BB-632
TXR-8101

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

008101

SEP 17 1990

SEP 17 1990

OFFICE OF
PESTICIDES AND
SUBSTANCES

MEMORANDUM

SUBJECT: 8F3572 - Fenoxycarb - New Chemical Registration
8F3572 - Fenoxycarb - Submission of Supplementary Data on an 30-Week Carcinogenicity/Toxicity Study in Mice
9H5582 - Fenoxycarb - Use in Food Handling Establishments and Amended Registration of TORUS 2E Insect Growth Regulator (EPA Registration No. 35977-26) - FINAL REPORT

TOX Chem. No.: 652C
Project Nos.: 9-0911, 9-1190, 9-1316A
Record Nos.: 239678, 242480, 242463
MRID Nos.: 40361801, 40361802, 40376901, 40376902, 40376903, 40376904, 40972701

FROM: William B. Greear, M.P.H. William B Greear 7/24/90
Review Section II
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: Joseph Tavano/Phil Hutton, PM Team 17
Insecticide-Rodenticide Branch
Registration Division (H7505C)

THRU: Marion P. Copley, D.V.M., Section Head
Review Section II
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

1

Printed on Recycled Paper

Conclusions

Toxicology Branch I (TB-I) has determined that the toxicological data base on fenoxycarb is inadequate and will not support terrestrial food crop usage. The following studies must be repeated; except for the oncogenicity study in rats in which the data requested in the body of the review may be used to upgrade the study. In the rat chronic/oncogenicity study, much of the data; e.g. body weight, hematology, histopathology require statistical analysis. Tissue accountability data must be provided in conjunction with a statistical analysis of the occurrence of histopathological lesions in all treated groups relative to the controls. Historical control data on the occurrence of pituitary tumors are specifically required as specified in the Data Evaluation Report. If the data are accepted, the study need not be repeated.

82-2 21-Day Dermal (end-use product)
83-1 Chronic Feeding* - Rodent
83-4 2-Generation Reproduction
85-1 Metabolism (low and repeated-dose studies)

* 2-years for food use

In addition, fenoxycarb should not be used in food handling establishments where it would constitute a food use.

The request to waive the data requirements for the following studies is inappropriate. The studies are not required.

82-3 90-Day Dermal
82-4 90-Day Inhalation
82-6 90-Day Neurotoxicity
85-3 Dermal Penetration

Requested Action

1) Under Project No. 9-0911, Maag Agrochemicals, Inc. has submitted a petition #8F3572 with an application for an amended registration for LOGIC Fire Ant Bait (EPA Registration No. 35977-4) to permit use on pastures and in citrus groves. 2) Under Project No. 9-1190, the sponsor has submitted supplementary data for a previously submitted 80-week chronic/oncogenic study in mice (MRID No. 40376902) under petition #8F3572. 3) Under Project No. 9-1316A, the sponsor has submitted an application for an amended registration for TORUS 2E Insect Growth Regulator (EPA Registration No. 35977-26) to allow use of the product in food handling establishments. 4) In addition, under Project No. 9-1316A the sponsor has submitted a food additive petition #9H5582 to establish a tolerance for fenoxycarb in food as

part of a food handling regulation under 40 CFR Part 193.

5) Under Projects Nos. 9-0911 and No. 9-1316A, the sponsor has submitted requests for data waivers of the following toxicological studies on the technical:

- o 90-Day Dermal
- o 90-Day Inhalation
- o 90-Day Neurotoxicity: Mammals
- o Dermal Penetration

Background

Fenoxycarb, ethyl[2-(p-phenoxyphenoxy)ethyl]carbamate, is a new chemical proposed for use as an insect growth regulator. This is the first time that the sponsor has proposed tolerances on terrestrial food crops (citrus fruits, grass, and grass hay). Several registrations have been approved for nonfood uses (EPA Registration Nos. 35977-26 and 35977-4). The following toxicological studies are required to support terrestrial food-crop usage:

Study No.	Study	Test Material
81-1	Acute Oral Toxicity	TGAI and EP
81-2	Acute Dermal Toxicity	TGAI and EP
81-3	Acute Inhalation Toxicity	TGAI and EP
81-4	Primary Eye Irritation	TGAI and EP
81-5	Primary Dermal Irritation	TGAI and EP
81-6	Dermal Sensitization	TGAI and EP
82-1	90-Day Feeding - Rodent	TGAI
	90-Day Feeding - Nonrodent	TGAI
82-2	21-Day Dermal	TGAI and EP
83-1	Chronic Feeding - Rodent	TGAI
	Chronic Feeding - Nonrodent	TGAI
83-2	Oncogenicity - 2 species	TGAI
83-3	Teratology - 2 species	TGAI
83-4	2-Generation Reproduction	TGAI
84-2	Mutagenicity - Gene mutation	TGAI
	- Structural chromosomal aberrations	TGAI
	- Other genotoxic effects	TGAI
85-1	Metabolism	PAI or PAIRA

TGAI = Technical grade of the active ingredient.
EP = End-use product.
PAI = Pure active ingredient.
PAIRA = Pure active ingredient, radiolabeled.

The following studies have been previously submitted and are used in support of the requested terrestrial food crop usage.

Studies on Fenoxycarb Technical

Study No.	Study	Core Grade	Fulfills Guideline Requirements
81-1	Acute Oral Toxicity	Guideline	Yes
81-2	Acute Dermal Toxicity	Guideline	Yes
81-3	Acute Inhalation Toxicity	Minimum	Yes
81-4	Primary Eye Irritation[1/]	Minimum	Yes
81-5	Primary Dermal Irritation[2/]	Minimum	Yes
81-6	Dermal Sensitization	Guideline	Yes
82-1	90-Day Feeding - Mouse	Guideline	Yes
82-2	21-Day Dermal	Guideline	Yes
83-1	Chronic Feeding (6-mos.) - Dog	Minimum	Yes
83-3	Teratology - Rat	Minimum	Yes
	Teratology - Rabbit	Minimum	Yes
84-2	Mutagenicity - Gene mutation (Ames)	Acceptable	Yes
	- Structural chromosomal aberration (micronucleus)	Acceptable	Yes
	- Other genotixic effects (mitotic recombination)	Acceptable	Yes
85-1	Metabolism	No Grade	No

[1/] 10% to 30% ai tested.
[2/] 40% ai in corn oil tested.

In the current submission, the following studies have been submitted in support of the requested terrestrial food-crop usage.

Studies on Fenoxycarb Technical

Study No.	Study	Core Grade	Fulfills Guideline Requirements
83-4	2-Generation Reproduction	Supplementary	No
83-5	Combined - Chronic Feeding - Rat	Supplementary	No
	- Oncogenicity - Rat	Supplementary	No
83-5	Combined - Chronic Feeding - Mouse	Supplementary	No
	- Oncogenicity - Mouse	**	
85-1	Metabolism - High dose		Partially*

*Low- and multiple-dose studies may be conducted to satisfy the full Guideline requirements.

** Classification is pending the outcome of the Peer Review Committee meeting.

The results on the newly submitted studies are summarized below:

83-4 - 2-Generation Reproduction Study in Rats (Hazleton No. 4623 161/124; September 1986; MRID No. 403769-03)

Results: NOEL (Reproduction) < 200 ppm (10 mg/kg/day)
LEL (Reproduction) = 200 ppm (10 mg/kg/day)
NOEL (Maternal toxicity) - Could not be determined

Groups of 30 male and female (F0) and 25 male and female Sprague-Dawley rats were administered 0, 200, 600, and 1800 ppm of fenoxycarb in the diet. Liver effects including increased absolute and relative liver weights in the 600 and 1800 ppm groups and increased incidences of focal necrosis and hypertrophy of the liver in the 1800 ppm group were observed. Because histopathological evaluation of the livers of F0 and F1 parental animals in the 200 and 600 ppm groups were not conducted, neither a NOEL nor LEL for maternal toxicity could be established. Significant decreases in pup weights occurred at all dose levels. In addition, further delays in development, i.e., pinna unfolding and eye opening were observed and appeared to be dose-related. The study is Core-Supplementary primarily because a NOEL was not determined for reproductive effects. Other reasons also include no histological examination of target organ, i.e., the liver, in parental rats in the 200 and 600 ppm groups, gross lesions were not histologically examined.

[The study is a data gap and a new study must be conducted.]

83-5 - Chronic Feeding/Oncogenicity in Rats (Hazleton No. 51911-61/123; November 1986; MRID No. 403769-01).

Results: NOEL < 200 ppm (10 mg/kg/day)
LEL = 200 ppm (10 mg/kg/day)

Groups of 60 male and female Charles River CD(SD)BR rats were administered 0, 200, 600, and 1800 ppm of fenoxycarb in the diet for 2 years. Liver lesions including microcystic degeneration, focal necrosis and fibrosis was observed in males in the 200 ppm group. In addition to the lesions observed at 200 ppm, rats in the 600 ppm group exhibited increases in alkaline phosphatase, SGOT and/or SGPT. Males exhibited additional liver lesions of hypertrophy and pigmented histiocytes whereas females exhibited increased liver weight. In the 1800 ppm group, males additionally exhibited increased follicular cysts and C-cell hyperplasia of the thyroid.

Females in the 1800 ppm group additionally exhibited anemia, increased absolute and relative liver weights, hypertrophy of the liver and cysts of the thymus. The study was classified Core-Supplementary because a NOEL was not demonstrated in the study and because of several deficiencies including no statistical analysis of data (body weight, food consumption, hematology and histopathology) and absence of data on SGOT, SGPT, and alkaline phosphatase in the 200 and 600 ppm groups at 25, 51, and 78 weeks. Most important, it was impossible to determine the percent incidence of lesions within groups of animals because the number of animal tissues available was not reported.

[The chronic toxicity section of the study is a data gap and a new study must be conducted. The oncogenicity section of the study could be upgraded from Core-Supplementary, provided the testing facility submits tissue accountability data and statistically analyzes the histopathology data.]

83-5 Chronic Feeding/Oncogenicity Inveresk Research No. B-104819; March 1987; MRID Nos. 40376902 and 40972701).

Results: NOEL/LEL - cannot be determined because a target organ, the liver, was not examined in all animals in the lower dose groups.

Fifty male CD-1 mice were administered 0, 30, 110, and 420 ppm of fenoxycarb in the diet for 80 weeks. Females received 0, 20, 80, and 320 ppm in the diet. Additionally, 10 rats/sex/group were sacrificed at 26 and 52 weeks. Additional groups of male mice receiving 0 and 420 ppm and female mice receiving 0 and 320 ppm were sacrificed at 58 weeks following a 6-week recovery period. There was a dose-related increase in the occurrence of alveolar/bronchiolar adenomas in males at all dose levels. In addition, liver lesions including localized perivascular lymphocytic infiltration, foci of pigmented macrophages, focal necrosis, and focal angiectasis was observed in females in the 320 ppm group.

[The chronic toxicity section of the study is Core-Supplementary because a target organ, the liver, was not examined in all animals in the lower dose groups. For food use, a new study will be required. The oncogenicity section of the report will be classified, pending the outcome of the Peer Review Committee meeting.]

85-1 - Metabolism in Rats (Inveresk Research No. 4217; October 1986; MRID No. 403769-04).

Results:

Ninety-eight percent of an oral dose of 3000 mg/kg of fenoxycarb was recovered; 50 percent in feces, 42 to 47 percent in urine, 0.09 percent in CO_2, and 0.08 percent in tissues within 96 hours. In a biliary excretion study, 37 and 63 percent was eliminated in the bile of males and females, respectively. Repeated low dose studies indicated that highest residues were found in liver, the material bioaccumulates in fat and metabolism was increased at low doses and with the administration of repeat doses.

[The high-dose study is acceptable. However, the low-dose and repeated dose studies must be conducted.]

Considerations

The toxicological data on file together with the newly submitted toxicological studies are inadequate to support terrestrial food-crop usage. The following studies are either inadequate or need to be conducted.

82-2 21-Day Dermal (end-use product)
83-1 Chronic Feeding - Rodent
83-2 Oncogenicity - Rat
83-4 2-Generation Reproduction
85-1 Metabolism - Low- and repeated-dose studies

The chronic feeding study in rodents and the 2-generation reproduction studies must be repeated. The oncogenicity study in rats may be upgraded to an acceptable status as indicated in the report. The low- and repeated-dose metabolism studies must be conducted. The 21-Day Dermal study on the end-use product has not yet been submitted.

The sponsor has requested that the data requirements for the following studies be waived. The waiver requests' rationale and EPA response for each waiver are listed below:

82-3 - 90-Day Dermal

The use of LOGIC Fire Ant Bait, a non-dusty granular material containing 1% fenoxycarb does not result in purposeful dermal application or prolonged exposure to the human skin. Both subchronic and chronic oral studies are available and have been submitted or are submitted with this application.

EPA Response

The study is not required. A waiver is not appropriate in this instance.

82-4 - 90-Day Inhalation

LOGIC Fire Ant Bait is a non-dusty granular product containing 1 percent of the active ingredient, fenoxycarb. The active ingredient is an EPA Category III pesticide. The other ingredients of the formulation are [redacted] materials. The use of the product will not result in repeated inhalation exposure at levels likely to be toxic.

EPA Response

The study is not required. A waiver is not appropriate in this instance.

82-5 - 90-Day Neurotoxicity

The active ingredient in LOGIC Fire Ant Bait is not a cholinesterase inhibitor. Data from the acute oral, dermal or inhalation studies show no evidence of neuropathy or neurotoxicity.

EPA Response

A study is not required at this time. A waiver is not appropriate in this instance.

85-3 - Dermal Penetration

LOGIC Fire Ant Bait is a non-dusty granular product containing 1 percent of the active ingredient, fenoxycarb. The active ingredient is an EPA Category III pesticide. The other ingredients in the formulation are [redacted] materials. The use of the product will not result in repeated dermal or inhalation exposure at levels likely to be toxic.

EPA Response

The study is not required. A waiver is not appropriate in this instance.

[A copy of the one-liner on fenoxycarb is attached. It should be noted that the newly submitted studies have yet to be incorporated.]

PADI

In a memorandum dated April 10, 1987, Dave G. Van Orner calculated the PADI to be 0.01 mg/kg/day based on a NOEL of 10.0 mg/kg/day in the interim report of the rat chronic

feeding/oncogenicity study and using a 1000-fold safety factor. This calculation was a one-time use under a Section 18 Emergency Exemption. Upon completion of an acceptable terrestrial field test, the information will be submitted to the HED and Agency R.E.D. Committee for determination of an appropriate T.R.D.
Attachment

TOXCHEM NO. 652C Phenoxy(phenoxy)ethyl]carbamic acid FILE LAST PRINTED: 08/07/89

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	CORE GRADE/ DOCUMENT#
Teratology Species: rat Hoffman LaRoche, Switz. B-104,875; 5/12/83	RO-13-5223 Tech.	071780	Teratogenic NOEL > 500 mg/kg (HDT) Embryotoxic NOEL = 150 mg/kg LEL = 500 mg/kg (increase in early resorptions) Maternal NOEL = 500 mg/kg (HDT). Levels tested by gavage in FU - albino strain - 0, 50, 100 and 500 mg/kg/day		Minimum 004178
Teratology Species: rabbit Hoffman LaRoche B-104-700; 2/13/84	RO-13-5223 Tech, batch 18	073304	Levels tested by gavage in Swiss hare strain - 0, 30, 100, and 300 mg/kg/day. Teratogenic NOEL > 300 mg/kg (HDT) Maternal NOEL = 100 mg/kg. Maternal LEL = 300 mg/kg (reduced body weight gain). Fetotoxic NOEL > 300 mg/kg (HDT).		Minimum 004319
Teratology Species: rabbit Hoffman LaRoche B-104-700; 2/13/84	RO-13-5223 Tech, batch 18	073304	Levels tested by gavage in Swiss hare strain - 0 and 200 mg/kg/day. Teratogenic NOEL > 200 mg/kg/day. Maternal NOEL < 200 mg/kg/day (reduced body weight gain).		Minimum 004319
Feeding/oncogenic-2 year Species: rat Hazleton Labs, Europe 4342-161; 5/85	Fenoxycarb Tech (96.6%) Lot 2	258112	1-YR. INTERIM REPORT. Levels tested in Sprague-Dawley Crl: CD(SD) Br strain - 0, 200, 600 and 1800 ppm. NOEL = 200 ppm (low dose). LEL = 600 ppm (elevated liver/BW ratios (males); dose related focal necrosis and centrilobular hypertrophy (males). Pigmented histiocytes (males). High dose: Body weight depression (both sexes); reduced platelet and WBC counts; elevated alk. phos.; significantly elevated liver body weight ratio (females); focal necrosis, pigmented histiocytes, centrilobular hypertrophy and fibrosis (male livers). The observations of centrilobular hypertrophy (mid and high dose) and focal necrosis in male livers show dose response in both incidence and severity. Low dose: Focal necrosis of male livers (2/10).		Guideline 004569
Feeding-3 month Species: rat Hoffman LaRoche B-104 802; 5/31/83	RO-13-5223 Tech 98%	071780	NOEL = 100 mg/kg. LEL = 300 mg/kg (increased liver weight accompanied by fatty changes, glycogen depletion, and increased multinucleated hepatocytes. Tumors absent. Levels tested in albino SPF strain - 0, 100, 300 and 900 mg/kg/day		Guideline 004178
Feeding-3 month Species: rat Hoffman LaRoche B-104 779; 9/5/83	RO-13-5223 Tech 98%	071779	NOEL = < 80 mg/kg/day (LDT) (liver wt. increase) LEL = 250 mg/kg (increased thyroid wt. body wt. decrease; decreased ChE, elevated cholesterol; decreased RBC, Hb, and PCV in females; increased follicular activity in thyroid. Hepatocyte hypertrophy and decreased glycogen in the liver). Levels tested in albino SPF strain 0, 80, 250 and 800 mg/kg/day		Guideline 004178
Feeding- 6 month oral Species: dog Hoffman LaRoche, Switz. B-104-927; 4/30/83	RO-13-5223 Tech 95-98% (gelatin capsule) lot 16 & 18.	071845	Levels tested in Beagles by capsule - 0, 50, 150, and 500 mg/kg/day. NOEL = 150 mg/kg/day. LEL = 500 mg/kg/day (reduced weight gain in females).		Minimum 004319

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	CORE GRADE/ DOCUMENT#
Dermal·3 week Species: rat Hazleton 4552-161/157; 7/3/85	Ro·13 5223/000 (96.6%)	258865	NOEL = 200 mg/kg/day. LEL = 2000 mg/kg/day (slight liver hypertrophy). Clinical signs: None. Clinical pathology: None Pathology: Increased liver weights and slight liver hypertrophy at 2000 mg/kg/day dose level (in males and females). Levels tested: 0 (vehicle control) 20, 200, and 2000 mg/kg/day (dermal) in Cr1:CD(SD)BR strain.		Guideline 004621
Inhalation·21 day Species: rat Res. and Consulting Co.; Switz 085500; 6/17/87	Fenoxycarb 96.6%	40355801	Levels tested: 0.0, 0.01, 0.10, and 1.13 mg/l for 6 hrs/day/5 days/week for 3 weeks. NOEL = 0.10 mg/l , LEL = 1.13 mg/l (decreased body weight gain in males and increased absolute liver weight in females)		Guideline 006897
Metabolism Species: dog Hoffman LaRoche 54 A 82; 3/14/83	RO·13·5223 Tech.	071780	Dosage at 50, 150 and 500 mg/kg/day. Elimination of parent compound 19 days after oral administration at 50 mg/kg/day for 26 weeks: fat 97% eliminated. Plasma 84% eliminated liver 31% eliminated. higher dosages showed higher elimination rates.		Supplementary 004178
Metabolism Species: rat HAAG 041/2368; 11/2/81	RO·13·5223 Tech.	247925 071856	Only one level tested · 50 mg/kg (14C labeled in the dioxyphenyl ring). Most radioactivity excreted in urine and feces (60·80%) in 24 hours and 90·92% by 96 hours. Organs did not show persistent residues. Identification of metabolites not presented.		Supplementary 002215
Metabolism Species: rat 6/21/83 041/3896	RO·13·5223 99% Tech. in rape oil; C14 labelled	071779	Fecal excretion averaged 53% of administered activity at 48 hours (males and females); urinary excretion 19% (24 hrs) Metabolites: two hydroxylation products, ether cleavage product p·hydroxyphenetole, and an amide condensation product. Metabolite feces·to·urine excretion ratios were 6.0 (males) and 3.5 (females) Metabolic conjugates not observed. Parent compound eliminated only in feces, and accounted for 3.1% and 0.5% of fecal activity (males and females). Large percentages of metabolites not identified.		Minimum 004178
Cholinesterase Species: housefly	RO·13·5223 Tech	247925	The carbamate Ro13·5223 did not cause any synaptic disturbance at the AChE locus at highest in vitro conc. tested, 2.5 x 10·4 M		Minimum 002215
Mutagenic·c. onucleus assay Species: mi › Hoffman LaRoche, Switz. B·96·679; 7/20/82	RO·13·5223 Tech in peanut oil	071856	Does not produce micronuclei in mouse PCEs at 5000 mg/kg (HDT)		Supplementary 004178 Acceptable 004178
Mutagenic·Ames Species: salmonella	RO·13·5223 Tech.	247925	Spot test (2400 ug/disk) was negative for His revertants. Quantitative Ames test at 37.5, 75, 150, and 300 ug/plate was negative for His revertants in TA 1535,1537, 1538, 98, 100 both with and without S·9 activation.		Acceptable 002215

INERT INGREDIENT INFORMATION IS NOT INCLUDED

TOXCHEM [illegible]. 652C· Phenoxyphenoxy)ethyl]carbamic acid FILE LAST PRINTED: 08/07/89

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	CORE GRADE/ DOCUMENT#
Mutagenic·recomb/convers assay Species: Sacc. cerevisiae D·7	RO·13·5223 Tech.	247925	Doses to D·7 yeast at 0.017, 0.040, 0.17, 0.40 mg/ml did not produce any mutation expressed by any of three phenotypic markers listed for D 7.		Acceptable 002215
Mutagenic Species: Chinese hamst. lung	RO·13·5223 Tech		HGPRT Locus not mutated by Ro 13·5223 to become 8·azaguanine resistant at 0, 1, 5, and 25 ug/ml with or without S·9 Thus, Ro·13·5223 negative in mammalian cell line for mutation.		Acceptable 002215
Mutagenic Species: Chin Hamst lung cell 1979	RO·13·5223, Tech	247925	Non mutagenic at 0, 25, 50, and 100 mg/ml.		Acceptable 002215
Dermal sensitization Species: guinea pig Hoffman LaRoche 041/0576; 11/15/79	Fenoxycarb	247925	0.025 mls of 100, 30, 10 and 3% a.i. applied to one flank for 21 days. Challenge doses at 21 and 35 days produced no allergic reactions 24 and 48 hours post challenge.		Guideline 002215
Dermal sensitization Species: guinea pig Hoffman LaRoche 2330a; 3/16/82	Formulation ACR 5023 (10.3% in [redacted]	071779	Not sensitizing at 0.1 ml in the guinea pig.		Guideline 004178
Dermal sensitization Species: guinea pig Hoffman LaRoche 2330; 1/4/83	Formulation ACR 5023 (10.0% in [redacted]	671850	Not sensitizing in guinea pig at 0.1 ml.		Guideline 004178
Acute Dermal LD50 Species: rat Hoffman LaRoche, Switz. B·97341; 5/5/82	Formulation ACR 5023 (10.% in [redacted]	071856	LD 50 = > 5000 mg/kg. Dyspnea, curved body position, ruffled fur, sedation, and diarrhea. No deaths.	3	Guideline 004178
Acute oral LD50 Species: rat	RO·13·5223 Tech.	247925	LD 50 > 16,800 mg/kg.	4	Guideline 002215
Acute Dermal LD50 Species: rat Huntingdon Res. Centre, Eng. B·93142; 2/2[illegible]/81	RO·13·5223 Tech in corn oil	247925	LD 50 > 2 g/kg(only level tested). Negative for irritation.	4	Guideline 002215
Primary eye [illegible]itation Species: ra[illegible]it	RO·13·5223 Tech.	247925	0.1 ml of 10% and 30% solutions (no washing) was applied with only mild redness which cleared by 24 hours. No corneal opacity, ulcerations, iris involvement, nor chemosis.	3	Minimum 002215

TOXCHEM NO. 652C· Phenoxyphenoxy)ethylicarbamic acid FILE LAST PRINTED: 08/07/89

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	CORFGRADE/ DOCUMENT#
Acute oral LD50 Species: [redacted]	RO·13·5223 10.3% a.i. in [redacted]	247925	LD 50 > 10,000 mg/kg.		Guideline 002215
Acute inhalation LC50 Species: rat Res. and Consulting Co.; Switz 3/16/82	RO·13·5223 10.3% a.i. in [redacted]	247925	LC 50 > 3.05 mg/L of formulation. Levels tested· 2.221 and 3.052 mg/L.	3	Supplementary 002215 Minimum 004178
Acute inhalation LC50 Species: rat Buntingdon Res. Centre, Eng.	RO·13·5223 Dust 0.26 g/m3 ..32.5%; respirable & aero· sol 0.48% g/m3 94.5% respirable	247925	Highest concentration of dust obtainable for dust and aerosol with the equipment employed. Too low concentration to assess hazard by inhalation alone. At concentration tested (4 hours) no significant effects observed during 14 days.		Supplementary 002215 Minimum 004178
Primary dermal irritation Species: rat 11/15/79	RO·13·5223 40% a.i. in corn oil	247925	PIS = 0.0 at 2000 mg/kg.	4	Minimum 002215
Primary dermal irritation Species: rat 11/15/79	RO·13·5223 Formulation 10.3%	247925	PIS = 0.0 at 1000, 3000, and·5000 mg/kg.	4	Minimum 002215
Primary eye irritation Species: rabbit 2/12/82	RO·13·5223 Formulation (10.3% w/w in [redacted]	247925	Mild and transitory redness in first hour.	4	Minimum 002215
Acute oral LD50 Species: mice	RO·13·5223 Tech.	247925	LD 50 > 8000 mg/kg.		Guideline 002215
Acute oral LD50 Species: rat	RO·13·5223 Tech.	247925	LD 50 > 10,000 mg/kg. 2/5 females died. Splenic hemopoesis.		Guideline 002215
Acute oral LD50 Species: rat Food and Drug Research Lab 78768; 12/16/83	Raid Fogger plus (formula· tion 0.6% fenoxycarb)	261392	LD 50 > 5.0 g/kg. Decreased activity, ataxia, salivation, rales, nasal discharge and diarrhea.	4	Guideline 005549
Acute Dermal LD50 Species: rabbit Food and Drug Research Lab 78768; 12/22/83	Raid Fogger plus (formula· tion 0.6% fenoxycarb)	261392'	LD 50 > 2.0 g/kg. Dry, flaking skin, soft stools and anorexia.	3	Guideline 005549

TOXCHEM NO. 652C· Phenoxyphenoxy)ethyl]carbamic acid FILE LAST PRINTED: 08/07/89

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	CORE GRADE/ DOCUMENT#
Acute inhalation LC50 Species: rat Food and Drug Research Lab 8349; 5/20/85	Raid Fogger plus (formulation 0.6% fenoxycarb)	261392	LC50 = 6.7 mg/L; slope = 15 (males), 4.8 (females). Alopecia, decreased activity, labored breathing, nasal discharge, salivation, tremors. Body wt decrease in males. Reddened lungs. Corneal opacity at top dose.	3	Minimum 005549
Acute inhalation LC50 Species: rat Food and Drug Research Lab 7876; 10/15/.4	Raid Fogger plus (formulation 0.6% fenoxycarb)	261392	Four Sprague-Dawley rats (1/5 males, 3/5 females) died within 15 days after a 4-hour, whole-body exposure to 5.1 mg/L (analytical concentration). Labored breathing, decreased activity, and (in those succumbing) , tremors, ataxia, and diarrhea. Reddened nasal passages and lungs in one two animals.		Supplementary 005549
Primary eye irritation Species: rabbit Food and Drug Research Lab 78768; 12/13/83	Raid Fogger plus (formulation 0.6% fenoxycarb)	261392	Irritation clearing in 7 days or less.	3	Guideline 004449
Primary dermal irritation Species: rabbit Food and Drug Research Lab 78768; 2/15/84	Raid Fogger plus (formulation 0.6% fenoxycarb)	261392	PIS = 3.4: Moderately irritating.	3	Guideline 005549
Dermal sensitization Species: guinea pig Food and Drug Research Lab 8349; 1/7/85	Raid Fogger plus (formulation 0.6% fenoxycarb)	261392	Negative for dermal sensitization when applied neat to female guinea pigs by modified Buehler test.		Guideline 005549
Acute intraperitoneal LD50 Species: rat	Fenoxycarb tech	247925	LD50 = 9220 mg/kg	4	Guideline 002215

Reviewed By: William B. Greear, M.P.H.
Review Section II, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M.
Review Section II, Toxicology Branch I - IRS (H7509C)

003101

DATA EVALUATION REPORT

Study Type: Guideline Series 83-5
Combined Chronic Toxicity/
Oncogenicity Studies - Mice

TOX Chem. No.: 652C
MRID No.: 40376902
40972701

Test Material: Fenoxycarb

Synonyms: Ethyl[2-(p-phenoxyphenoxy)ethyl]carbamate; RO 13-5223/000; N-[2-(p-phenoxyphenoxy)ethyl]carbamic acid; BW data ACR 5023

Study No.: Research Report No. B-104'819/Inveresk Research International Report No. 3390/IRI Project No. 430624

Sponsor: Maag Agrochemicals
Research and Development
HLR Sciences, Inc.
Vero Beach, FL 32961

Testing Facility: Inveresk Research International
Musselburg, Scotland

Title of Report: 80 Week Carcinogenicity/Toxicity Study in Mice.

Authors: D.J. Everett, K.A. Scott, P. Hudson, and F. Macnaughton

Report Issued: March 1987

Conclusions:

Chronic Toxicity - NOEL/LEL - could not be determined because a target organ, the liver, was not examined in all animals in the lower dose groups.

Males in the high dose (420 ppm) group exhibited an increase in the absolute and relative liver weight. Females in the high dose (320 ppm) group had liver changes including localized perivascular lymphocytic infiltration, foci of pigmented macrophages, focal necrosis and focal angiectasis.

Carcinogenicity

There was a dose-related increase in alveolar/bronchiolar adenomas and carcinomas, and Hardarian gland adenomas in males. (The increase in tumor sites will receive further examination by HED's Peer Review Committee.)

Classification: Chronic Toxicity: Supplementary (a target organ, the liver was not examined in all animals in the lower dose groups)

Carcinogenicity: Classification is pending the outcome of the Peer Review Committee meeting.

A. Materials:

1. Test Compound - RO 13-5223/000; Description: a white powder; Batch No. 83; Purity: not reported; Contaminants: not reported.

2. Test Animals - Species: mouse; Strain: CD-1; Age: not reported; Weight: males - 22 to 31 g, females - 16 to 26 g; Source: Charles River (U.K.) Limited, Manston, England.

B. Study Design:

1. Animal Assignments - Animals were randomly assigned to the following test groups:

Chronic Toxicity Study

Test Group	Dose in Diet (ppm)	Sacrifice 26 Week* Male	26 Week* Female	52 Week** Male	52 Week** Female	58 Week*** Male	58 Week*** Female
Control (T)	0	10	10	10	10	10	10
Low (T)	Male 30, Female 20	10	10	10	10	--	--
Mid (T)	Male 110, Female 80	10	10	10	10	--	--
High (T)	Male 420, Female 320	10	10	10	10	10	10

*Bleed but no necropsy.
**Bleed and necropsy.
***Bleed and necropsy after a 6-week recovery period

Carcinogenicity Study

Test Group	Dose in Diet (ppm)	Sacrifice 80 Weeks Male	Sacrifice 80 Weeks Female
Control (C)	0	50	50
Low (C)	Male 30, Female 20	50	50
Mid (C)	Male 110, Female 80	50	50
High (C)	Male 420, Female 320	50	50

On receipt of the animals, 10 males and 10 females were provided a clinical examination, necropsy, histopathological examination of major organs and evaluation of bacterial and parasitic status. Mild acute bronchiolitis was noted, therefore, an additional 10 mice/sex were sacrificed and examined. It was concluded that the health status of the mice was acceptable. The remaining mice were housed in a barrier maintained room at a temperature of 21 + 2 °C and a target relative humidity of 50 percent with 12 to 15 air changes per hour. A 12-hour on/12-hour

off light cycle was maintained. The mice were housed singly in suspended, polypropylene cages with stainless steel grid tops. Sterilized white wood shavings were used as bedding material. Food (S.D.S. Ground Maintenance Diet No. 1) and water were available ad libitum.

Replacement animals were introduced prior to the end of 4 weeks dosing as required.

2. Diet Preparation - A 100 ppm premix was prepared by mixing the test material with the untreated diet. The formulated diets were then prepared by mixing the premix with the untreated diet for 20 min. Fresh diets were prepared weekly up to week 14 and then were prepared every 2 weeks. Analysis of the test diets was periodically conducted over a 73 week period; however, the methods were not described.

   Results - During the first week the test diets varied considerably (up to 26.5%) from targeted concentrations. Thereafter, the test diets generally varied less than 10 percent from the targeted concentrations. The homogeneity of the test diets was good.

3. Statistics - Data obtained at intervals were analyzed for homogeneity of variance using the "F-max" test. When group variances appeared to be homogeneous a parametric ANOVA was used and pairwise comparisons made via a Student t-test. Tumor and histopathological lesion incidence were analyzed using chi-squared and Fishers Exact Probability test. A trend analysis was conducted on male histopathology data. The parameters analyzed were total lifetime incidences of lung and Harderian gland tumors. The level of significance was $p < 0.05$.

4. Quality Assurance examinations were conducted at 25 intervals between January 31, 1984 and August 14, 1985. The statement was signed on April 15, 1987 by D. Watson.

C. Methods and Results

1. Observations - The frequency of observation of the mice for clinical signs of toxicity and mortality was not stated.

   Results - It was stated that there were no clinical signs of toxicity (data were not presented). Survival was comparable among the control and treated animals.

Survival data for Week 80 of the Carcinogenicity study is provided below:

Test Group	No. of Survivors at Week 80	
	Males	Females
Control (C)	42/50	41/50
Low (C)	46/50	39/50
Mid (C)	43/50	43/50
High (C)	39/50	43/50

2. Body Weight - Individual animal body weight was determined 1 week prior to initiation of the study, at weekly intervals thereafter for 14 weeks and then at 2-week intervals until termination.

   Results - Body weight and body weight gains were comparable among the control and treated groups in the carcinogenicity and the chronic toxicity studies.

3. Food Consumption and Compound Intake - Individual animal food consumption was determined over 1 week prior to dosing and at weekly intervals thereafter for 14 weeks and then over 2-week periods thereafter.

   Results - Food consumption was comparable among the control and treated groups in the carcinogenicity and chronic toxicity studies. Mean compound intake is provided in the following table:

   Mean Compound Intake (mg/kg/day)

   Carcinogenicity Study

Males			Females		
Low (C)	Mid (C)	High (C)	Low (C)	Mid (C)	High (C)
(30 ppm)	(110 ppm)	(420 ppm)	(20 ppm)	(80 ppm)	(320 ppm)
5.3	19.3	73.9	4.4	16.9	72.2

   Chronic Toxicity Study

Males			Females		
Low (T)	Mid (T)	High (T)	Low (T)	Mid (T)	High (T)
(30 ppm)	(110 ppm)	(420 ppm)	(20 ppm)	(80 ppm)	(320 ppm)
6.0	21.7	81.8	4.8	18.2	71.6

4. Blood samples were taken from 10 mice/sex prior to dosing and from 10 mice/sex from each chronic toxicity group at Week 26 and 52. Samples were taken from 10 mice/sex/group

at necropsy during Week 59 for determination of alkaline phosphatase. Blood samples were also taken from 10 mice/sex/group in the carcinogenicity study at Week 80. Samples were obtained via the orbital sinus under light anesthesia 1 week prior to death and from the vena cava at necropsy. The CHECKED (X) parameters were determined:

a. Hematology

X		X	
X	Hematocrit (HCT)		Total plasma protein (TP)
X	Hemoglobin (HGB)	X	Leukocyte differential count
X	Leukocyte count (WBC)	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)	X	Mean corpuscular HGB conc. (MCHC)
X	Platelet count	X	Mean corpuscular volume (MCV)
	Erythrocyte morphology		Clotting time
		X	Reticulocyte count

After 52 and 78 weeks, blood was taken by tailsnip from each animal and a blood smear prepared. A leukocyte differential count was conducted on all high dose and control animals.

Results - Animals in the treated groups compared favorably with the controls.

b. Clinical Chemistry

X	Electrolytes
X	Calcium
X	Chloride
	Magnesium
	Phosphorus
X	Potassium
X	Sodium
	Enzymes
X	Alkaline phosphatase
	Cholinesterase
	Creatinine phosphokinase
X	Lactic acid dehydrogenase (LDH)
X	Serum alanine aminotransferase (SGPT)
X	Serum aspartate aminotransferase (SGOT)
	Gamma glutamyltransferase

X	Other
X	Albumin
	Blood creatinine
X	Blood urea nitrogen
	Cholesterol
	Globulins
X	Glucose
X	Total bilirubin
X	Total protein
	Triglycerides
	Thyroxine (T_4)
	Triiodothyronine (T_3)
	Albumin/Globulin ratio

Results - At 26 weeks, SGOT was elevated in males in the high-dose group. Alkaline phosphatase was increased in all male treated groups and showed a dose-response relationship; however, statistical significance was not attained. At 52 weeks, alkaline phosphatase was

increased in males in the high-dose group. At 80 weeks, LDH was increased in males in the high dose group (see the table below). The increase in SGOT in males in the high-dose group at 26 weeks is considered to be of no biological significance because increases were not observed at 52 and 80 weeks and there were no histological changes in the liver. Alkaline phosphatase was similarly increased in the male high-dose group at 52 weeks but not at 80 weeks. This increase is also considered to be within normal variation. The increase in LDH at 80 weeks in males in the high-dose group was not preceded by changes at 26 and 52 weeks. No liver or heart pathology was noted in males. The variability in LDH was high as exemplified by the difference between LDH values in control and high-dose females in Week 80: 508 (controls), 367 (high-dose). Therefore, the increase in LDH is probably a sporadic event.

Selected Group Mean Clinical Chemistry Data

	Dose Group							
	Control (T)		Low (T)		Mid (T)		High (T)	
	M	F	M	F	M	F	M	F
	Week 26							
SGOT (IU/l)	68	91	76	100	77	132**	90	103
SGPT (IU/l)	37	41	46	42	45	66	43	43
LDH (IU/l)	511	514	471	649	469	856	525	634
Alk. Phos. (IU/l)	98	131	126	145	138	132	172	146
	Control (T)		Low (T)		Mid (T)		High (T)	
	M	F	M	F	M	F	M	F
	Week 52							
SGOT (IU/l)	81	86	61	81	62	73	74	81
SGPT (IU/l)	59	49	45	35	43	31	43	40
LDH (IU/l)	485	428	448	435	411	338	504	356
Alk. Phos. (IU/l)	108	151	106	141	102	167	178*	167

*Significantly different from controls at $p < 0.05$.
**Significantly different from controls at $p < 0.01$.

Selected Group Mean Clinical Chemistry Data (cont'd)

	Dose Group							
	Control (C)		Low (C)		Mid (C)		High (C)	
	M	F	M	F	M	F	M	F
	Week 80							
SGOT (IU/l)	80	91	88	76	73	100	94	76
SGPT (IU/l)	48	49	47	32	29	50	56	33
LDH (IU/l)	492	508	552	403	516	656	699*	367
Alk. Phos. (IU/l)	137	131	102	115	166	150	145	126

*Significantly different from controls at $p < 0.05$.

5. Urinalysis - Data were obtained from the same animals that were bled during the pretrial week, Weeks 26, 51, and 80. The CHECKED (X) parameters were determined.

X		X	
|X|	Appearance	|X|	Glucose
|X|	Volume	|X|	Ketones
|X|	Specific gravity	|X|	Bilirubin
|X|	pH	|X|	Blood
|X|	Sediment (microscopic)	| |	Nitrate
|X|	Protein	|X|	Urobilinogen
		| |	Reducing substances

Results - The results of the urinalysis were unremarkable.

6. Sacrifice and Pathology - At 52 weeks, 10 animals/sex/group in the chronic toxicity study were sacrificed. Ten animals/sex in the control and high (T) dose group were sacrificed and necropsied at 58 weeks. At 80 weeks, all the animals were sacrificed and necropsied. The CHECKED (X) tissues were collected for histopathological examination. The (XX) organs in addition were weighed for 10 mice/group, except for the 58-week recovery group in which only the livers were weighed. Histological examination was conducted on all control and high-dose animals and all premature decedents. Lungs, Harderian glands and kidneys were examined from the low- and mid-dose males.

X	Digestive system	X	Cardiovasc./Hemat.	X	Neurologic
X	Tongue		Aorta	XX	Brain
X	Salivary glands*	XX	Heart	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow	X	Spinal cord (3 levels)*
X	Stomach	X	Lymph nodes	X	Pituitary
X	Duodenum*	X	Spleen	X	Eyes (optic n.)
X	Jejunum	X	Thymus		Glandular
X	Ileum		Urogenital	XX	Adrenals
X	Cecum*	XX	Kidneys		Lacrimal gland
X	Colon	X	Urinary bladder	X	Mammary gland
X	Rectum*	XX	Testes	X	Parathyroids
XX	Liver		Epididymides	X	Thyroids
X	Gallbladder	X	Prostate		Other
X	Pancreas*	X	Seminal vesicle*	X	Bone
	Respiratory	X	Ovaries	X	Skeletal muscle*
	Trachea	X	Uterus	X	Skin
X	Lung			X	All gross lesions and masses
				X	Harderian gland*

*Tissues were not examined in animals from the chronic toxicity groups.

a. Organ Weights - At the interim (52 weeks) and terminal (80 weeks) sacrifices, the absolute and relative weights of the of males in the high-dose group were increased. At the 52-week sacrifice, absolute weights were 2.07, 2.19, 2.27, and 2.44 g in the control, low-, mid-, and high-dose male groups, respectively. The relative weights were 5.2, 5.4, 5.4, and 5.9 in the control, low-, mid-, and high-dose groups, respectively. At terminal sacrifice, liver weights in males were 2.38, 2.46, 2.27, and 2.44 g in the control, low-, mid-, and high-dose groups, respectively. The relative weights were 4.7, 5.7, 5.2, and 6.3 in the control, low-, mid-, and high-dose groups, respectively. No effects on organ weights were observed in the recovery group. (It was noted that the relative weight of the testes of males in the low-dose group was incorrectly entered as 2.94. The correct entry is 0.94.)

b. Gross Pathology - It was stated that there were no treatment-related findings The data should have been summarized for each test group to show:

1) The types of lesion observed.

2) The number of animals showing the lesion.

3) The percentage of animals in each group displaying each type of lesion.

(This problem is considered to be a minor deficiency.)

c. Microscopic Pathology

1) Non-neoplastic - There appears to be adverse effects observed in the liver of the females in the high-dose groups. The incidence of these lesions are provided in the table below:

Selected Liver Lesions in Female Mice

	Dose (ppm)			
Lesion	0	20	80	320
Localized perivascular lymphocytic infiltration	2/49(4%)	0/8	0/7	5/49(10%)
Foci of pigmented macrophages	0/49	0/8	1/7(14%)	6/49(12%)
Focal necrosis	2/49(4%)	0/8	0/7	5/50(25%)
Focal angiectasis	7/49(14%)	0/8	0/8	15/50(30%)

In addition, there was an increased incidence of dilation of Bowman's capsules in treated males. The incidence was 1/50, 11/49, 6/50, and 9/49 in the control, low-, mid-, and high-dose groups, respectively. It was indicated that the lesion may represent an early stage of nephropathy which is an age related degenerative change in the kidneys of mice.

2) Neoplastic - On the first examination of the slides it was determined that there was an increased incidence of alveolar/bronchiolar tumors in treated male mice. The incidence is shown in the table below. In Table #2 (attached), the incidence in mice according to the severity of the lesion, is provided.

Alveolar/Bronchiolar Tumors in Mice

Males
Dose (ppm)

Lesion	0	30	110	420
Alveolar/bronchiolar				
- Adenoma only	5/50(10%)	7/50(14%)	7/50(14%)	13/50(26%)
- Carcinoma only	2/50(4%)	5/50(10%)	6/50(12%)	7/50(14%)
- Adenoma associated with carcinoma	0/50	1/50 (2%)	1/50(2%)	0/50
Lung tumor bearing animals	7/50(14%)	13/50(26%)	14/50(28%)	20/50(40%)

Females
Dose (ppm)

Lesion	0	20	80	320
Alveolar/bronchiolar				
- Adenoma only	8/49(16%)	0/10	0/7	5/50(10%)
- Carcinoma	1/49(2%)	0/10	0/7	2/50(4%)
Lung tumor bearing animals	9/49(18%)	0/10	0/7	7/50(14%)

The data on males demonstrated a statistically significant trend with increasing dose ($p < 0.01$). The sponsor decided to have these results verified by an "outside expert", Dr. F.J.C. Roe. His findings are presented below:

Incidence of Lung Tumors in Males[1]

Dose Level (ppm)

Lesion	0	30	110	420
No. with "lung tumor"	11/50(22%)	16/50(32%)	18/50(36%)	25/50(50%)
No. with "malignant tumor"	2/50(4%)	6/50(12%)	6/50(12%)	7/50(14%)
No. with > 1 tumor	2/50(4%)	1/50(2%)	4/50(8%)	7/50(14%)
No. with tumor > 3 mm	2/50(4%)	4/50(8%)	2/50(4%)	6/50(12%)

[1]Includes first and second set of slides.

[The incidence of alveolar/bronchiolar tumors in rats at IRI was reported to range from 15 to 25%.]

An increase in the incidence of adenoma of the Harderian gland was observed in treated males. The slides were read twice. The first reading was performed by IRI; the second reading was performed by F.J.C. Roe.

Incidence of Harderian Gland Tumors in Male Mice

Lesion	Dose (ppm) 0	30	110	420
First Reading*				
Harderian gland tumor	1/50(2%)	8/50(16%)	5/50(10%)	8/50(16%)
Second Reading*				
Harderian gland tumor	7/50(14%)	10/50(20%)	7/50(14%)	13/50(26%)
Data from Table 33**				
Harderian gland				
- Adenoma	2/50(4%)	7/50(14%)	5/50(10%)	10/47(21%)
- Adenoma (serial sections)	5/50(10%)	2/50(4%)	1/50(2%)	3/47(6%)
- Adenocarcinomas	0/50	1/50 (2%)	1/50 (2%)	0/47

*Data extracted from body of the report p. 27.
**Data extracted from Table 33, p. 92.

It is clear a discrepancy exists with respect to the number of animals examined in the high-dose group which requires an explanation from the sponsor. (It is believed that Table 33 reflects the results of the second reading.)

D. Discussion

The study consisted of a carcinogenicity study of 80 weeks in duration utilizing three dosage levels (males: 30, 110, and 420 ppm; females: 20, 80, and 320 ppm) and a chronic toxicity study of 52 weeks plus a 6-week recovery phase for a control and a high-dose group. There were no clinical signs of toxicity reported and mortality was similar for control and treated animals. Test material intake for the low-, mid-, and high-dose groups was 5.3, 19.3, and 73.9 mg/kg/day for males and 4.4, 16.9, and 72.2 mg/kg/day for females in the carcinogenicity study. In the chronic toxicity study, test material intake for the low-, mid-, and high-dose groups was 6.0, 21.7, and 81.8 mg/kg/day for males and 4.8, 18.2, and 71.6 mg/kg/day for females. Treatment did not affect

the hematology parameters that were measured. Several changes occurred in the values for clinical chemistry parameters; however, there appeared to be no relationship with treatment. The results of the urinalysis were unremarkable. At the interim (26-week) and terminal (52-week) sacrifice in the chronic toxicity study, the absolute and relative weights of the liver were increased in males in the high-dose group. No treatment related changes were reported for the gross necropsy examination at 26, 52, or 80 weeks. On histological examination, there was an increased incidence of various liver lesions in female mice in the high-dose group over an 80-week period. The lesions included localized perivascular lymphocytic infiltration, foci of pigmented macrophages, focal necrosis and focal angiectasis. There was an increased incidence of alveolar/bronchiolar adenomas in male mice when compared to controls. The incidences exceeded those found in historical controls at the laboratory conducting the study. There also appeared to be a dose-related increase in alveolar/bronchiolar carcinomas. The number of males with multiple lung tumors also was increased in the mid- and high-dose groups. The incidence of Harderian Gland tumors were variable but appeared to be slightly increased in males in the high-dose group. (The sponsor should 1) submit historical control data depicting the incidence of Harderian gland tumors and 2) verify the number of animals with lung tissues that were histologically examined in the male high-dose group.

It is not apparent that a MTD was administered. No discussion on dose selection was provided. In an earlier 90-day study in mice (#B-104 709, 9/5/83), the NOEL was determined to be 100 mg/kg/day and the LEL was 300 mg/kg/day based on increased liver weight and liver pathology (i.e. fatty changes, glycogen depletion and increased multinucleated hepatocytes).

The increase in alveolar/bronchiolar adenomas and carcinomas, and Harderian gland adenomas will be examined further by HED's Peer Review Committee.

Neither a NOEL or LEL could be determined because a target organ, the liver, was examined in all control and high-dose animals, but was not examined in all animals at lower dose levels.

Attachment

Table 2: Identity of male mice with primary lung tumors as seen in the original set of sections

	Group 1	Group 2	Group 3	Group 4
Lung tumors				
Worst grade = 4		66 99	147	153
Worst grade = 3	10 28	54 57 62 68	113 129 132 134 148	154 157 187 195 196 200
Worst grade = 2	5 14	52 92	116 150	152 160 172
Worst grade = 1	8 20 41	67 71 78 68 94	102 119 141 142 144	151 164 167 175 176 177 179 186 189 193

Reviewed By: William B. Greear, M.P.H.
Review Section II, Toxicology Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M.
Review Section II, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT 033101

Study Type: Guidelines Series 83-5
2-Year Chronic/Oncogenicity - Rat

TOX Chem No.: 652C

MRID No.: 40376901

Test Material: Fenoxycarb

Synonyms: Ethyl[2-(p-phenoxyphenoxy)ethyl]carbamate; Ro 13-5223/000; N-[2-(p-phenoxyphenoxy)ethyl]carbamic acid; ACR 5023

Study No.: Hazleton Report No. 5191-161/123

Sponsor: Maag Agrochemicals
Research and Development
HLR Sciences, Inc.
Vero Beach, FL 32961

Testing Facility: Hazleton Laboratories Europe, Ltd.
North Yorkshire, England HG3 IPY

Title of Report: Fenoxycarb (Ro 13-5223/000): 104-Week Oral (Dietary Administration) Carcinogenicity and Toxicity Study in the Rat with a 52-Week Interim Kill.

Author: M.J. Goodyer

Report Issued: November 1986

Conclusions:

NOEL < 200 ppm (10 mg/kg/day)
LEL = 200 ppm (10 mg/kg/day) based on liver lesions in males: microcystic degeneration, focal necrosis, and fibrosis.

In addition, in the 600 ppm group, alkaline phosphatase, SGOT and/or SGPT were increased and the relative weight of the liver was increased in females. Males exhibited additional liver lesions: hypertrophy and pigmented histiocytes. In the 1800 ppm group females also exhibited anemia, increased absolute and relative weight of the liver, hypertrophy of the liver and cysts of the thymus. Males in the 1800 ppm group also had a slight

increase in carcinoma of the pituitary and increased incidence of follicular cysts and C-cell hyperplasia of the thyroid.

Carcinogenicity: Inconclusive pending submission of historical control data on the occurrence of pituitary tumors in Crl:CD(SD)BR rats.

Classifications: Supplementary

Justification of Classification:

Chronic: A NOEL was not demonstrated. Also based on deficiencies as indicated in section E. Deficiencies.

Oncogenicity: Based on deficiencies as indicated in section E. Deficiencies.

A. Materials:

1. Test Compound - Ro 13-5223/000; Description: Not reported; Lot No.: 2; Purity: 96.6%; Contaminants: Not reported.

2. Test Animals - Species: Rat; Strain: Crl:CD(SD)BR Sprague-Dawley derived; Age: 6 weeks at start of study; Weight: males 135-200 g; females 99-153 g; Source: Charles River (UK) Ltd., Manston Road, Margate.

B. Study Design:

1. Animal Assignments - Animals were assigned* to the following test groups:

Test Group	Dose in Diet (ppm)**	Main Study 104 Weeks Male	Main Study 104 Weeks Female	Interim Sacrifice 52 Weeks Male	Interim Sacrifice 52 Weeks Female
Control	0	50	50	10	10
Low	200	50	50	10	10
Mid	600	50	50	10	10
High	1800	50	50	10	10

On receipt of the animals, 10 males and 10 females were sacrificed for a histopathological pre-screening of the liver, lung, and kidney. (The pre-screen was unremarkable). The remaining animals were allowed to acclimate to laboratory conditions for 2 weeks. The rats were housed in groups of five in stainless steel wire mesh cages suspended over cardboard-lined trays in a single room. The temperature and relative humidity were maintained at 19 to 25 °C and 40 to 70 percent, respectively. A 12-hour on/12-hour off lighting cycle was employed. Food and water were available ad libitum.

2. Diet Preparation - Separate batches of diet were prepared for each treatment group at weekly intervals. The diet was stored at room temperature. It was stated that the stability and homogeneity of the formulated diets were investigated by Hazleton Laboratories Europe, Ltd. prior to the start of the study. The concentration of the test material in each of the high- and low-dose diets was determined in Week 1 and at 13-week intervals, thereafter. Week 1 samples were analyzed in duplicate and a single

---

*It was not stated whether the assignment was random.
**Dose levels were stated to have been selected by the sponsor after examining data from a 6-week range-finding study.

analysis of the Week 13 sample was conducted. All remaining analyses were conducted in triplicate.

Results - Stability and homogeneity data on the formulated diets were not provided. The concentration of the test material in the low- and high-dose groups ranged from 89.7 to 104.0 percent and 94.0 to 99.0 percent of their expected values, respectively, over the 104-week period.

3. Statistics - Data were manipulated to provide group mean values and standard deviations. SGOT, SGPT and alkaline phosphatase were analyzed using a Kruskal-Wallis test for between group differences, followed by the Wilcoxon Rank Sum test. Prior to analysis of liver weights from animals at the interim and terminal sacrifice, the weights were adjusted using the formula:

$$\text{adjusted weight} = \text{actual weight} \times \left(\frac{100}{\text{body weight}}\right)^{b}$$

where "b (the allometric coefficient)" is specific to the organ, sex, age, and species of the animal. The value of "b" was derived from logarithmic regression analysis of historical control data. The allometric coefficient "b" was determined to be 1.25 and 0.75 for males and females at the interim sacrifice and 1.00 and 0.75 for males and females at the terminal sacrifice, respectively. The Terpstra-Jonckheere test with a 2-sided risk was applied successively to 1) all groups, 2) all groups omitting the highest dose level group, 3) all groups omitting the two highest dose levels, etc., until a result not significant ($p > .05$) was obtained. The groups were then analyzed using the Kruskal-Wallis test, and significant differences ($p < .01$) among these groups investigated by a Wilcoxon Rank Sum test (2 sided). A significant difference from the control occurs ". . . if either Terpstra-Jonckheere test is significant ($p < .05$), when the group is that with the highest dose level included, or if the group is one of those among which a significant Kruskal-Wallis test occurs and the Wilcoxon test reveals a significant pairwise difference from the control ($p < .05$)."

4. Quality Assurance examinations were conducted at 21 intervals between September 1983 and November 1986. The statement was signed by Pamela R. Cooper on November 26, 1986.

C. Methods and Results:

1. Observations - The frequency of observation of the animals for clinical signs of toxicity and mortality was not provided.

Results - It was stated that there were no adverse effects seen in clinical signs of toxicity or mortality in all the treated groups of animals. Data supporting the statement that there were no adverse clinical signs of toxicity were not provided. Survival did not appear to be adversely affected by treatment. Although survival was slightly lower in the female high-dose group at Week 104, at Week 100 survival was comparable with 38/50 (76%) and 39/50 (78%) females alive in the high-dose and control group, respectively. Survival data at Week 104 is provided in the table below:

Number of Surviving Animals (Week 104)/Number of Animals Alive After the Interim Sacrifice

	Dose Level (ppm)			
	0	200	600	1800
Males	38/50(76%)	34/50(68%)	34/51(67%)	37/50(74%)
Females	38/50(76%)	39/50(78%)	29/50(58%)	33/50(66%)

2. Body Weight - Individual animal body weights were determined before treatment on the first day of the study, at weekly intervals up to Week 16 and then at 4-week intervals until Week 104.

Results - From Week 1 through Week 100, males in the 1800 ppm group had slightly decreased body weights when compared to the control and other treatment groups (see Table I). The mean body weight of males in the 1800 ppm group was 6.6% less than the controls at 13 weeks. The decreased body weights in males in the 1800 ppm group did not appear to be significant. [A statistical analysis of the data was not conducted.]

Table I. Mean Male Body Weight (g) at Monthly Intervals

Group (ppm)	Week						
	0	16	32	48	64	80	104
Control	169.2	512.9	592.2	658.5	694.7	706.9	736.6
200	172.4	495.7	577.5	650.0	676.6	688.6	707.1
600	169.8	506.9	590.3	663.4	699.9	718.9	747.8
1800	166.1	476.0	554.7	612.5	653.3	668.7	711.2

3. Food Consumption and Compound Intake - Food consumption was determined for each cage of animals at weekly intervals to Week 16 and at 4-week intervals until Week 104.

Results - It was reported that mean cage food consumption (g/week) was generally lower in males in the 1800 ppm group when compared to the control and other treatment groups from Week 1 through Week 76 (see Table II). At 13 weeks, mean cage food consumption in males in the 1800 ppm group was only 7% less than controls. However, there was considerable variation in the amount of food consumed in the treatment groups. The decrease in food consumption in males appears to be minor and not of significance. Food consumption data were not provided at Week 96 due to a "recording error." The ranges for mean compound intake (mg/kg/day) are provided in the table below:

Table II. Mean Cage Food Consumption (g) in Males at Selected Intervals

Group (ppm)	Week						
	0	16	32	48	64	80	104
Control	172.3	180.3	164.9	165.6	168.1	162.3	151.6
200	170.5	171.0	162.6	158.5	165.9	155.4	143.0
600	171.3	178.5	168.8	164.9	170.0	161.8	146.8
1800	160.3	168.3	159.9	153.6	159.1	155.6	143.2

Mean Compound Intake (mg/kg/day)

Sex	Group			
	Control	200 ppm	600 ppm	1800 ppm
Males	0	5.4-24.7	16.6-75.1	52.6-217.2
Females	0	7.2-23.5	23.1-70.8	66.9-212.8

The sponsor should provide information on the time-weighted average daily intake of the test material.

4. Ophthalmological Examinations were conducted on all animals prior to initiation of the study and on 10 rats/sex in the control and 1800 ppm groups in Weeks 51 and 102.

   Results - It was stated that no adverse effects were noted. Individual animal data were not submitted.

5. Blood was collected from 10 rats/sex in the control and 1800 ppm groups at Weeks 25, 51, 78, and 102. Samples were obtained by orbital sinus puncture under light anesthesia following overnight deprivation of food.

The CHECKED(X) parameters were determined.

a. Hematology

X		X	
X	Hematocrit (HCT)		Total plasma protein (TP)
X	Hemoglobin (HGB)	X	Leukocyte differential count
X	Leukocyte count (WBC)	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)	X	Mean corpuscular HGB conc. (MCHC)
X	Platelet count		Mean corpuscular volume (MCV)
	Erythrocyte morphology		Clotting time

Results - At Week 102, two females in the 1800 ppm group (#467 and #469) had anemia with very large decreases in HGB, RBC and PCV. For example, the HGB, RBC, and PCV for #467 was 6.7 g/dl, 2.92 million/cm^2 and 16.7 percent. Female control values at 102 weeks ranged from 12.1 to 17.0 g/dl, 5.37 to 7.52 million/cm^2 and 31.8 to 42.7% for HGB, RBC and HCT, respectively. Hematological parameters were not examined in these two females at earlier intervals so the progression of this condition could not be followed.

b. Clinical Chemistry

	Electrolytes		Other
X	Calcium	X	Albumin
	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
	Phosphorus	X	Cholesterol
X	Potassium		Globulins
X	Sodium	X	Glucose
	Enzymes	X	Total bilirubin
X	Alkaline phosphate	X	Total protein
	Cholinesterase		Triglycerides
	Creatinine phosphokinase		Thyroxine (T_4)
	Lactic acid dehydrogenase (LDH)		Triiodothyronine (T_3)
X	Serum alanine aminotransferase (SGPT)*	X	Albumin/Globulin
X	Serum aspartase aminotransferase* (SGPT)*		(A/G)
	Gamma glutamyltransferase		

*Also measured in the 200 and 600 ppm groups in Week 102.

Results - At Weeks 25, 51, and 78, alkaline phosphatase was increased in males in the 1800 ppm group. SGOT and SGPT were also increased in males in the 1800 ppm group. At Week 78, there also appeared to be an increase in LDH in males in the 1800 ppm group. Because the increase in LDH did not occur at any other sampling times, it was considered not to be treatment-related. At Week 102, SGOT, SGPT, and alkaline phosphatase were increased in

females in the 600 and 1800 ppm groups. It should be noted that analyses were not conducted in males and females in the 200 and 600 ppm groups at 25, 51 and 78 weeks. Therefore, it could not be ascertained whether treatment-related changes occurred in the 200 and 600 ppm groups at the earlier sampling times.

The group mean data are summarized in the table below:

Selected Group Mean Clinical Chemistry Data

	Dose Level (ppm)							
	Control		200		600		1800	
	Male	Female	Male	Female	Male	Female	Male	Female
				Week 25				
SGOT (Iu/L)	92	76					156	78
SGPT (Iu/L)	46	28					66	32
Alk. Phos. (Iu/L)	143	73					200**	107
				Week 51				
SGOT (Iu/L)	100	73					79	145
SGPT (Iu/L)	53	34					113	32
Alk. Phos. (Iu/L)	158	60					243**	119**
				Week 78				
SGOT (Iu/L)	88	88					292*	111
SGPT (Iu/L)	45	41					193**	54
Alk. Phos. (Iu/L)	143	84					272**	131
				Week 102				
SGOT (Iu/L)	78	85	90	79	197**	107	153*	104
SGPT (Iu/L)	29	37	36	34	82**	41	73**	34
Alk. Phos. (Iu/L)	136	72	163	74	202	94*	286**	104*

*Statistically significant at $p < 0.05$.
**Statistically significant at $p < 0.01$.

6. Urinalysis - Determined on 10 rats/sex in the control and 1800 ppm groups prior to treatment and in Weeks 25, 51, 78, and 102. The CHECKED (X) parameters were determined.

X		X	
X	Appearance	X	Glucose
X	Volume	X	Ketones
X	Specific gravity	X	Bilirubin

X	pH	X	Blood
X	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen
		X	Reducing substances

Results - Unremarkable.

6. Sacrifice and Pathology - All animals that died and that were sacrificed at the interim and final kill were subject to gross pathological examination and the CHECKED (X) tissues were collected for histopathological examination The (XX) organs in addition were weighed for all interim sacrificed animals and for 10 rats/sex group at termination.

X		X		X	
Digestive System		Cardiovasc./Hemat.		Neurologic	
X	Tongue	X	Aorta	XX	Brain
X	Salivary glands	XX	Heart	X	Peripheral nerve
X	Esophagus		Bone marrow	X	Spinal cord (3 levels)
X	Stomach	X	Lymph nodes	X	Pituitary
X	Duoderum	XX	Spleen	X	Eyes (optic n.)
X	Jejunum	X	Thymus	Glandular	
X	Ileum	Urogenital		XX	Adrenals
X	Cecum	XX	Kidneys		Lacrimal gland
X	Colon	X	Urinary bladder	X	Mammary gland
	Rectum	XX	Testes	X	Parathyroids
XX	Liver	X	Epididymides	XX	Thyroids
	Gallbladder	X	Prostate	Other	
X	Pancreas	X	Seminal vesicle	X	Bone
Respiratory		XX	Ovaries	X	Skeletal muscle
X	Trachea	X	Uterus	X	Skin
XX	Lung			X	All gross lesions and masses
				X	Harderian gland
				X	Head (3 sections)

a. Organ Weight - At the interim sacrifice, the absolute weight of the thyroid was slightly increased and the spleen decreased in males in the 1800 ppm group. The relative weight of the liver was decreased in males and females in the 600 and 1800 ppm groups. At terminal sacrifice, the absolute weight of the liver was slightly increased in females in the 1800 ppm group. The relative weight of the heart and the kidney were increased in females in the 1800 ppm group. The relative weight of the spleen was slightly increased in males in the 1800 ppm group. The relative weight of the liver was increased in females in the 600 and 1800 ppm groups. Only the changes in liver weight are considered to be related to treatment. The changes in the other organs are erratic and probably spurious.

b. Gross Pathology - Unremarkable.

c. Microscopic Pathology

1) Non-neoplastic - There was an increase in the incidence of cysts of the thymus in females in the 1800 ppm group. There was 3, 1, 1 and 10 females with cysts of the thymus in the 0, 200, 600, and 1800 ppm groups, respectively. There was an increase in the incidence of follicular cysts and C-cell hyperplasia of the thyroid in males in the 1800 ppm group. Follicular cysts occurred in 1, 1, 1, and 6 males and C-cell hyperplasia occurred in 14, 0, 4, and 24 males in the 0, 200, 600, and 1800 ppm groups, respectively. The incidence of foamy histiocytes and granuloma of the lungs was increased in males and females in the 1800 ppm group as indicated in the following table.

Selected Lesions of the Lung

	Males				Females			
Dose (ppm)	0	200	600	1800	0	200	600	1800
Foamy histiocytes	6	6	6	12	11	3	11	31
Granuloma	0	0	0	4	1	0	1	5

There was an increased incidence of liver lesions in males and females in the treated groups. As indicated in the table below, microcystic degeneration, focal necrosis and fibrosis were increased in all male treated groups. Hypertrophy was increased in males in the 600 and 1800 ppm groups and in females in the 1800 ppm group. Pigmented histiocytes occurred with increased frequency in males in the 600 and 1800 ppm groups.

Selected Liver Lesions

	Males				Females			
Dose (ppm)	0	200	600	1800	0	200	600	1800
Microcystic degeneration	13	19	23	28	0	1	1	3
Focal necrosis	1	6	18	19	2	2	6	0
Fibrosis	0	3	3	12	0	0	0	6
Hypertrophy	0	0	8	22	0	0	0	10
Pigmented histiocytes	0	0	2	4	0	0	0	0

2) Neoplastic - There appeared to be an increased incidence of carcinoma of the pituitary in males. The increase exhibited a dose-response relationship. The incidence of pituitary neoplasms is presented in the table below.

Pituitary Neoplasms

	Males				Females			
Dose (ppm)	0	200	600	1800	0	200	600	1800
Adenoma	27	12	15	20	32	13	25	35
Carcinoma	1	2	2	6	14	14	10	9

[Historical control data are required to confirm or refute the suggestion of oncogenicity of the test material as manifested by carcinoma of the pituitary in males.]

D. Discussion:

The control and treated groups were comparable with respect to clinical signs and mortality. Survival ranged from 67 to 76 percent in males and 58 to 78 percent in females. Body weight and food consumption were not significantly affected by treatment. The ophthalmologic examination was unremarkable. Anemia was present in two females in the 1800 ppm group at Week 102. The anemia was manifested by relatively large decreases in HGB, RBC and HCT. Alkaline phosphatase was increased in males and females in the 1800 ppm group at 25, 51, and 78 weeks. In addition, SGOT and SGPT were increased in males in the 1800 ppm group. It should be noted that rats in the 200 and 600 ppm groups did not receive a clinical chemistry examination at 25, 51, and 78 weeks. Because changes were observed at the high dose, rats in the lower dose group(s) should have been examined. At Week 102, alkaline phosphatase, SGOT, and SGPT were increased in females in the 600 and 1800 ppm groups. Increases in SGOT and alkaline phosphatase were also observed in females in the 600 and 1800 ppm groups. The increases in alkaline phosphatase, SGOT and SGPT may be related to treatment and correlates with increased liver weights and liver pathology observed in treated animals. The results of the urinalysis were unremarkable. At terminal sacrifice, the absolute weight of the liver was increased in females in the 1800 ppm group. The relative weight of the liver was also increased in females in the 600 and 1800 ppm groups. Females in the 1800 ppm group had an increased incidence of cysts of the thymus. Males in the 1800 ppm group had an increased incidence of follicular cysts and C-cell hyperplasia of the thyroid. The incidence of foamy cells and granuloma of the lung was increased in

males and females in the 1800 ppm group. Several liver lesions occurred in the treated groups that were related to treatment. Males in all the treated groups exhibited a dose-response relationship with respect to the occurrence of microcystic degeneration, focal necrosis, and fibrosis. Hypertrophy and the presence of pigmented histiocytes were present in the male 600 and 1800 ppm groups. Females only exhibited a slight increase in hypertrophy at the 1800 ppm dose level. There was a slight increase in the incidence of carcinoma of the pituitary in males. It could not be determined if this was treatment related. There was neither an increase in pituitary adenoma in males nor an increase in pituitary neoplasms in females. Historical control data should be obtained for further consideration in analyzing the increased incidence of pituitary carcinoma in males in the 1800 ppm group.

E. Deficiencies:

The study suffers from several deficiencies. Many of the parameters that were measured were not statistically analyzed. Examples of this are no statistical analysis of body weight, food consumption, hematology values and the results of the histopathology examination. In the clinical chemistry examination, no determinations were made for SGOT, SGPT, and alkaline phosphatase for rats in the 200 and 600 ppm groups at 25, 51, and 78 weeks even though positive results were obtained for the 1800 ppm group. Tissue accountability tables are absent, therefore, it is impossible to determine how many animals had a complete set of tissues examined. It is unknown how many sets of tissues (or partial sets) were lost to autolysis, cannibalism, etc. Most important, it is impossible to determine the actual percent incidence of lesions within groups of animals. Also, conspicuously missing from the individual pathology sheets is the date of death of the animal which would be of use in analyzing the data. The sponsor should provide information on the time-weighted average daily intake of the test material. Historical control data are required for the pituitary tumors as noted above. This should present the data by study for 2+ years on either side of this present study. the data should be from the same laboratory, using the same strain of rat and be for the same duration. The tumors should be listed for the malignant Tumors, benign tumors and pituitary tumor bearing animals (sexes separate).

EPA No.: 68D80056
DYNAMAC No.: 185-A
TASK No.: 1-85A
December 15, 1989

83-4

000101

DATA EVALUATION RECORD

FENOXYCARB

Two-Generation Reproductive Toxicity Study in Rats

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: Robert J. Weir Jr.

Date: Dec 15, 1989

41

EPA No.: 68D80056
DYNAMAC No.: 185-A
TASK No.: 1-85A
December 15, 1989

035101

DATA EVALUATION RECORD

FENOXYCARB

Two-Generation Reproductive Toxicity Study in Rats

REVIEWED BY:

Patricia Turck, M.S.
Principal Reviewer
Dynamac Corporation

Signature: Patricia Turck
Date: December 15, 1989

Robert J. Weir, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: Roman J Pienta for
Date: Dec 15, 1989

APPROVED BY:

Roman J. Pienta, Ph.D.
Department Manager
Dynamac Corporation

Signature: Roman J Pienta
Date: Dec 15, 1989

William Greear, MPH
EPA Reviewer, Section II
Toxicology Branch I
(H-7509C)

Signature: William B. Greear
Date: 12/19/89

Marion Copley, D.V.M.,
D.A.B.T.
EPA Section Head, Section II
Toxicology Branch I(H-7509C)

Signature:
Date: (12/17)

DATA EVALUATION RECORD

033101

STUDY TYPE: Reproductive toxicity; Guideline §83-4.

MRID NUMBER: 403769-03.

TEST MATERIAL: Ro 13-5223/000.

SYNONYM(S): Fenoxycarb.

STUDY NUMBER(S): 4623-161/124.

SPONSOR: Hoffman-LaRoche and Co., Basle, Switzerland and Maag Agrochemicals Research & Development HLR Sciences, Inc., Vero Beach, FL.

TESTING FACILITY: Hazleton Laboratories Europe, North Yorkshire, England.

TITLE OF REPORT: Ro 13-5223/000: 2-Generation Oral (dietary administration) Reproduction Study in the Rat.

AUTHOR(S): Barker, L., and M. Goodyer.

REPORT ISSUED: September 1986.

CONCLUSIONS:

In a reproductive toxicity study in which groups of Sprague-Dawley rats were fed diets containing 0, 200, 600, or 1800 ppm of Ro 13-5223/000 continuously for two generations, liver effects that included increased absolute and relative (to body weight) liver weight at the mid- and high-dose levels and increased incidences of focal necrosis and hypertrophy of the liver at the high-dose level were observed. However, since histopathological evaluation of the livers of F_3 and F_1 parental animals from the low- and mid-dose groups were not conducted, neither a NOEL nor a LOEL for parental toxicity could be established.

The LOEL for reproductive toxicity was equal to or less than 200 ppm, based on significant decreases in pup weight at all dose levels. Further delays in development, i.e., pinna unfolding and eye opening, were also observed, and appeared to be dose related. This could not be assessed, however, because individual data for these parameters were not presented. The NOEL for reproductive toxicity was not established.

Classification: CORE Supplementary Data.

A. MATERIALS:

Test Compound: Purity: 96.6% pure; description: white crystalline substance; lot No.: 2; contaminants: not reported.

Vehicle(s): None used.

Test Animals: Species: rat; strain: Sprague-Dawley (Crl:CD (SD)BR); source: Charles River Laboratories, Ltd., England; age: F_0 animals were approximately 6 weeks old and F_1 animals were 3.5-6.5 weeks old at initiation of treatment; weight: F_0 males were 200-285 g and F_0 females were 106-178 g at initiation of treatment.

F_1 males were 132-225 g and F_1 females were 115-178 g at initiation of treatment.

B. STUDY DESIGN:

This study was designed to assess the reproductive toxicity potential of Ro 13-5223/000 when administered orally in the diet to rats for two successive generations.

Mating: At sexual maturation (F_0--80 days of treatment, F_1--100 days of treatment), parental animals within the same dietary group were paired one male:one female for up to 21 days to produce F_a litters. If mating did not occur within 10 days, the male was replaced with a proven male from the same test group. Sibling pairings were avoided. The estrous cycle of each female was monitored daily by vaginal lavage. Day 0 of gestation was designated as the day on which sperm was found. One week after the weaning of the first litter, parental animals were again paired to produce F_b litters.

1. Group Arrangement:

Test Group	Dietary Concentration (ppm)	Number Assigned F_0 Males	F_0 Females	F_1 Males	F_1 Females
1 Control	0	30	30	25	25
2 Low dose	200	30	30	25	25
3 Mid dose	600	30	30	25	25
4 High dose	1800	30	30	25	25

Dosing: The test material was administered in the diet. The test diets were fed ad libitum from initiation of treatment until terminal sacrifice. Test diet was prepared weekly and any diet remaining after 1 week was discarded. Homogeneity and stability of the test material in the diet were determined before study initiation. Results indicated that homogeneity was acceptable. The test material was stable for 1 week at room temperature. Concentration analyses of the test material in the diet were performed during weeks 1, 12, 25, 37, 49, and 61 of the study. The dose levels were chosen based on the results of a preliminary 6-week range-finding study. However, no other information on this study was provided.

Observations: The animals were checked for mortality twice daily and for signs of toxicity once daily. Any animals dying during the study were subjected to gross necropsy. The uteri of females dying during the study were examined, and the number and type of implantations were recorded. During gestation, pregnant females were observed twice daily for parturition.

Body weights of parental males were recorded weekly; body weight of females was recorded weekly until pregnancy was confirmed. Body weights of pregnant females were recorded on days 0, 6, 12, 15, and 20 of gestation and on days 1, 7, 14, and 21 of lactation. After weaning, the body weights of parental females were recorded weekly. Food consumption was measured weekly during the premating period only. The dates of mating and parturition and the duration of gestation were recorded for each pregnant female.

The following data were recorded for each litter:

- The number of pups born alive and dead;
- The number of pups alive on days 1, 4, 7, 14, and 21 of lactation;
- Pup weights (individual) on days 1, 4, 7, 14, and 21 of lactation;
- Sex of pups alive on days 1, 4, 7, and 21 of lactation; and
- General condition of pups during the lactation period.

Litters were randomly culled on day 4 of lactation to a maximum of eight pups (four/sex if possible).

Pups discarded after culling were subjected to gross necropsy.

The following developmental parameters were recorded for all pups from each litter:

- Pinna unfolding;
- Day on which growth of fur was first observed;
- Tooth eruption; and
- Eye opening.

On day 21 of lactation, two male and two female pups from each litter were chosen, and the following functional tests were performed on each:

- Grip strength;
- Papillary reflex of both eyes;
- Visual placing response; and
- Auditory response.

At the end of the second mating for each generation, all parental males were killed and necropsied. Parental females were killed and necropsied after weaning of the second litters for each generation. All animals were subjected to a complete gross necropsy. The liver and reproductive organs, including testes, epididymides, seminal vesicles, and prostrate for parental males and the uterus, vagina, and ovaries for parental females, were saved in 10% neutral-buffered formalin. The liver, testes, uteri, and ovaries were weighed before fixation.

The above organs from control and high-dose parental animals were histologically examined.

After weaning, all F_{1a}, F_{2a}, F_{2b}, and F_{1b} pups not selected as parental animals were subjected to macroscopic examination. The following tissues and organs were taken from one male and one female from each litter and preserved in 10% neutral buffered formalin (organs and tissues weighed and/or histologically examined are indicated):

[ab]Adrenals
[ab]Brain (fore-, mid-, hind-)
Cecum
Colon
[b]Duodenum
[b]Eyes (both)
Femur (including bone marrow)
[a]Heart
Ileum
Jejunum
[ab]Kidney
[ab]Liver (two lobes)
[b]Lung (two sections, coronal cut)
[b]Mesenteric lymph node
[a]Ovaries/uterus
[b]Testes/epididymides/prostate/seminal vesicles
[a]Pancreas
[a]Pituitary
Salivary gland (mandibular)
Spinal cord (cervical and lumbar)
[b]Spleen
[b]Stomach
[b]Thymus
[b]Thyroids
Trachea
[b]Urinary bladder
[b]Vagina
All gross lesions

In addition, the livers from five male and five female F_{1b} pups from each group were histologically examined.

---

[a]Weighed before fixation.

[b]Histologically examined from control and high-dose F_{2b} pups.

Statistical Analysis:

Body weight gain, food consumption, duration of gestation, fetal weight, pup weight, and organ weights were analyzed by analysis of variance or the Kruskal-Wallis and Wilcoxon rank-sum tests. Discrete data such as preweaning loss and the number of pups dead were analyzed by Fisher's test with a Monte Carlo simulation.[1] All tests were carried out to the 1 and 5% levels of significance for a two-sided risk.

Compliance:

- A signed Statement of No Data Confidentiality Claim, dated March 3, 1987, was provided.
- A signed Statement of Compliance with EPA GLP's was not provided. However, the statement certifying that the study was conducted according to protocol and to the laboratory's Standard Operating Procedures was provided.
- A signed Quality Assurance Statement, dated September 9, 1986, was provided.

C. RESULTS:

1. Test Material: Analyses of the test diets revealed that actual mean test material concentrations ranged from 95.5-105.0% of target concentrations during the study. The mean test material intake was 10.2-22.5, 30.5-66.7, and 92.2-200.0 mg/kg/day for low-, mid-, and high-dose males and 12.4-22.9, 37.7-67.4, and 111.7-194.5 mg/kg/day for low-, mid-, and high-dose females, respectively, during the study.

2. Parental Toxicity:

Mortality: The investigators supplied the following information.

Upon necropsy, the two F_0 males dying had red fluid in the abdominal cavity and enlarged livers (Table 1). Five, two, zero, and one F_0 females from the control and low-, mid-, and high-dose groups, respectively, died or were sacrificed

[1]Van Julsingha, E. B. Two new procedures for use in teratology studies designed to evaluate the safety of agents (Thesis).

Note: No other information on this reference was provided.

TABLE 1. Summary of the Number of Parental Animals Dying or Sacrificed *in extremis* (% Mortality) Before Study Termination[a]

Dietary Concentration (ppm)	F_0 Generation		F_1 Generation	
	Males	Females	Males	Females
No. animals/group	30	30	25	25
0	0	5(17)	0	4(16)
200	1(3)	4(13)	0	2(8)
600	0	0	1(4)	1(4)
1800	1(3)	2(7)	0	1(4)

[a]Data were extracted from study No. 4623-161/124, Appendices 6 and 12.

in extremis during the last 2 days of gestation (second mating) apparently because of dystocia. The investigators attributed these deaths to unusually large litters. One high-dose F_0 female had an ectopic pregnancy, but delivered 13 pups. She died on postpartum day 1; necropsy revealed an abnormal heart, pale and mottled liver, and dark areas in the stomach mucosa. In addition, one low-dose F_1 female died on postpartum day 1; no gross lesions were observed at necropsy.

For the F_1 parental generation, the mid-dose male killed *in extremis* (week 24) during the study had severe mottling of the kidneys and a pale liver as well as broken upper incisors (Table 1). Three, two, one, and zero F_1 females died or were sacrificed *in extremis* on day 21, 22, or 23 of gestation (second mating). As seen in the F_1 generation, dystocia was associated with these deaths.

The three control females and one low-dose female dying during the study had mottled or pale livers. However, no consistent findings were observed in the treated groups compared to controls at necropsy. In addition to these deaths, one control and one high-dose F_1 female died on postpartum day 1. The high-dose female delivered seven dead pups. At necropsy, this female had one pup in the vagina and five in the abdominal cavity. In addition, a pale liver was observed. The investigators considered all the mortalities in both generations to be unrelated to ingestion of the test material.

Clinical Observations: The investigators reported that no abnormalities were observed. However, no individual or summary data were provided.

Body Weight: Mean body weights for selected premating intervals are presented in Table 2. Mean body weights were similar between control and low- and mid-dose F_0 animals during the premating (weeks 0-11) period. Slight decreases in body weight gain (not shown in Table 2) were observed in the high-dose animals when compared to controls. However, the decreases were not statistically significant, except for that recorded for high-dose F_0 females ($p<0.05$) during weeks 0-4 and for high-dose F_0 males ($p<0.01$) during weeks 8-12. Mean (± S.D.) body weight gains for the F_0 females for weeks 0-4 were 71 ± 13, 75 ± 13, 70 ± 11, and 64 ± 8 g for the control, low-, mid-, and high-dose groups, respectively. For the F_0 males, body weight gains were 50 ± 13, 62 ± 21, 48 ± 12, and 46 ± 9 g for the control, low-, mid-, and high-dose groups, respectively, during weeks 8-12. Body weights and body weight gain were similar among dams from control and test groups during the gestation and lactation periods.

In the F_1 generation, initial parental body weights were approximately 8 and 5% lower for high-dose males and females, respectively, than for controls. The investigators reported that during the F_1 premating period (weeks 0-12), body weight gains were "generally" similar between control and high-dose animals, except for weeks 8-12 when a significant decrease ($p<0.05$) was observed for high-dose F_1 females when compared to controls. Mean body weight gains were 23 ± 8, 20 ± 6, 21 ± 7, and 16 ± 11 g for control and low-, mid-, and high-dose F_1 females, respectively, for weeks 8-12. Body weights and body weight gains (not shown in Table 2) for the low- and mid-dose animals were comparable to controls. Also, no differences in body weight gain for treated females were observed during gestation or lactation when compared to controls.

Food Consumption: Food consumption during the premating interval for both parental generations was similar between controls and the low- and mid-dose groups (Table 3). Food consumption for high-dose F_0 females and F_1 males and females was slightly, but not significantly, lower than controls throughout the premating interval.

Gross and Microscopic Pathology: No compound-related effects were noted at necropsy; incidences of macroscopic findings were similar for all treatment groups when compared to controls for both the F_0 and F_1 parental generations.

Absolute and relative (to body weight) liver weights and relative testicular weight were significantly ($p<0.01$) greater than controls for high-dose F_0 males (Table 4).

TABLE 2. Summary of Body Weights for Rats Fed Ro 13-5223/000 for Two Generations[a]

Dietary Concentration (ppm)	Mean Body Weights (± S.D.) at Week: 0	6	12	18	24
F: Males					
0	184 ± 14	406 ± 40	481 ± 49	518 ± 57	572 ± 61
200	187 ± 9	406 ± 27	486 ± 32**	533 ± 43	589 ± 42
600	187 ± 8	406 ± 37	481 ± 47	528 ± 56	572 ± 58
1800	186 ± 11	393 ± 31	468 ± 39	524 ± 45	569 ± 49
F: Females					
0	145 ± 10	242 ± 20	258 ± 23[b]	--[c]	--
200	142 ± 8	244 ± 18	260 ± 21	--	--
600	143 ± 9	243 ± 17	259 ± 19	--	--
1800	141 ± 8	231 ± 16	245 ± 16	--	--
F: Males					
0	192 ± 22	426 ± 41	514 ± 57	548 ± 59	593 ± 66
200	192 ± 13	421 ± 26	507 ± 33	548 ± 33	590 ± 43
600	186 ± 24	423 ± 44	516 ± 53	559 ± 52	600 ± 66
1800	176 ± 17	394 ± 34	483 ± 44	519 ± 45	565 ± 54
F: Females					
0	147 ± 15	248 ± 23	283 ± 27	--	--
200	145 ± 12	246 ± 18	279 ± 21	--	--
600	144 ± 11	242 ± 20	275 ± 24	--	--
1800	140 ± 14	232 ± 20	260 ± 23**	--	--

[a]Data extracted from study No. 4623-161/124, Table 1 and Appendix 1.

[b]Body weights represent week 11 of the study. Mating began on week 12.

[c]Gestation and lactation body weights were recorded for females during this time period.

**The body weight gain for the interval between weeks 8-12 was significantly different from controls at $p<0.01$.

TABLE 3. Summary of Food Consumption (g/Animal/Week) in Rats Fed Ro 13-5223/000 for Two Generations[a]

Dietary Concentration (ppm)	Mean Food Consumption (± S.D.) at Week: 1	4	8	11	14
F_0 Males					
0	165 ± 8	174 ± 23	182 ± 10	186 ± 10	--[b]
200	168 ± 3	189 ± 11	178 ± 6	183 ± 7	--
600	167 ± 7	189 ± 7	182 ± 9	180 ± 7	--
1800	164 ± 11	185 ± 11	181 ± 11	180 ± 9	--
F_0 Females					
0	130 ± 26	136 ± 14	136 ± 9	132 ± 7	--
200	124 ± 11	140 ± 12	138 ± 7	128 ± 6	--
600	122 ± 4	133 ± 7	136 ± 8	131 ± 7	--
1800	115 ± 7	129 ± 6	131 ± 10	123 ± 7	--
F_1 Males					
0	166 ± 9	191 ± 8	176 ± 13	173 ± 16	187 ± 13
200	162 ± 7	191 ± 2	179 ± 6	179 ± 5	187 ± 5
600	160 ± 7	189 ± 10	178 ± 8	178 ± 8	190 ± 6
1800	151 ± 5	183 ± 8	172 ± 11	170 ± 4	178 ± 5
F_1 Females					
0	119 ± 4	146 ± 7	129 ± 9	121 ± 8	131 ± 11
200	117 ± 3	144 ± 3	129 ± 3	119 ± 3	130 ± 6
600	117 ± 6	140 ± 7	127 ± 7	118 ± 6	128 ± 6
1800	109 ± 5	129 ± 9	120 ± 5	111 ± 6	123 ± 7

[a]Data were extracted from study No. 4623-161/124, Tables 2 and 9 and Appendices 1 and 9.

[b]The premating period ended on study week 11 for the F_0 generation.

TABLE 4. Summary of the Effects on Organ Weights of Rats Fed Ro 13-5223/000 for Two Generations[a]

Dietary Concentration (ppm)	Final Body Weight (g)	Liver Weight		Gonad Weight	
		Absolute (g)	Relative (%)	Absolute (g)	Relative (%)
F$_1$ Males					
0	569 ± 59	17.9 ± 3.2	3.1 ± 0.4	3.61 ± 0.42	0.64 ± 0.07
200	582 ± 39	18.3 ± 2.1	3.1 ± 0.3	3.75 ± 0.42	0.65 ± 0.08
600	566 ± 56	18.5 ± 2.7	3.3 ± 0.3	3.72 ± 0.50	0.66 ± 0.09
1800	562 ± 50	21.1 ± 3.0**	3.7 ± 0.3**	3.90 ± 0.46	0.70 ± 0.09**
F$_1$ Females					
0	331 ± 26	12.3 ± 2.0	3.7 ± 0.4	0.09 ± 0.02	0.027 ± 0.006
200	331 ± 29	12.8 ± 1.7	3.9 ± 0.4	0.09 ± 0.03	0.028 ± 0.008
600	324 ± 24	13.2 ± 1.4	4.1 ± 0.4	0.09 ± 0.02	0.029 ± 0.008
1800	308 ± 22	14.9 ± 1.6**	4.8 ± 0.4	0.10 ± 0.02	0.032 ± 0.005
F$_2$ Males					
0	589 ± 73	17.7 ± 3.7	3.0 ± 0.3	3.94 ± 0.63	0.68 ± 0.15
200	587 ± 47	17.2 ± 2.7	2.9 ± 0.5	3.94 ± 0.54	0.67 ± 0.11
600	604 ± 54	18.7 ± 2.4	3.1 ± 0.3	4.05 ± 0.37	0.67 ± 0.08
1800	571 ± 52	19.7 ± 2.8	3.4 ± 0.3**	3.96 ± 0.52	0.70 ± 0.10
F$_2$ Females					
0	357 ± 41	14.2 ± 2.5	4.0 ± 0.7	0.098 ± 0.035	0.027 ± 0.009
200	347 ± 33	14.3 ± 2.5	4.1 ± 0.7	0.086 ± 0.019	0.025 ± 0.007
600	340 ± 28	16.2 ± 2.7*	4.7 ± 0.7**	0.088 ± 0.024	0.026 ± 0.007
1800	325 ± 29	18.2 ± 2.8**	5.6 ± 0.6**	0.092 ± 0.026	0.028 ± 0.008

[a]Data were extracted from study No. 4623-161/124, Tables 6 and 13 and Appendices 6 and 13.

*Significantly different from controls at $p<0.05$

**Significantly different from controls at $p<0.01$.

In addition, absolute liver weight for high-dose F_1 females was significantly increased ($p<0.01$) when compared to controls. For the F_1 generation, relative liver weight in high-dose males and absolute and relative liver weight in mid- and high-dose females were significantly greater than controls (Table 4). No other significant changes in organ weights were observed in the F_2 and F_1 parents.

Histopathological evaluation revealed slight hypertrophy and necrosis of the liver in high-dose males and females from both parental generations when compared to controls. Incidences are presented in Table 5. No other compound-related histologic findings were observed. However, the livers of low- and mid-dose animals, except for three low-dose and one mid-dose F_0 females, were not histologically examined.

3. Reproductive Toxicity: The numbers of matings and pregnancies and the fertility and gestation indices for treated animals from all generations (F_{1a}, F_{1b}, F_{2a}, F_{2b}) were similar to control animals. The mean gestation length was significantly shorter during the F_{1b} mating for mid- ($p<0.05$) and high-dose ($p<0.01$) F_0 dams, during the F_{2a} mating for high-dose F_1 dams ($p<0.01$), and during the F_{2b} mating for mid- and high-dose F_1 dams ($p<0.01$) (Tables 6 and 7). The gestation length for low-dose F_0 and F_1 dams was similar to controls. Survival of offspring was not adversely affected by ingestion of the test material, although the viability from days 1 to 4 of lactation (viability index 1, Tables 6 and 7) was slightly, but not significantly, reduced for low-dose F_{1b} and F_{2a} pups and for mid-dose F_{2a} pups. Viability indices for all other generations were similar among control and test groups.

No compound-related clinical signs of toxicity were observed in offspring from parents fed the test material during the study. Body weights of offspring at day 1 of lactation were similar among control and test groups from all generations. However, F_{1a} pup weights were significantly lower in the low- and high-dose groups on days 4 (not shown in Table 6) and 7 and for low-, mid- and high-dose groups on days 14 and 21 of lactation. For F_{1b} pups, body weights were slightly, but not significantly, lower at the mid-dose level and significantly lower ($p<0.01$) at the high-dose level on days 14 and 21 of lactation. Similar reductions were observed in the F_{2a} and F_{2b} pups. Pup weights were slightly reduced for all F_{2a} treated groups on day 4 of lactation and were significantly decreased on day 7 (Table 7). Significant decreases were also observed on days 14 and 21 of lactation for mid- and high-dose F_{2a} pups. Consistent, significantly reduced body weights were observed for low-, mid-, and high-dose F_{2a} pups throughout the lactation period, with the exception of day 1 when body weights were similar among control and treatment groups.

TABLE 5. Summary of Histopathological Liver Effects in Rats Fed Ro 13-5223/000 For Two Generations[a]

	Dietary Concentration (ppm)							
	F_1				F_2			
	Male		Female		Male		Female	
	0	1800	0	1800	0	1800	0	1800
No. Examined	30	30	30	30	25	25	25	25
Hypertrophy	0	20	0	13	0	24	0	14
Focal Necrosis	2	5	0	1	1	14	1	0
Lobular/Centrilobular Necrosis	0	1	2	2	1	0	3	0

[a]Data were extracted from study No. 4623-161/124, Tables 7 and 14 and Appendices 5 and 12.

TABLE 6. Summary of Effects of Dietary Administration of Ro 13-5223/000 on F_1 Reproductive Parameters and Offspring Survival and Body Weight[a]

	Dietary Concentration (ppm)							
	0		200		600		1800	
	F_{1a}	F_{1b}	F_{1a}	F_{1b}	F_{1a}	F_{1b}	F_{1a}	F_{1b}
No. Matings	30	30	30	29	30	30	30	30
No. Pregnancies	29	28	30	27	29	28	30	29
Fertility Index (%)	97	93	100	93	97	93	100	97
Gestation Index (%)	100	82	97	89	100	100	100	93
Mean Gestation Length (days)	21.5	21.7	21.4	21.3	21.3	21.3*	21.3	21.2**
Total No. Pups Born	419	311	419	338	413	389	424	361
Mean Litter Size at Birth	14.4	13.5	14.4	14.1	14.2	13.9	14.1	13.4
Total No. Pups Alive, Day 1	404	300	400	301	399	379	414	333
Mean No. Live Pups/Litter	13.9	13.0	13.8	12.5	13.8	13.5	13.8	12.3
Live Birth Index (%)[b]	96.4	96.5	95.5	89.1	96.6	97.4	97.6	92.2
Total No. Pups Alive, Day 4	367	274	347	271	360	343	387	317
Mean No. Live Pups/Litter	12.7	11.9	12.0	11.3	12.4	12.3	12.9	11.7
Viability Index 1 (%)[c]	90.8	91.3	86.8	90.0	90.2	90.5	93.5	95.2
Total No. Pups Alive, Day 21	223	174	212	153	223	205	238	195
Mean No. Live Pups/Litter	7.7	7.6	7.3	6.4	7.7	7.3	7.90	7.2
Viability Index 2 (%)[d]	99.5	98.0	98.2	97.2	99.5	95.5	99.2	95.7
Lactation Index (%)	12.6	12.9	18.1	21.0	13.1	12.9	9.2	13.3
Mean Pup Weight, Day 1	5.7	5.9	5.6	5.8	5.6	5.6	5.6	5.8
Mean Pup Weight, Day 7 (g)	13.1	13.5	11.9*	13.4	12.4	12.8	11.9*	12.3
Mean Pup Weight, Day 21 (g)	49.3	49.0	45.1**	48.1	45.7**	46.8	43.7**	44.2**

[a]Data were extracted from study No. 4623-161/124, Tables 4 and 5 and Appendix 4.

[b]Live Birth Index = $\frac{\text{No. pups alive per litter on day 1}}{\text{No. pups alive per litter born}}$ x 100.

[c]Viability Index 1 = $\frac{\text{No. pups alive per litter on day 4 before culling}}{\text{No. pups alive per litter born}}$ x 100.

[d]Viability Index 2 = $\frac{\text{No. pups alive per litter on day 21}}{\text{No. pups alive per litter on Day 4 after culling}}$ x 100; calculated by the reviewers.

*Significantly different from controls at $p<0.05$.

**Significantly different from controls at $p<0.01$.

TABLE 7. Summary of Effects of Dietary Administration of Ro 13-5223/000 on F_2 Reproductive Parameters and Offspring Survival and Body Weight[a]

	Dietary Concentration (ppm)							
	0		200		600		1800	
	F_{2a}	F_{2b}	F_{2a}	F_{2b}	F_{2a}	F_{2b}	F_{2a}	F_{2b}
No. Matings	25	25	25	25	25	25	25	25
No. Pregnancies	21	20	23	21	23	23	24	24
Fertility Index (%)	84	80	92	84	92	92	96	96
Gestation Index (%)	100	85	100	90	100	96	100	100
Mean Gestation Length (days)	21.7	21.8	21.6	21.4	21.4	21.2**	21.3**	21.3**
Total No. Pups Born	276	207	318	264	323	306	325	322
Mean Litter Size at Birth	13.1	12.9	13.8	13.9	14.0	13.9	13.5	14.0
Total No. Pup Alive, Day 1	229	182	290	259*	305	284	317**	308
Mean No. Live Pups/Litter	10.9	11.4	12.6	13.6	13.3	12.9	13.2	13.4
Live Birth Index (%)[b]	82.7	87.9	91.2	98.1	94.4	92.8	97.5	95.7
Total No. Pups Alive, Day 4	211	178	233	250	250	274	291*	295
Mean No. Live Pups/Litter	10.0	11.1	10.1	13.2	10.9	12.5	12.1	12.8
Viability Index 1 (%)	92.1	97.8	80.3	96.2	82.0	96.7	91.8	95.8
Total No. Pups Alive, Day 21	143	114	150	148	158	163	182	177
Mean No. Live Pups/Litter	6.8	7.1	6.5	7.8	6.9	7.4	7.6	7.7
Viability Index 2 (%)	100	97.5	97.0	97.4	98.7	97.7	98.9	96.2
Lactation Index (%)	23.8	15.5	28.0	6.8	23.2	11.8	11.1	10.6
Mean Pup Weight, Day 1 (g)	6.1	6.3	5.6	6.0	5.6	5.8	5.8	6.0
Mean Pup Weight, Day 7 (g)	13.1	14.7	11.6*	13.1*	11.8*	12.5**	11.6**	11.6**
Mean Pup Weight, Day 21 (g)	47.5	50.4	44.1	44.9**	43.9**	43.9**	41.7**	39.8**

[a]Data were extracted from study No. 4623-161/124, Tables 11 and 12 and Appendix 11.

[b,c,d]See explanation, Table 6.

*Significantly different from controls at $p<0.05$.

**Significantly different from controls at $p<0.01$.

Physical (eye opening, pinna unfolding, etc.) and functional (grip strength, papillary reflex, etc.) development of offspring were not affected by ingestion of the test material by parental animals.

No abnormalities that could be attributed to the test material were observed at the necropsy of pups from any generation. Changes in absolute organ weights were found, particularly in F_{1a} pups (Table 8). However, the only effect considered to be compound related by the investigators was an increase in relative (to body weight) liver weight of offspring. Relative liver weight was slightly, but not significantly, increased for high-dose F_{1a} and F_{1b} males and females. Significant increases were observed in high-dose F_{1a} females ($p<0.05$), high-dose F_{1b} males ($p<0.01$), mid- and high-dose F_{1b} females ($p<0.01$), and high-dose F_{1a} males and females ($p<0.05$). All other changes in organ weights were considered to be related to reduced body weight and were not directly attributed to the test material.

Histopathological evaluation of the livers of offspring did not reveal any abnormalities.

D. DISCUSSION/CONCLUSIONS:

a. Parental Toxicity: Several females from each group died during the second gestation period of both parental generations. This was probably due to the age of the animals; by the second mating, females were approximately 8 months old and beyond the prime age for reproduction (Charles River Technical Bulletin, 1982).

Marginal (nonsignificant) effects on body weight and food consumption were observed in high-dose animals when compared to controls during the study. Significant increases in absolute and/or relative liver weights were observed in high-dose F_0 and F_1 females. Histopathological examination of livers from high-dose animals revealed increased incidences of hypertrophy and focal necrosis when compared to control incidences. However, histopathological examination of livers from low- and mid-dose animals was not performed at the sponsor's request. Therefore, the NOEL and LOEL for parental toxicity were not established.

b. Reproductive Toxicity: A significant decrease in the length of gestation was observed in mid- and high-dose dams. However, fertility and reproductive performances were not affected by the administration of the test

TABLE 8. Summary of Mean Absolute and Relative Organ Weights for Selected Offspring of Rats Fed Ro 13-5223/000 for Two Generations[a]

Dietary Concentration (ppm)	Body Weight (g)	Liver Weight (g)[b]	Liver Weight (%)[c]	Brain Weight (g)	Brain Weight (%)	Heart Weight (g)	Heart Weight (%)	Adrenal Weight (g)	Adrenal Weight (%)	Kidney Weight (g)	Kidney Weight (%)
F_{1a} males											
0	53	2.23	4.22	1.41	2.70	0.30	0.57	0.018	0.034	0.63	1.20
200	46	1.86**	4.02*	1.36**	3.00**	0.27**	0.59**	0.014**	0.031	0.54**	1.18
600	47	1.92**	4.07	1.39	3.00**	0.27**	0.57	0.017	0.038	0.56**	1.19
1800	46	1.98**	4.30	1.40	3.10**	0.26**	0.57	0.015*	0.033	0.54**	1.19
F_{1a} females											
0	50	2.12	4.20	1.36	2.76	0.28	0.56	0.015	0.031	0.62	1.24
200	44	1.72**	3.92**	1.31**	3.02	0.26	0.58	0.014	0.032	0.53**	1.20
600	45	1.89**	4.18	1.36	3.08**	0.27	0.59	0.017	0.038**	0.56**	1.25
1800	44	1.95	4.41*	1.35	3.09**	0.26	0.58	0.016	0.035	0.53**	1.22
F_{1b} males											
0	185	8.79	4.75	1.69	0.92	0.73	0.40	0.029	0.016	1.55	0.84
200	181	8.93	4.88	1.71	0.97	0.78	0.43**	0.028	0.016	1.56	0.86
600	184	9.27	5.00	1.70	0.93	0.75	0.41	0.030	0.0.7	1.60	0.87
1800	178	9.99	5.63**	1.70	0.96	0.72	0.41	0.028	0.016	1.47	0.83
F_{1b} females											
0	145	6.67	4.57	1.61	1.11	0.62	0.42	0.037	0.025	1.24	0.86
200	142	6.68	4.68	1.61	1.15	0.68	0.48	0.033	0.023	1.21	0.85
600	145	7.32*	5.04**	1.59	1.11	0.62	0.43	0.036	0.025	1.25	0.86
1800	138	7.55**	5.46**	1.60	1.17	0.58	0.41	0.036	0.026	1.16	0.84

(continued)

TABLE 8. (Continued)

Dietary Concentration (ppm)	Body Weight (g)	Liver Weight (g)[b]	Liver Weight (%)[c]	Brain Weight (g)	Brain Weight (%)	Heart Weight (g)	Heart Weight (%)	Adrenal Weight (g)	Adrenal Weight (%)	Kidney Weight (g)	Kidney Weight (%)
F_{2a} males											
0	48	1.82	3.81	1.36	2.90	0.27	0.58	0.017	0.036	0.56	1.18
200	45	1.71	3.81	1.31	3.02	0.25	0.56	0.016	0.036	0.52	1.16
600	45	1.75	3.89	1.37	3.09	0.25	0.56	0.017	0.038	0.53	1.19
1800	42	1.70	4.07*	1.38	3.33**	0.24	0.59	0.014	0.034	0.50	1.21
F_{2a} females											
0	45	1.74	3.40	1.33	3.03	0.24	0.55	0.014	0.032	0.54	1.23
200	41	1.60	3.86	1.29	3.22	0.24	0.57	0.015	0.036	0.50	1.20
600	42	1.68	3.98	1.30	3.12	0.24	0.57	0.016	0.038	0.52	1.23
1800	41	1.66	4.08*	1.31	3.27	0.23	0.57	0.014	0.035	0.50	1.24
F_{2b} males											
0	51	2.10	4.09	1.40	2.75	0.28	0.55	0.014	0.027	0.58	1.13
200	45	1.83	4.01	1.34	3.01	0.26	0.57	0.014	0.032	0.54	1.19*
600	44	1.75*	3.97	1.33	3.18*	0.24**	0.56	0.014	0.032	0.52	1.19*
1800	40	1.67*	4.16	1.34	3.44**	0.23**	0.58	0.012	0.029	0.48**	1.20**
F_{2b} females											
0	49	2.02	4.14	1.37	2.83	0.27	0.55	0.016	0.033	0.59	1.20
200	44	1.74*	3.95	1.33	3.07*	0.25	0.57	0.016	0.037	0.52*	1.19
600	43	1.75*	4.03	1.33	3.11*	0.24*	0.55	0.014	0.033	0.53*	1.22
1800	38	1.63**	4.31	1.29**	3.45**	0.22**	0.58	0.013	0.034	0.47**	1.24

[a]Data were extracted from study No. 4623-161/124, Tables 6 and 13.
[b]Represents absolute organ weight.
[c]Represents relative (to body weight) organ weight.
*Significantly different from controls at $p<0.05$.
**Significantly different from controls at $p<0.01$.

material. Pup viability was similar among controls and the mid- and high-dose groups. Viability was slightly (not significantly) lower for low-dose pups during days 1-4 of lactation. However, this was primarily due to the loss of entire litters by two to three females and was not considered to be compound related. Pup weights were similar among control and test groups on day 1 of lactation. However, significant decreases in body weight were observed in offspring from all treated animals from day 4 or 7 to weaning, except during the F_{1b} generation when significant decreases were observed only at the high-dose level on days 14 and 21 of lactation. Increases in relative liver weight were consistently noted in high-dose pups when compared to controls. Other changes in absolute, but not relative, organ weights were observed, and therefore, were attributed to reduced body weight and not to the administration of the test material. A further indication of delayed development was noted. The time period for pinna unfolding and eye opening appeared to increase with increasing dose when compared with controls. However, no individual data were presented for these parameters, and a statistical analysis of these data could not be performed.

The LOEL for reproductive toxicity was equal to or less than 200 ppm, based on significant decreases in pup weight at all levels of exposure to the test material. Further delays in development, i.e., pinna unfolding and eye opening with increasing dose was apparent, but no individual data for these parameters were presented. Therefore, those affects could not be adequately assessed. The NOEL was not established.

c. Study Deficiencies: The following deficiencies were noted:

1. Gross lesions were not histologically examined.

2. Livers from low- and mid-dose parental animal were not histologically examined at the sponsor's request.

3. Individual data on developmental parameters were not presented.

4. Data on the number and type of implantations found in pregnant animals dying or sacrificed in extremis during late gestation (days 21, 22, or 23) were not presented, although the protocol states that these data were recorded.

61

E. CLASSIFICATION: CORE Supplementary data.
Reproductive Toxicity NOEL = not established.
Reproductive Toxicity LOEL = 200 ppm.
Parental NOEL and LOEL were not established.

F. RISK ASSESSMENT: Not appropriate.

G. [illegible]

CONFIDENTIAL INFORMATION
[illegible]
NATIONAL [illegible] (22151)

EPA: 68D30056
DYNAMAC No.: 185-B
TASK No.: 1-85B
June 29, 1989

35-1

000101

DATA EVALUATION RECORD

FENOXYCARB

Metabolism in Rats

STUDY IDENTIFICATION: Cameron, B. D., Dunsire, J. P., and Ning, A. C. W. S. The metabolism of [^{14}C]-labelled Ro 13-5223/024 in the rat. (Unpublished report No. 4217 prepared by Inveresk Research International, Musselburgh, Scotland, for MAAG Agrochemicals, Dielsdorf, Switzerland; dated October, 1986.) MRID No. 40376904.

APPROVED BY:

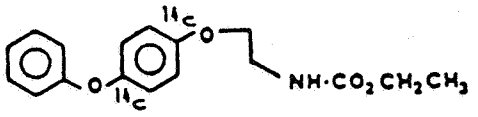
Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: [signature]
Date: 6/27/89

67

1. CHEMICAL: Fenoxycarb; Ro 13-5223/024; ethyl (2-[4-phenoxy-phenoxy]ethyl) carbamate.

2. TEST MATERIAL: [^{14}C]Ro 13-5223/024 was from batch No. JJ-I/98 with a specific activity of 36.06 µCi/mg and a radiochemical purity of >96 percent. The chemical structure and position of radiocarbons (denoted by asterisks) is as follows:



000101

3. STUDY/ACTION TYPE: Metabolism in rats.

4. STUDY IDENTIFICATION: Cameron, B. D., Dunsire, J. P., and Ning, A. C. W. S. The metabolism of [^{14}C]-labelled Ro 13-5223/024 in the rat. (Unpublished report No. 4217 prepared by Inveresk Research International, Musselburgh, Scotland, for MAAG Agrochemicals, Dielsdorf, Switzerland; dated October, 1986.) MRID No. 40376904.

5. REVIEWED BY:

Nicolas P. Hajjar, Ph.D.
Principal Reviewer
Dynamac Corporation

Signature: Nicolas P. Hajjar
Date: June 29, 1989

Robert J. Weir, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: Robert J. Weir
Date: 6/27/89

6. APPROVED BY:

Roman J. Pienta, Ph.D.
Department Manager
Dynamac Corporation

Signature: Roman J Pienta
Date: 6-27-89

William Greear, M.P.H.
EPA Reviewer, Section II
Toxicology Branch I
(H-7509C)

Signature: William B Greear
Date: 7/3/89

Marion Copley, D.V.M., D.A.B.T.
EPA Section Head,
Section II
Toxicology Branch I
(H-7509C)

Signature: Marion Copley
Date: 8/28/89

74
64

7. CONCLUSIONS:

The metabolism of [^{14}C]Ro 13-5223/024 was studied in groups of male and female Sprague-Dawley rats following oral administration at 3000 mg/kg. Total recovery of radioactivity 96 hours post-dosing was about 98 percent of the dose. About 50 percent of the dose was eliminated in the feces and 42 to 47 percent in the urine (and cage wash). About 0.09 percent of the dose was eliminated as [^{14}C]CO_2, and about 0.08 percent was detected in the tissues. The higher [^{14}C] residues were found in the liver, fat, kidney and muscle (≤42 µg/g) with residues being slightly higher in females than males. Most of the radioactivity found in the urine was associated with sulfate and glucuronide conjugates of ring- or ethyl-hydroxylated metabolites. Unchanged parent compound accounted for 0.8 percent of the urinary radioactivity. Over 83 percent of the radioactivity found in the feces was unchanged parent compound.

In a biliary excretion study, one female and one male rat dosed with 50 mg/kg [^{14}C]Ro 13-5223/024 eliminated about 37 and 63 percent of the dose in the bile, respectively. Most of the biliary radioactivity was associated with sulfate conjugates. Daily dosing with [^{14}C]Ro 13-5223/024 at 50 mg/kg resulted in gradual increases in [^{14}C] residues in five tissues examined (liver, kidney, fat, plasma, and carcass). The highest residues were detected in the liver. After 28 days of dosing, residue levels decreased with time. However, the rate of [^{14}C] elimination from fat was much slower, suggesting bioaccumulation. The metabolic profiles in the urine of three male rats collected 24 hours after 1 or 28 doses were similar to those obtained in the high-dose study. However, in the feces, the metabolic profile was different. The parent compound accounted for only 36 percent of the radioactivity in the feces after 1 dose and for 8 percent after 28 doses. The data suggest increased metabolism at lower doses as well as with repeated dosing.

The high-dose study is acceptable, whereas the other two studies provide supplementary data. Single low-dose and repeated-dose studies are required to fulfill EPA's guidelines.

Items 8-11--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods:

1. The dosing solutions were prepared by mixing appropriate amounts of [^{14}C] and unlabeled Ro 13-5223/024 in acetonitrile. The acetonitrile was

[1]Only the items appropriate to this DER have been included.

evaporated, and the test material was dissolved in 50 mL rapeseed oil. The target doses were 50 and 3000 mg/kg.

2. Male and female Charles River C.D. Sprague-Dawley rats (age and source not specified) weighing between 160 and 240 g each were used. Animals were fasted overnight prior to dosing.

3. The following three experiments were performed.

   (a) Excretion and Retention of Radioactivity Following Administration of a Single Oral Dose at 3000 mg/kg: Five rats/sex were dosed by gavage and the animals were housed in all-glass metabolism cages for 96 hours. Urine and feces were collected separately from all animals at 6, 24, 48, 72, and 96 hours postdosing. Expired [^{14}C]CO_2 was collected from one male and one female at 6, 24, and 48 hours postdosing. Animals were then sacrificed and tissues and organs were trimmed and frozen. Urine and feces collected on days 1, 2, and 3 were analyzed for metabolites by thin-layer chromatography (TLC). Radioactivity levels in the kidneys and liver were ≤1000 dpm/g and consequently were not analyzed by TLC.

   (b) Biliary Excretion of Radioactivity Following Administration of a Single Oral Dose at 50 mg/kg. Biliary excretion was determined in one male and one female bile duct-cannulated rat. Urine and feces were collected at 6 and 24 hours, whereas bile samples were collected hourly for 24 hours postdosing. Total radioactivity was measured in urine, bile, feces, gastrointestinal tract, remaining carcass, and cage wash. Bile samples were collected at 0 to 1, 1 to 2, 12 to 13, or 21 to 22 hours postdosing were analyzed by TLC.

   (c) Accumulation and Retention of Total Radioactivity Following Repeated Oral Administration at 50 mg/kg. Eighteen rats/sex were dosed daily for up to 28 days. Groups of three rats each were sacrificed at various intervals during the dosing period and up to 14 days postdosing. Following sacrifice, the liver, kidney, fat, plasma, and residual carcass were trimmed and radioassayed. Urine and feces were collected separately from three males 24 hours after the 1st dose and 24, 48, 72, and 96 hours after the 28th dose. The samples were then radioassayed.

Pooled plasma samples from males collected 24 hours after the 1st and 21st [^{14}C] doses were analyzed by TLC for metabolites. For females, samples collected 24 hours after the 1st and 28th dose were analyzed by TLC. Pooled urine and fecal samples collected 24 hours after the 1st and 28th dose were also analyzed by TLC. Liver samples from one male receiving a single dose and one female receiving 28 doses were analyzed for metabolites by TLC.

4. Tissues and feces were homogenized and duplicate aliquots were combusted prior to radioassay by liquid scintillation counting (LSC). Plasma, cage wash, and urine samples were radioassayed directly. Analysis for metabolites were conducted as follows: urine and bile were freeze dried, then dissolved in methanol, and analyzed directly by TLC. Selected samples were subjected to sulfatase and glucuronidase hydrolysis, then analyzed by TLC. Feces, plasma, and liver samples were extracted twice with methanol and the extract was analyzed by TLC. Three solvent systems were used for TLC analysis.

B. Protocol: See Appendix A.

12. REPORTED RESULTS:

A. Excretion and Retention of Radioactivity Following Administration of a Single Oral Dose at 3000 mg/kg. Animals receiving this dose showed pharmacotoxic signs. All the rats recovered within 24 hours except for one male rat that died during this period. The actual doses administered to males and females were 3180 and 3372 mg/kg, respectively. Ninety-six hours following dosing, about 98 percent of the administered dose was recovered. Most (>90 percent) of the radioactivity was eliminated in the urine and feces (Table 1). Less than 0.1 percent of the dose was detected as [^{14}C]CO_2. [^{14}C] residue levels in tissues were very low, with the highest levels noted in liver, kidneys, muscle, and fat (≤42 µg/g, Table 2).

In the pooled 24-hour urine sample examined, most of the radioactivity was associated with the origin of the chromatogram and consisted of very polar substances (Table 3). Unchanged parent compound accounted for 0.8 percent of the TLC-applied radioactivity. Two hydroxylated and two unknown metabolites were separated by TLC. About

67

TABLE 1. Cumulative Excretion of Total Radioactivity 96 Hours Following Oral Administration of [^{14}C]Ro 13-5223/024 to Rats at 3000 mg/kg.

Sample	[^{14}C] Recovery (expressed as % of dose)[a] Males	Females
Urine	44.03	36.89
Feces	49.14	51.42
GI tract	0.59	1.19
Carcass	0.83	2.57
[^{14}C]CO_2	0.09	0.09
Cage wash	3.34	5.62
Tissues/organs	0.08	0.07
Total	98.10	97.85

[a]Results are means from four males or five females.

TABLE 2. Radioactive Residue Levels in Tissues of Rats 96 Hours Following Oral Administration of [^{14}C]Ro 13-5223/024 at 3000 mg/kg

Tissue	Tissue [^{14}C] Residue Levels (μg/g)[a]	
	Males	Females
Bone	9	12
Brain	1	2
Fat	16	34
Heart	4	5
Skeletal muscle	5	28
Gonads	3	19
Liver	32	42
Lung	6	7
Spleen	4	4
Kidney	17	13
Stomach and contents	7	20
Intestines and contents	198	345
Plasma	10	7
Blood cells	5	5

[a]Results are means from four males or five females.

Table 3

The Nature of Radioactivity in Urine and Faeces Following a Single High Dose of [^{14}C]-Ro 13-5223/024 (Dose Level ca 3000 mg.kg^{-1})

T.l.c. Solvent System: Ethyl acetate:acetic acid (99:1 v/v)

Results expressed as % of total radioactivity on plate

Rf Value	Corresponding Standard	Pooled 0-24 h	Pooled 0-24 h After Glucuronidase Treatment	Pooled 0-24 h After Sulphatase Treatment	41d 24-48 h	41d 48-72 h
Urine						
0.84-1.00	Ro 13-5223	0.8	3.4	4.2	4.6	0.3*
0.78-0.84	Ro 16-8797	5.4	28.9	36.4	26.7	1.3
0.51-0.78	Unknown	1.0	5.6	9.3	2.4	0.2*
0.43-0.51	Ro 17-3192	0.1**	0.9	17.0	0.9	0.1*
0.07-0.43	Unknown	5.6	7.2	24.4	3.2	6.2
0.00-0.07	Origin	87.0	54.0	8.6	61.9	91.7
% dose in sample investigated		A mean of 7.2			19	20
Faeces						
0.81-1.00	Ro 13-5223	83.7			27.5	12.7
0.74-0.81	Ro 16-8797	7.9			33.8	31.5
0.50-0.74	Unknown	3.1			6.9	13.8
0.42-0.50	Ro 17-3192	0.6*			4.9	5.5
0.03-0.42	Unknown	2.2			9.0	16.2
0.00-0.03	Origin	2.5			18.0	20.4
% dose in sample investigated		A mean of 12.8			14	18

* = Results derived from data <30 dpm above background
** = Results derived from data <10 dpm above background

80

70

Table 3

Source: CBI Table 8, CBI p. 45.

5 percent corresponded to standard Ro 16-8797 (Table 4). Most of the radioactivity associated with the origin was in the form of sulfate and glucuronide conjugates as indicated by the TLC analysis following enzyme hydrolysis (Table 3). Most of the radioactivity found in the feces was associated with the parent compound. The hydroxylated derivative Ro 16-8797 accounted for 8 percent of the TLC applied radioactivity (Table 3).

B. Biliary Excretion of Radioactivity Following Administration of a Single Oral Dose of 50 mg/kg. Total recovery of administered radioactivity 24 hours after dosing was >97 percent. Biliary excretion accounted for 63 and 37 percent of the doses in the male and female rat used, respectively (Table 5). Approximately 9 percent of the dose was detected in the gastrointestinal tract (GI) of the male rat, but 51 percent was found in the female GI. Most of the radioactivity in the bile (>88 percent) was associated with very polar substances and remained at the origin of the chromatogram (Table 6). Enzyme hydrolysis revealed the presence of sulfate and glucuronide conjugates.

C. Accumulation and Retention of Total Radioactivity Following Repeated Oral Administration of 50 mg/kg. Radioactive residue levels in the tissues examined increased as the number of doses increased (Tables 7 and 8). The highest levels were noted in the liver. When dosing was stopped, residue levels decreased with time. However, the rate of [^{14}C] elimination from fat was much slower than that in the other tissues examined. Metabolic profiles in the urine of three male rats collected 24 hours after 1 or 28 doses were similar to those determined in the high-dose study (Table 9). However, the metabolic profile in feces was different in that the parent compound accounted for only 36 and 8 percent of the radioactivity applied to the chromatogram after 1 and 28 doses, respectively. This was accompanied by an increase in polar metabolites (Table 9). The metabolic profile in the plasma from male rats 24 hours after a single dose indicated that 58 percent of the applied radioactivity was the unchanged parent compound, whereas most of the radioactivity was in the form of metabolites in the female (Table 10). In the male and female rats receiving 28 doses, the metabolic profile was similar and most of the radioactivity was associated with polar metabolites (Table 10). The radioactivity in the liver similarly consisted of primarily polar material (Table 11).

82

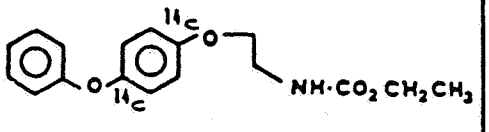
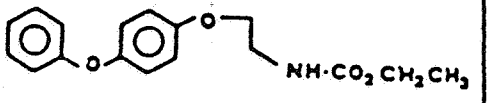
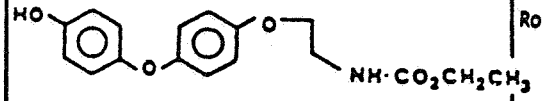
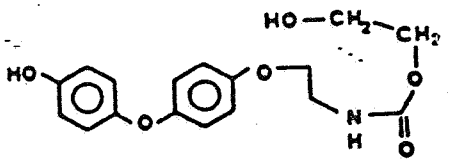
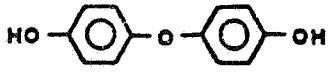
72

APPENDIX 2 (continued)

038101

Table 4

^{14}C - Ro 13-5223/024: Metabolism in the rat (IRI)
Test article + rat metabolites

Structure	Designation	Amount	Analysis
	Ro 13-5223/024	200.4 mg = 7.22 mCi	Specific activity = 36.06 µCi/mg Chemical purity > 99% Radiochem. purity > 98% Batch JJ-I/98 (ZFE; May 1981)
	Ro 13-5223/000	24 g	98%; Lot 18 (31.3.82)
	Ro 16-8797	37 mg	≥ 95%
	Ro 17-3192	10 mg	≥ 95%
	Ro 1-1374	25 mg	Aldrich

RES-DrPr/NSt
22.11.1985

Table 4

038101

Source: CBI p. 87.

74
84

038107

Table 5

Phase 2

Cumulative Recovery of Total Radioactivity Following Single Oral Administration of [^{14}C]-Ro 13-5223/024 to One Male and One Female Bile Duct Cannulated Rat.
Dose Level ca 50 mg.kg^{-1}

Results expressed as % administered dose recovered

Time (h)	Animal No./Sex 39♂	40♀
Bile		
0-1	0.77	1.02
0-2	4.97	1.75
0-3	8.11	2.15
0-4	11.80	2.40
0-5	17.59	2.57
0-6	23.75	2.72
0-7	28.83	3.02
0-8	34.13	3.13
0-9	38.35	3.86
0-10	40.84	4.91
0-11	42.52	5.82
0-12	44.49	7.01
0-13	46.67	11.22
0-14	48.01	16.85
0-15	48.89	22.65
0-16	49.57	27.03
0-17	50.18	30.47
0-18	50.67	32.47
0-19	51.08	33.54
0-20	52.46	34.54
0-21	55.45	35.25
0-22	58.45	35.93
0-23	61.20	36.51
0-24	62.80	36.92
Urine		
0-6	0.75	0.18
0-24	11.33	5.29
Faeces		
0-6	0.08	0.00*
0-24	12.11	2.44
GI Tract		
24	9.12	51.20
Carcass		
24	1.51	1.51
Cage Wash		
24	0.19	0.71
Total		
0-24	97.06	98.07

* = Results derived from data <30 dpm above background

75
~~85~~

Table 5

Source: CBI Table 4, CBI p. 36.

Table 6

The Nature of Radioactivity in Bile Following a Single Low Dose of [^{14}C]-Ro 13-5223/024 (Dose Level ca 50 mg.kg^{-1})

T.l.c. Solvent System: Ethyl Acetate:Acetic Acid (99:1 v/v)

Results expressed as % of total radioactivity on plate

Rf Value	Corresponding Standard	39 ♂ 1-2 h	39 ♂ 12-13 h	39 ♂ 21-22 h	39 ♂ 1-2 h Following Glucuronidase Treatment	39 ♂ 1-2 h Following Sulphatase Treatment
0.73-1.00	Ro 13-5223	0.0**	0.4*	1.1	1.6	1.6
0.66-0.73	Ro 16-8797	0.3	3.4	9.5	15.3	13.7
0.45-0.66	Unknown	0.2*	0.3*	0.6	0.9	19.0
0.35-0.45	Ro 17-3192	0.1**	0.1**	0.1**	0.3*	10.8
0.05-0.35	Unknown	0.1*	0.8	0.6	1.0	33.2
0.00-0.05	Origin	99.3	95.0	88.2	80.8	21.7
% dose in sample investigated		4.2	2.2	3.0	4.2	4.2

* = Results derived from data <30 dpm above background
** = Results derived from data <10 dpm above background

Table 6

038101

Source: CBI Table 9, CBI p. 46.

033101

Table 7

Phase 3

Mean Levels of Total Radioactivity in Selected Organs, Tissues and Body Fluids at Various Time Points During and After 28 Day Repeated Oral Administration of ^{14}C]-Ro 13-5223/024 to Male Rats
Daily Oral Dose Level ca 50 mg.kg^{-1}

Results expressed as µg equiv.g^{-1} ± S.D.

Doses† Received	Numbers of Rats	+ Plasma	Carcass	Liver	Kidney	Fat
1	3♂ (1-3)	0.5 ± 0.2	1.8 ± 0.5	3.2 ± 0.8	1.3 ± 0.3	0.6 ± 0.1
7	3♂ (4-6)	0.7 ± 0.3	2.1 ± 1.2	4.6 ± 1.3	2.2 ± 0.5	1.7 ± 0.2
21	3♂ (7-9)	1.3 ± 0.3	3.8 ± 1.1	9.1 ± 1.1	4.1 ± 0.5	2.2 ± 1.1
Days After 28 Multiple Doses						
2	3♂ (10-12)	0.8 ± 0.7	2.1 ± 1.5	5.5 ± 2.2	2.6 ± 1.5	1.4 ± 0.6
4	3♂ (13-15)	0.2 ± 0.1	0.8 ± 0.3	2.2 ± 0.3	1.0 ± 0.1	1.0 ± 0.2
10	3♂ (16-18)	C.1* ± 0.0	0.6 ± 0.1	1.0 ± 0.1	0.4 ± 0.1	1.2 ± 0.6

+ = Results expressed as µg equiv.ml^{-1} ± S.D.
* = Results derived from data <30 dpm above background
† = Samples taken 24 h after the corresponding dose

Table 7

Source: CBI Table 6, CBI p. 43

80
~~90~~

003101

Table 8

Phase 3

Mean Levels of Total Radioactivity in Selected Organs, Tissues and Body Fluids at Various Time Points During and After 28 Day Repeated Oral Administration of [^{14}C]-Ro 13-5223/024 to Female Rats
Daily Oral Dose Level ca 50 mg.kg^{-1}

Results expressed as µg equiv.g^{-1} ± S.D.

Doses Received	Numbers of Rats	Plasma	Carcass	Liver	Kidney	Fat
3	3♀ (20-22)	0.4 ± 0.1	2.6 ± 1.4	6.1 ± 1.8	1.1 ± 0.7	0.7 ± 0.4
14	3♀ (23-25)	0.5 ± 0.1	3.3 ± 0.6	7.6 ± 0.5	1.2 ± 0.2	1.3 ± 0.5
28	3♀ (26-28)	1.9 ± 0.2	5.6 ± 1.8	13.0 ± 2.9	2.1 ± 1.1	2.7 ± 0.7
Days After 28 Multiple Doses						
3	3♀ (29-31)	0.1 ± 0.1	1.3 ± 0.5	3.1 ± 0.4	0.9 ± 0.2	1.6 ± 0.5
7	3♀ (32-34)	0.1 ± 0.0	0.8 ± 0.1	1.4 ± 0.1	0.6 ± 0.2	1.6 ± 0.6
14	3♀ (35-37)	**0.0 ± 0.0	0.6 ± 0.1	0.7 ± 0.1	0.3 ± 0.1	1.1 ± 0.4

81

Table 8

Source: CBI Table 7, CBI p. 44.

008101

Table 9

The Nature of Radioactivity in Urine and Faeces Following Acute and Chronic Administration of ^{14}C-Ro 13-5223/024 (Dose Level ca 50 mg.kg^{-1}.day^{-1})

T.l.c. Solvent System: Ethyl acetate:acetic acid (99:1 v/v)

Results expressed as % of total radioactivity or plate

Rf Value	Corresponding Standard	Acute 0-24 h	Acute 0-24 h Following Glucuronidase Treatment	Acute 0-24 h Following Sulphatase Treatment	Chronic 0-24 h	Chronic 0-24 h Following Glucuronidase Treatment	Chronic 0-24 h Following Sulphatase Treatment
Urine							
0.63-1.00	Ro 13-5223	0.1**	0.2	2.3	0.0**	0.2	1.9
0.37-0.63	Ro 1-1373	0.1*	0.6	4.1	0.3	0.3	3.2
0.30-0.37	Ro 17-3192	0.2	0.8	9.8		0.3	5.0
0.03-0.30	Unknown	3.0	3.2	57.8	1.8	2.0	56.4
0.00-0.03	Origin	96.6	95.2	26.0	97.1	97.1	33.4
Mean % dose in sample investigated			27			3+	
Faeces							
0.81-1.00	Ro 13-5223	36.2			8.4		
0.74-0.81	Ro 16-8797	1.9			0.9		
0.50-0.74	Unknown	5.5			3.9		
0.42-0.50	Ro 17-3192	5.1			2.7		
0.03-0.42	Unknown	29.7			50.8		
0.00-0.03	Origin	21.5			33.3		
Mean % dose in sample investigated			43			1+	

* = Results derived from data <30 dpm above background
** = Results derived from data <10 dpm above background
+ = Expressed as % of total radioactive dose received over 28 days

83

83

Table 9

008101

Source: CBI Table 10, CBI p. 47.

89

~~91~~

008101

Table 10

The Nature of Radioactivity in Plasma Following Acute and Chronic Administration of [^{14}C]-Ro 13-5223/024 (Dose Level ca 50 mg.kg^{-1}.day^{-1})

T.l.c. Solvent System: Ethyl acetate:acetic acid (99:1 v/v)

Results expressed as % of total radioactivity on plate

Rf Value	Corresponding Standard	+ ♂ Acute	♀ ♀ Acute	++ ♂ Chronic	♀♀ ♀ Chronic
0.62-1.00		5**	22*	4*	4**
0.53-0.62	Ro 13-5223	58	10*	0	1*
0.07-0.53		11*	16*	6*	15*
0.00-0.07	Origin	26	52	90	79
Mean µg equiv.ml^{-1} in sample investigated		0.5	0.4	1.4	0.9

* = Results derived from data <30 dpm above background
** = Results derived from data <10 dpm above background
\+ = Pooled plasma from 3♂ rats sacrificed 24 h after first dose
++ = Pooled plasma from 3♂ rats sacrificed 24 h after twenty first dose
♀ = Pooled plasma from 3♀ rats sacrificed 24 h after third dose
♀♀ = Pooled plasma from 3♀ rats sacrificed 24 h after twenty eighth dose

Table 10

008101

Source: CBI Table 11, CBI p. 48.

86

86

038101

Table 11

The Nature of Radioactivity in Liver Following Acute and Chronic Administration of l^{14}C-Ro 13-5223/034 (Dose Level ca 50 mg.kg^{-1}.day^{-1})

T.l.c. Solvent System: Chloroform:methanol:acetic acid (80:20:1 v/v/v)

Results expressed as % of total radioactivity on plate

Rf Value	Corresponding Standard	Acute (1♂)	Chronic (27♀)
0.83-1.00	Ro 13-5223	0**	5**
0.77-0.83	Ro 16-8797	3**	6*
0.66-0.77	Ro 17-3192	1**	14*
0.04-0.66	Unknown	34	57
0.00-0.04	Origin	63	18
µg equiv.g^{-1} in sample investigated		3.8	16.3

* = Results derived from data <30 dpm above background
** = Results derived from data <10 dpm above background

~~97~~
87

Table 11

038101

Source: CBI Table 12, CBI p. 49.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

[^{14}C]Ro 13-5223/024 is well absorbed after oral administration at both dose levels, widely distributed, and extensively metabolized. Excretion of radioactivity is quantitative, the bulk of the dose being recovered after about 72 hours. Slightly more was excreted in the feces than in urine. Studies with bile duct-cannulated rats indicate that biliary excretion plays a major part in the excretion of the compound. Only a very small proportion of the radioactivity excreted, after both high- and low-dose administration, consisted of unchanged pesticide; the major part was excreted as polar metabolites, mostly sulphate conjugates.

Radioactivity is accumulated in major tissues during multiple administration, and although initial clearance of radioactivity on cessation of dosing is rapid, detectable levels are still observed in liver, kidney, and fat 14 days after the last dose.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. These studies were adequately conducted and the authors' conclusions are supported by the results presented. Adequate numbers of animals were used for the elimination and tissue residue studies (Study Nos. 1 and 3), and the methods and materials were appropriate. However, for the biliary excretion study and some of the samples analyzed by TLC, only one animal/sample was used. Thus, these data do not provide adequate quantitative information.

The high-dose study fulfills EPA's guidelines; however, single low-dose and repeated-dose studies are needed to evaluate the elimination and distribution kinetics under nonsaturating conditions. This is particularly true since the metabolic patterns obtained in the biliary excretion and accumulation studies (50 mg/kg) were different from those noted following administration of a 2000-mg/kg dose.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Protocol, CBI pp. 69 to 83

APPENDIX A
Protocol
CBI pp. 69-85.

Fenoxycarb toxicology review

Page _____ is not included in this copy.

Pages 91 through 107 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

- The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
