	0.33	0.30[b]	1.39
72-96	0.10	0.20	0.19	---	0.49
96-120	0.10	0.10	0.06	---	0.26
120-144	0.04	0.09	0.06	---	0.19
144-168	0.06	0.05	0.29	---	0.40
Total	31.77	54.19	6.89	3.37[b]	96.22

[a] --- = Not determined.
[b] Radioactivity recovered from only one animal.

Table 8. Tissue Distribution of Radioactivity at 7 Days Following an Oral Administration of [14C]-Mancozeb to Mice. (Source: Data excerpted from Tables 2, 5, 8 and 11 of the Study Report)

	PPM (Mean ug Mancozeb equivalents per gram weight of specimen, N = 5)					
	Dose Level					
	Single 2.5 mg/kg		Repeated 2.5 mg/kg		Single 150 mg/kg	
	Male	Female	Male	Female	Male	Female
Bone Mineral	0.02	0.01	0.01	0.01	3.84	3.82
Bone Marrow	0.09	0.03	0.07	0.06	5.94	2.73
Brain	0.00	0.01	0.01	0.00	1.17	1.20
Fat	0.01	0.00	0.01	0.01	1.98	2.34
Heart	0.01	0.01	0.02	0.02	3.95	4.13
Testes/ovary	0.01	0.04	0.01	0.03	2.37	8.13
Spleen	0.02	0.02	0.03	0.02	5.96	6.81
Lungs	0.02	0.04	0.03	0.03	4.78	4.45
Kidney	0.02	0.03	0.03	0.04	4.99	5.78
Liver	0.02	0.02	0.04	0.03	6.31	7.48
Skeletal muscle	0.01	0.01	0.01	0.01	1.99	2.16
Adrenal	0.05	0.03	0.10	0.06	7.19	11.80
Thyroid	0.33	0.31	0.29	0.50	48.47	37.51
Thymus	0.01	0.02	0.03	0.13	5.57	5.03
Whole blood	0.01	0.01	0.02	0.01	2.83	2.97
Plasma	0.00	0.00	0.01	0.01	1.22	1.59
GI tract	0.00	0.01	0.01	0.00	1.53	2.02
Carcass	0.01	0.01	0.01	0.01	2.63	3.06

Table 9. Tissue Distribution of Radioactivity at 1, 8, and 24 hours Following an Oral Administration of [14C]-Mancozeb to Mice. Dosing Group E - Dose level 2.5 mg/kg. (Source: Data excerpted from Tables 15 and 16 of the Study Report)

	PPM (Mean ug Mancozeb equivalents per gram weight of specimen, N = 3)					
	Sampling Time (Hours)					
	Males			Females		
	1	8	24	1	8	24
Bone Mineral	0.19	0.37	0.03	0.23	0.12	0.04
Bone Marrow	0.67	0.64	0.04	1.12	0.69	0.10
Brain	0.14	0.05	0.01	0.16	0.05	0.01
Fat	0.18	0.42	0.04	0.22	0.08	0.03
Heart	0.25	0.09	0.02	0.31	0.10	0.03
Testes/ovary	0.19	0.06	0.08	0.94	0.73	0.10
Spleen	0.45	0.13	0.17	0.50	0.17	0.07
Lungs	0.62	0.43	0.17	0.63	0.40	1.24
Kidney	1.44	0.53	0.17	1.72	0.66	0.38
Liver	1.26	0.80	0.02	1.61	0.96	0.21
Skeletal muscle	0.19	0.51	0.12	0.23	0.12	0.02
Adrenal	1.45	0.49	0.10	0.65	0.72	0.06
Thyroid	3.10	5.52	2.68	2.20	6.71	1.20
Thymus	0.76	0.13	0.07	0.29	0.14	0.07
Whole blood	0.25	0.12	0.04	0.34	0.14	0.04
Plasma	0.28	0.15	0.06	0.37	0.19	0.07
GI tract	17.71	7.66	0.07	9.53	9.66	0.15
Carcass	0.29	0.71	0.02	0.26	0.48	0.04

Table 10. The Amounts of ETU and Unidentified Metabolites of Mancozeb in Pooled Urine Samples Following an Oral Administration of [14C]-Mancozeb to Mice. (Source: Data excerpted from Table 19 of the Study Report, values are average of 4-5 animals)

	Sex	Sampling time (hr.)	% ETU in Urine	% Dose in pooled urine	ETU as % of dose	% of Unidentified metabolites in urine
Single 2.5 mg/kg	male	0-8	5.34	20.92	1.12	94.66
		8-24	---[a]	7.87	---	100.00
	female	0-8	10.78	21.60	2.33	89.22
		8-24	14.23	16.00	2.28	85.77
Repeated 2.5 mg/kg	male	0-8	1.52	23.14	0.35	98.48
		8-24	4.37	10.02	0.44	95.63
	female	0-8	5.80	23.72	1.38	94.20
		8-24	4.06	7.64	0.31	95.94
Single 150 mg/kg	male	0-8	1.69	26.13	0.44	98.31
		8-24	4.00	15.74	0.63	96.00
	female	0-8	2.23	16.37	0.37	97.77
		8-24	5.35	12.78	0.68	94.65

[a] --- = Not detected.