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METABOLISM DEPARTMENT
AGRICULTURAL DIVISION
CIBA-GEIGY CORPORATION
VERO BEACH, FLORIDA

BIOLOGICAL REPORT FOR THE METABOLISM OF
[14 C]-METALAXYL IN CHICKENS

Project Number: 409925
Study Number: M91-409-001A
Protocol Number: 158-88 and Amendments 5, 6

Biological Phase
Initiation Date: 7/20/91
Completion Date: 7/24/91

Report Number: BIOL-91011

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Date: 11/1/91

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GOOD LABORATORY PRACTICES COMPLIANCE STATEMENT

Protocol 158-88, plus Amendments 5, 6

Biological Phase

The biological phase of study M91-409-001A has been performed in compliance with EPA Good Laboratory Practice Standards (40 CFR 160).

5.120 Woo

11/1/91
Date

Biological Coordinator

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GENERAL INFORMATION

Sponsor:

CIBA-GEIGY Corporation
Agricultural Division
410 Swing Road
P.O. Box 18300
Greensboro, NC 27419

Test Material: [ϕ - 14 C]-metalaxyl
Batch Number: JAK-VI-18
Specific Activity: 49.0 μ Ci/mg
Radiochemical purity: 99.0%
Chemical purity: 95.8%

Study Director:

5.1.2.e WOO Ph.D.
CIBA-GEIGY Corporation
Metabolism Department
Greensboro, NC

Study Participants:

5.1.2.e WOO

Testing Facility:

Biological Phase

CIBA-GEIGY Corporation
Agricultural Division
Vero Beach Research Center
Metabolism Department
7145 58th Avenue
Vero Beach, FL 32967

Archives:

The original biological data for this study are contained in Vero Beach notebook #3927 and archived with a copy of the protocol at the Ciba-Geigy Vero Beach Research Center, Vero Beach, FL. The original Biological Report, BIOL-91011, is archived at CIBA-GEIGY Corporation, Greensboro, NC.

I. OBJECTIVES

The objectives of this phase of the study were: first, to dose four healthy hens with [ϕ - 14 C]-metalaxyl for five consecutive days; second, to collect daily samples of excreta, eggs, and selected tissues for analysis of the metabolites; and third, to determine if metalaxyl administration had any effect on the general health and physiological functions of the animal.

II. SUMMARY

Four laying hens were orally administered approximately 12 mg of [ϕ - 14 C]-metalaxyl for five consecutive days via gelatin capsules containing microgranular cellulose as filler. All test animals appeared normal and healthy throughout the acclimation and test periods. All necropsies were normal.

Excreta were collected for five consecutive test days and averaged 155 g/day, excluding test day five which was only six hours prior to sacrifice. Egg production during the test period ranged 60-100%. Feed consumption during the test period averaged 133 g/day, excluding test day five. All other parameters were normal.

All requested samples were collected and stored as described in Protocol 158-88¹ and Amendments 5, 6 pending completion of Analytical Phase I.

III. MATERIALS AND METHODS

A. Test Substance

Company Code: CGA-48988
Common Name: metalaxyl
Trade Name: Ridomil®

Radiolabeled Test Substance

Label: [¹⁴C] in phenyl ring
Batch Number: JAK-VI-18
Specific Activity: 49.0 µCi/mg
Radiochemical Purity: 99.0%
Chemical Purity: 95.8%

B. Test Animal

Species: White Leghorn Chicken
Strain: H&N
Number, sex: Four, female
Source: Bronson Farms,
Sorrento, FL
Body Weights: Given TABLE I
Age: Approximately 54
weeks
Identification: Hen #6 = leg band #1
Hen #7 = leg band #3
Hen #8 = leg band #22
Hen #9 = leg band #16

C. Maintenance of Animals

Each hen was offered 160 g/day of Layena®, a complete and balanced layer ration manufactured by Purina Mills, Inc. Commercial drinking water (Deer Park) was made available ad libitum. The hens were acclimated to the metabolism cages 5 days prior to the administration of the first dose capsule. A description of the cages used in this study can be found in SOP 4.74² "Procedures for Housing Test Animals at the Vero Beach Research Center."

A model 8368-60, Cole Parmer hygromograph was used to record room temperature and relative humidity, 24 hours/day.

Treatment room lights were on 24 hours per day.

D. Test Substance Receipt

Twenty-two dosing capsules and one stability control capsule arrived at the Vero Beach Research Center (VBRC) at room temperature in good condition. The study director was notified as per Protocol 158-88¹, and Amendments 5, 6 and the capsules were stored frozen in Metabolism Department freezer #18. The VBRC reference number assigned to these capsules was R-91.

E. Administration of Dose

Four hens were each administered a daily oral dose of approximately 12 mg of [ϕ -¹⁴C]-metaxyl for five consecutive days. This corresponds to an approximate 100 ppm feed level based on 120 g of feed per day. The exact amount of test material given to each animal is listed (TABLE II).

F. Sample Collection

Excreta and eggs were collected daily for five test days (TABLES VI and VII). Blood samples were drawn from each hen just prior to their sacrifice via vacutainer tubes containing EDTA anticoagulant. During sacrifice, the samples were collected and weighed in the following order (TABLE VIII).

1. skin and attached fat
2. breast muscle
3. thigh muscle
4. fat (peritoneal)
5. liver
6. dose day 5 eggs

G. Sample Storage

Eggs from test days 1-4 were stored refrigerated prior to being radioassayed and thereafter stored frozen. Test day 5 eggs

and blood were radioassayed immediately after collection and thereafter stored frozen.

Excreta, skin, peritoneal fat, liver, breast, and thigh were stored at freezing temperatures prior to radioanalysis and thereafter stored frozen.

IV. CIRCUMSTANCES AFFECTING THE STUDY

No circumstances occurred that adversely affected the integrity or outcome of the study.

V. RESULTS AND DISCUSSION

A. Pre-acclimation

Prior to acclimation all hens were sprayed for mites on 4/3/91 with Permethrin 25% wp. This is not expected to have any effect on the study.

B. Acclimation

The test animals were acclimated for five days, 7/15-20/91. During this period the hens consumed, on average, 186-214 ml of water and 112-145 g of feed per day (TABLES IV, V). Average daily production of excreta ranged 132-173 g (TABLE VI), and egg production was 80-100%.

Two days prior to dose initiation, eggs and excreta were collected from all hens for background determination of radioactivity.

C. Administration of Dose

The hens were administered capsules, containing approximately 12 mg of [ϕ - ^{14}C]-metalaxyl, orally by hand for five consecutive days without negative incidents (TABLE II). This corresponds to an average daily dose of 6.91 mg/kg, equivalent to approximately 100 ppm in the feed (TABLE III).

During the dosing period the hens consumed, on average, 176-239 ml of water and 110-153 g of feed per day (TABLES IV, V). Average

daily production of excreta per hen ranged 134-195 g and egg production was 60-100% (TABLES VI, VII).

D. Test Animal Health

All test animals remained in good general health throughout the acclimation and test periods as determined in criteria listed in SOP 4.98³.

E. Sacrifice

Approximately 0.5 hour before sacrifice, all hens were photographed and weighed.

The hens were sacrificed with CO₂ gas. Dry ice plus water were placed in a wooden box fitted with a conical opening. The hens were lowered head first into the gas environment and asphyxiated. The procedure was performed quick and humane.

The hens were sacrificed between 6.05-6.92 hours after the last dose administration.

F. Necropsy

All of the gross necropsies were normal.

G. Environmental Conditions

The room temperatures and humidity ranged from 70-75°F and 55-95% respectively during the acclimation and test periods.

VI. CONCLUSIONS

Each of the test animals were administered a daily oral dose of approximately 12 mg of [ϕ -¹⁴C]-metalaxyl for five consecutive days. This corresponded to an average daily dose of 6.91 mg/kg of body weight and was equivalent to an approximate feeding level of 100 ppm.

Excreta and eggs were collected for five consecutive days during the dose administration period. Excreta production averaged 155 g/day

and egg production was 60-100%. Samples were collected, weighed, and stored according to Protocol 158-88¹ and Amendment 5, 6.

All test animals remained in good general health throughout the biological phase of the study with no apparent side effects from the test substance on physiological functions.

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TABLE I
BODY WEIGHTS OF HENS ORALLY ADMINISTERED
[ϕ - 14 C]-METALAXYL

<u>Animal Number</u>	<u>Dose Initiation</u>	<u>Sacrifice</u>	<u>Average</u>
Hen 6	1.62	1.67	1.65
Hen 7	1.70	1.74	1.72
Hen 8	1.96	1.99	1.98
Hen 9	1.75	1.71	1.73

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TABLE II
DAILY DOSAGE OF [ϕ - 14 C]-METALAXYL ORALLY
ADMINISTERED TO HENS

Hen 6				Hen 7		
Day	Cap No.	mg	mCi	Cap No.	mg	mCi
1	2	12.063	0.566	16	12.315	0.578
2	13	12.211	0.573	5	12.263	0.576
3	20	12.043	0.565	22	11.966	0.562
4	6	12.041	0.565	8	12.285	0.577
5	14	12.099	0.568	21	12.156	0.571
Average		12.091	0.567		12.197	0.573
Standard Deviation		.071	.003		.142	.007
Hen 8				Hen 9		
Day	Cap No.	mg	mCi	Cap No.	mg	mCi
1	15	11.994	0.563	7	12.152	0.570
2	4	12.470	0.585	12	12.396	0.582
3	11	12.233	0.574	3	12.004	0.563
4	10	11.955	0.561	9	12.472	0.585
5	17	12.275	0.576	19	11.921	0.560
Average		12.185	0.572		12.189	0.572
Standard Deviation		.213	.010		.240	.011

TABLE III

TOTAL AMOUNT OF ORAL DOSE FOR [ϕ - 14 C]-METALAXYL
ADMINISTERED TO HENS

<u>Animal Number</u>	<u>Average mg Daily Dose</u>	<u>Average kg Body Weight</u>	<u>Dose mg/kg</u>	<u>PPM</u>
6	12.09	1.65	7.33	110
7	12.20	1.72	7.09	87
8	12.19	1.98	6.16	80
9	12.19	1.73	7.05	97

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TABLE IV
DAILY WATER INTAKE (ml)

<u>Pre-dose</u>	<u>HEN 6</u>	<u>HEN 7</u>	<u>HEN 8</u>	<u>HEN 9</u>
Day -5	210	160	220	150
Day -4	175	200	200	215
Day -3	180	200	220	190
Day -2	175	210	220	230
Day -1	190	230	210	220
Average	186	200	214	201
<u>Dosing Period</u>				
Day 1	185	245	235	220
Day 2	180	240	240	185
Day 3	180	235	240	200
Day 4	160	230	240	165
Day 5	75	80	85	50
*Average	176	238	239	193

*Day 5 water intakes were not utilized in the averages because of the short time period (~6 hours) between the last capsule administration and sacrifice.

TABLE V
DAILY FEED INTAKE (g)

<u>Pre-dose</u>	<u>HEN 6</u>	<u>HEN 7</u>	<u>HEN 8</u>	<u>HEN 9</u>
Day -5	126	96	143	78
Day -4	119	118	144	92
Day -3	117	128	145	111
Day -2	111	127	147	136
Day -1	119	133	144	143
Average	118	120	145	112
<u>Dosing Period</u>				
Day 1	116	133	150	129
Day 2	96	142	154	120
Day 3	115	144	156	121
Day 4	112	143	151	133
Day 5	36	47	63	49
*Average	110	141	153	126

*Day 5 feed intakes were not utilized in the averages because of the short time period (~6 hours) between the last capsule administration and sacrifice.

TABLE VI
DAILY EXCRETA PRODUCTION (g)

<u>Pre-dose</u>	<u>HEN 6</u>	<u>HEN 7</u>	<u>HEN 8</u>	<u>HEN 9</u>
Day -5	120	97	157	93
Day -4	116	144	176	96
Day -3	170	156	194	126
Day -2	140	148	180	165
Day -1	130	149	159	180
Average	135	139	173	132
<u>Dosing Period</u>				
Day 1	140	144	197	155
Day 2	125	151	200	135
Day 3	108	153	192	136
Day 4	163	149	192	147
Day 5	37	52	52	56
*Average	134	149	195	143

*Day 5 excreta productions were not utilized in the averages because of the short time period (~6 hours) between the last capsule administration and sacrifice.

TABLE VII
DAILY EGG PRODUCTION AND SAMPLE WEIGHTS (g)

Pre-dose	HEN 6			HEN 7		
	White	Yolk	Total	White	Yolk	Total
Day -2	32	16	48	36	18	54
Day -1	39	16	55	37	18	55
<u>Dose Period</u>						
Day 1	32	16	48	36	18	54
Day 2	No Egg			35	18	53
Day 3	36	16	52	36	18	54
Day 4	No Egg			37	17	54
Day 5	41	17	58	37	17	54
Pre-dose	HEN 8			HEN 9		
	White	Yolk	Total	White	Yolk	Total
Day -2	34	17	51	35	17	52
Day -1	33	17	50	35	17	52
<u>Dose Period</u>						
Day 1	35	18	53	36	17	53
Day 2	35	18	53	38	17	55
Day 3	35	19	54	36	17	53
Day 4	35	19	54	37	17	54
Day 5	34	20	54	No Egg		

TABLE VIII
SAMPLES COLLECTED DURING SACRIFICE

	HEN# 6	HEN# 7	HEN# 8	HEN# 9
WHOLE BLOOD	6.9 g	6.6 g	6.9 g	7.0 g
SKIN & ATTACHED FAT	68.0 g	62.4 g	76.1 g	68.6 g
BREAST MUSCLE	156.6 g	150.0 g	185.8 g	146.7 g
THIGH MUSCLE	164.7 g	173.9 g	181.7 g	183.0 g
PERITONEAL FAT	30.2 g	50.2 g	73.7 g	70.2 g
LIVER	54.9 g	59.5 g	64.4 g	54.3 g
DAY 5 EGGS	57.9 g	53.9 g	53.5 g	No Egg

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