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

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JAN 3 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP #8F3572/FAP #9H5582/0G03879 - Fenoxycarb
Resubmission of Toxicology Data (Including New Studies)
in Response to the Toxicology Memorandum of September
17, 1990

Tox. Chem. No.: 652C
PC No.: 125301
DP Nos.: D179471, D179493,
D179484, D188212

Submission Nos.: S419703,
S419242,
S419726
S435433

FROM: William B. Greear, M.P.H. William B. Greear 12/21/93
Review Section IV, Toxicology Branch I
Health Evaluation Division (H7509C)

TO: Marion Johnson/Richard Mountford, PM #10
Herbicide-Fungicide Branch
Registration Division (H7505C)

THRU: Marion P.Copley,D.V.M., Section Head Marion Copley 12/21/93
Review Section IV, Toxicology Branch I
Health Evaluation Division H7509C) KB 12/28/93

I. CONCLUSIONS:

The toxicological data base does not support the request for tolerances for residues of fenoxycarb on citrus and pastures and does not support the use of fenoxycarb in food handling establishments. (Refer to the body of the review for details.)

II. REQUESTED ACTION:

Under a cover letter dated June 2, 1992, Carolyn B. Bussey of the Ciba-Geigy Corporation has submitted additional data in response to Tox Branch-I's memorandum dated September 17, 1990. The sponsor has submitted the following new toxicology studies for review in support of their tolerance requests:

o "Acute Inhalation Toxicity Study", Study No. 911362, January

1 of 75

22, 1992, MRID No. 423438-02.

- "Chronic Feeding Toxicity Study in Dogs", Study No. B-153 778, June 30, 1988, MRID No.: 423556-01.

- "Chromosome Analysis in Human Peripheral Blood Lymphocytes Treated In Vitro with the Insect Growth Regulator Ro 13-5223/000 in Absence and in Presence of a Metabolic Activation System", Study No. B-153, 586, February 21, 1989, MRID No. 423438-10.

In addition, data were submitted in response to Tox Branch-I's memorandum are listed below.

Tox. Ref. No.

1. "Toxicological Evaluation of Fenoxycarb (CGA-114597 Technical) Emphasis on the Re-examination of Chronic Rodent and Two-Generation Reproduction Studies", MRID No. 423438-01, April 24, 1992

2. "Fenoxycarb Ro 13-5223/000: 104-week Oral (Dietary Administration) Carcinogenicity and Toxicity Study in the Rat with a 52-Week Interim Kill 104-Week Report Replaces #5191-161/23, MRID #40376901", MRID #423438-03, March 2, 1992, Volume 1, 2 and 3 of Study

3. "Fenoxycarb Re-examination of the Pituitary Gland, Thyroid Gland, and Liver From Male Rats A Supplement to a Chronic Toxicity Study in Rats Original HLE Project No. 5191-161/123 EPA MRID Number 40376901", MRID No. 423438-04, November 21, 1991

4. "Fenoxycarb (Ro 13-5223/000) Historical Control Data From 18 Studies Conducted at Hazleton Laboratories Europe with Animal Termination Dates Between 1983-1988: Thyroid and Pituitary Tumor Data", MRID No. 423438-05, March 17, 1992

5. "Fenoxycarb A Supplement to an 80-Week Carcinogenicity Study in Mice Original IRI Project #430624 EPA MRID Numbers 40376902 and 40972701", MRID No. 423438-08, March 17, 1992

6. "Ro 13-5223/000 (Fenoxycarb) Re-Examination of the Lungs and Harderian Glands: A Supplement to a Chronic Toxicity Study ir Mice Original IRI Project No. 430624 EPA MRID Numbers 40376902 and 40972701", MRID No. 423438-07, November 21, 1991

7. "Fenoxycarb A Supplement to a Carcinogenicity Study in Mice original Project No. 430624 IRI Project No. 450719

2

EPA MRID Numbers 40376902 and 40972701", MRID No. 423438-06, March 17, 1992

8. "Fenoxycarb Technical Pathology Peer Review of Liver of Female Mice A Supplement to a Carcinogenicity Study in Mice Original Project No. 430624 IRI Project No. 450719 EPA MRID Numbers 40376902 and 40972701", MRID No. 423438-09, November 21, 1991

9. "Fenoxycarb a Supplement to a 2-Generation Oral Reproduction Study in the Rat Original Project #4223-161/124 EPA MRID Number 40376903", MRID No. 423438-12, April 1992

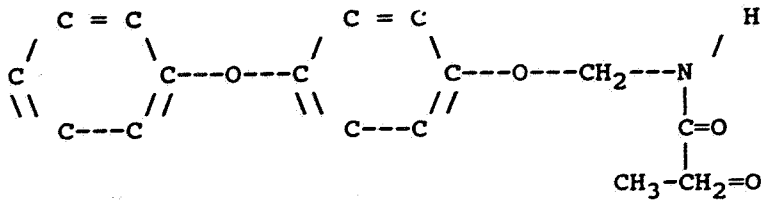
10. "Fenoxycarb Amendment to Ro 13-5223/000: 2-Generation Oral (Dietary Administration) Reproduction Study in the Rat MRID No. 40376903", MRID No. 423438-11, April 1992

11. "Revised Toxicological Evaluation of Fenoxycarb (CGA-114597) Technical Emphasis on the Re-examination of Chronic Rodent and Two-Generation Reproduction Studies MRID Nos. 403769-02, 409727-01, 403769-03; MRID No. 423641-01, June 17, 1992

III. PRODUCT INFORMATION

Fenoxycarb; #652C
Updated: March, 1991

Fenoxycarb is an insecticide (insect growth regulator). Its chemical name is ethyl (2-[4-phenoxyphenoxy] ethyl) carbamate. Its proprietary names are INSEGAR and LOGIC. Its chemical structure is as follows:



Fenoxycarb has a molecular weight of 301.3 and the empirical formula $C_{17}H_{19}O_4N$.

The physical and chemical properties of fenoxycarb are described in the Registration Standard for Fenoxycarb (EPA, 1985; unpublished). Technical fenoxycarb is registered for use as an insecticide/miticide by the U.S. EPA under Registration Number 35977-5. The assigned Shaughnessy number is 128801 and the CAS Registry Number is 72490-01-8. Chemically, fenoxycarb is an O-ethyl carbamate ester derivative. Its mechanism of action against pests appears to be as an insect growth regulator, acting as a juvenile hormone mimic. In this regard, it is different from other carbamate insecticides and miticides.

IV. TOXICOLOGICAL DATA REQUIREMENTS (40 CFR 158.340)

Technical Fenoxycarb:

	Required	Satisfied
81-1 Acute Oral Toxicity	Y	Y
81-2 Acute Dermal Toxicity	Y	Y
81-3 Acute Inhalation Toxicity	Y	Y
81-4 Primary Eye Irritation	Y	Y
81-5 Primary Dermal Irritation	Y	Y
81-6 Dermal Sensitization	Y	Y
81-7 Acute Delayed Neurotox.(hen)	N	-
81-8 Acute Neurotoxicity-Mammal	N	-
82-1 Subchronic Oral (rodent)	Y	Y[1]
82-1 Subchronic Oral (nonrodent)	Y	Y
82-2 21-Day Dermal	N	Y
82-3 90-Day Dermal	N	-
82-4 90-Day Inhalation	N	-
82-5 90-Day Neurotoxicity (hen)	N	-
82-5 90-Day Neurotoxicity (mammal)	N	-
83-1 Chronic Toxicity (rodent)	N[2]	-
83-1 Chronic Toxicity (nonrodent)	Y	Y
83-2 Oncogenicity (2 species)	Y	N[3]
83-3 Developmental (2 species)	Y	Y
83-4 Reproduction	R	-
83-5 Chronic/Oncogenicity	-	-
84-2 Muta: Gene Mutation - Bacterial	Y	Y
84-2 Muta: Gene Mutation - Mammalian	Y	Y
84-2 Mutagenicity - Struct. Chrom. Aber.	Y	Y
84-2 Mutagenicity - Other Genotoxic Effect	N	-
85-1 General Metabolism	Y	N[4]
85-2 Dermal Penetration	N	-
86-1 Domestic Animal Safety	N	-

Y - Yes; N - No

[1] The chronic dog study satisfies the data requirement for a subchronic oral study in dogs.

[2] See 83-5

[3] The mouse carcinogenicity study (females) is a data gap due to inadequate dose selection.

[4] A data gap exists for low and repeated dose studies.

V TOXICOLOGY PROFILE

Fenoxycarb: 652C
PC Code: 125301
Updated: December, 1993

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TB-1
TOX ONELINERS

CASWELL#: 652C
CAS-REG#: 79127-80-3

P.C. CODE 125301- N-[2-(p-Phenoxyphenoxy)ethyl]carbamic acid FILE LAST PRINTED: 09/07/93

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	CORE GRADE/ DOCUMENT#
83-1(a) and 83-2(a) Feeding/carcinogenic-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 o 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
83-1(a) and 83-2(b) Feeding/carcinogenic-80 week Species: mice Inveresk Research, Scotland 3390; B-104819; 3/87	RO-13-5223 Tech (Fenoxy-carb) See attached	403769-02 409727-01	Doses: 0, 30, 110 and 420 ppm (M); 0, 20, 80 & 320 ppm (F); or 0, 5.3, 19.3 & 73.9 mg/kg/day (M); 0, 6.0, 21.7 & 81.8 mg/kg/day (F) by diet in strain CD-1. NOEL/LEL could not be determined because a target organ, the liver, was not examined in all animals in the lower dose groups. Liver lesions, including localized perivascular lymphocytic infiltration, foci of pigmented macrophages, focal necrosis and focal angiectasis? were present in females in the 320 ppm group. Males in the 420 ppm group also exhibited increased absolute and relative liver weights. There was a possible dose-related increase in alveolar/bronchiolar adenomas and carcinomas and Harderian gland adenomas in males.		Onco-Pending P.R. 008101 Supp.- Chronic 008101
83-1(a) and 83-2(a) Feeding/carcinogenic-2 year Species: rat Hazleton 5191-161/123; 11/86	RO-13-5223 Tech 96.6% (Fenoxycarb) See attached	403769-01	Doses: 0, 200, 600 & 1800 ppm. Route: oral (diet). Strain: Crl:CD(SD)BR NOEL < 200 ppm. LEL = 200 ppm 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 relative and absolute weight of the liver, hypertrophy of the liver and cysts of the thymus. Males in the 1800 ppm group also had an increased incidence of follicular cysts and C-cell hyperplasia of the thyroid and a possible increase in pituitary carcinomas.		Supp-Chronic & onco 008101
83-3(a) Developmental Toxicity Study 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
83-3(b) Developmental Toxicity Study Species: rabbit Hoffman LaRoche	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		Minimum 004319

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CASWELL#: 652C
CAS-REG#: 79127-80-3

P.C. CODE 125301- N-[2-(p-Phenoxyphenoxy)ethyl]carbamic acid FILE LAST PRINTED: 09/07/93

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
83-3(b) Developmental Toxicity Study 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
83-4 Reproduction-2 generation Species: rat Hazleton Labs, Europe 4623-161/124; 9/86	RO-13-5223 Lot 2, 96.6% See attached	403769-03	Dose levels: 200, 600 and 1800 ppm in diet (10, 30 & 90 mg/kg/day) to strain Sprague-Dawley. Reprod NOEL < 200 ppm (10 mg/kg/day) Reprod LEL = 200 ppm (10 mg/kg/day) based on decreased pup weights and delays in development (pinna unfolding and eye opening) at all dose levels. Maternal NOEL could not be determined because liver lesions were not addressed in the 200 and 600 ppm groups.		Supplementary 098101
82-1(a) Feeding-3 month Species: mice 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 004567
82-1(a) 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
82-1(b) 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
82-2 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 Crl: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

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TOX ONELINERS

P.C. CODE 125301- N-[2-(p-Phenoxyphenoxy)ethyl]carbamic acid FILE LAST PRINTED: 09/07/93

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-2(b) Mutagenic-micronucleus assay Species: mice Hoffman LaRoche, Switz. 3-96-679; 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
84-2(a) 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
84-2(b) 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
84-4 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
84-4 Mutagenic Species: Chin Hamst lung cell 1979	RO-13-5223, Tech	247925	Non mutagenic at 0, 25, 50, and 100 mg/ml.		Acceptable 002215
85-1 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
85-1 Metabolism Species: rat Inveresk Research, Scotland 4217 & RES-MKT JSS; 10/86	C14-RO-13-5223, purity 98%	403769-04 412414-01	Oral: 3000 mg/kg (High-dose). 98% of dose recovered in 96 hrs. 50% eliminated in feces, 42-47% in urine, 0.09% in Co2 and 0.08% in tissues. Residues in liver, fat, kidney and muscle. 83% of radioactivity in feces was parent. 0.8% of urine radioactivity was parent. Male (27%) and female (22.5%) urinary metabolites were identified. The major metabolites were Ro 43-4756, Ro-76-8797 & Ro 43-4764. Biliary: 50 mg/kg. 37 and 63% eliminated in bile in males & females respectively. Repeated Oral: 50 mg/kg. Highest residues in liver. After 28 days residue levels decreased with time. Material bioaccumulates in fat. Metabolism increased at low dose and with repeated dosing. Low & Repeated doses remain data gaps		Supplementary 008101 Acceptable 008146

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TOX ONELINERS

P.C. CODE 125301- N-[2-(p-Phenoxyphenoxy)ethyl]carbamic acid FILE LAST PRINTED: 09/07/93

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-1 Acute oral LD50 Species: rat	RO-13-5223 Tech.	247925	LD 50 > 10,000 mg/kg. 2/5 females died. Splenic hemopoesis.	4	Guideline 002215
81-2 Acute Dermal LD50 Species: rat Huntingdon Res. Centre, Eng. 93142; 2/20/81	RO-13-5223 Tech in corn oil	247925	LD 50 > 2 g/kg(only level tested). Negative for irritation.	4	Guideline 002215
81-3 Acute inhalation LC_{50} Species: rat Ciba-Geigy 111362; 1/22/92	Fenoxycarb Tech (97.6%) Lot# 139044	423438-02	LC_{50} > 4.434 mg/l	3	Acceptable
81-4 Primary eye irritation Species: rabbit	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
81-6 Dermal sensitization Species: guinea pig Hoffman LaRoche 1/0576; 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

Fenoxycarb TOX No 032 [illegible] EPA

Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
[illegible] LC50 - rat [illegible] 1362, 01/22/92	Fenoxycarb Tech 97.6% Lot # 139044	MRID # 423438-02	LC_{50} > 4,434 mg/m³ in males and females Dose levels: 4,434 mg/m³ Route: inhalation Strain: (RII/1 x RII/2)F1 No deaths occurred; at dyspnea, at. piloerection, at. hunched posture and weight loss were observed.	III	Acceptable
83-1b Chronic - dog 1-year Lot offmann-La Roche #B-153778, 6/30/88	Fenoxycarb 96.6%	MRID # 423556-01	NOEL = 25 mg/kg/day LEL = 80 mg/kg/day (based on decreases in adrenal wt. and decreased inorganic phosphorus in males at 260 mg/kg/day there was a decrease in body wt. gain, decreased feed consumption		Guideline
84-2) Mutagenicity: Chromosome aberration Hoffmann-La Roche, #128-M-88, Feb. 21, 1989	Fenoxycarb tech. (% ai not stated)	428438-10	Reportedly negative for inducing chromosome aberrations in human lymphocytes cultured in vitro exposed w/without activation to 25 ug/ml -S9 and 50-100 ug/ml +S9. Major deficiencies exist.		UN acceptable

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add on to the MRID no. and core grade. Do not change citation and material sections

P. C. No: 125301 TOXCHEM NO.: 652C Chemical Name: Fenoxycarb

CITATION	MATERIAL	MRID NUMBER	RESULTS	TOX CAT	CORE GRADE DOC.#
(no change) 2-gen repro (83-4) Species: RAT Lab. Name:Hazleton Lab. Europe Study No: 4623-161/124 Date: Sept 1986	no change	42343803 (add) 42343811 42343812	(replace with the following:) Two generation reproduction study - rat: Fenoxycarb was administered in the diet to male and female Sprague-Dawley rats, at dose levels of 0, 200, 600 or 1800 ppm (approximately 0, 16, 47 and 140 mg/kg/day) for two generations. Maternal toxicity was observed at 600 and 1800 ppm as liver effects, including increased absolute and relative organ weight. At 1800 ppm there was also increased incidences of slight focal necrosis and hypertrophy (0 % controls, 43-96 % high dose) however, low and mid dose livers were not examined histologically. The systemic LEL and NOEL could not be determined since livers were not evaluated at all doses. Reproductive toxicity was observed at all three dose levels as a decrease in pup weight (decrement ranging from 2-21 % depending on dose and generation/litter. The registrant presented a DNOEL (derived NOEL) using analysis of variance and regression). The reported mean DNOELs for the F_1 and F_2 generations are 39±28.87 ppm and 83.53±13.66 ppm, respectively. At 600 and 1800 ppm there is delayed pinna unfolding and eye opening. The reproductive LEL is 200 ppm based on decreased pup weight at day 21. The DNOEL of 40 ppm could be used or a safety factor of between 5 and 10 could be added to the LEL to account for no NOEL.		(add) minimum

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P. C. No: 125301 TOXCHEM NO.: 652C Chemical Name: Fenoxycarb

CITATION	MATERIAL	MRID NUMBER 4a176902	RESULTS	TOX CAT	CORE GRADE DOC.#
(note changes) chr/onco (83-1,2) Species: Mouse Lab. Name: Inveresk Research Int Study No: 3390 Date: March 1987	no change	40 972701 (add) 42343806 42343807 42343808 42343809 42364101	(replace with the following:) Chronic/onco feeding study - mouse: Fenoxycarb was administered in the diet to 50 male and 50 female CD-1 mice at dose levels of 0, 30, 110 or 420 ppm for males (approximate dose 0, 6.0, 21.7 and 81.8 mg/kg/day) and 0, 20, 80 or 320 ppm for females (approximately 0, 4.8, 18.2 and 71.6 mg/kg/day) for 80 weeks. In addition 10/sex/dose were sacrificed at 52 weeks, and 10/sex at 0 and high dose were sacrificed at 58 weeks (52 weeks dosing and 6 weeks recovery period). Systemic toxicity observed at any level. The systemic LEL was greater that 420 ppm and 320 ppm for males and females respectively. The NOEL was equal to or greater that the 420 ppm and 320 ppm for males and females respectively. There was evidence of carcinogenic potential. Alveolar/bronchiolar adenomas were increased in males in the 420 ppm group and there was a possible increase in Harderian gland tumors in the male 420 ppm group. Dosing did not appear adequate for males or for females due to the absence of biologically relevant effects. The above issues will be referred to the HED Cancer Peer Review Committee. Classification: Core-supplementary for carcinogenicity and for chronic feeding. This study does not satisfy the guideline requirement for a cancer study in female mice (83-2) (inadequate dose selection) or for a chronic study in mice (83-1). The Peer Review Committee will determine to need for an additional male study (inadequate dose selection). However, a mouse chronic study is not required.		(add) supplementary

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P. C. No: 125301 TOXCHEM NO.: 652C Chemical Name: Fenoxycarb

CITATION	MATERIAL	MRID NUMBER	RESULTS	TOX CAT	CORE GRADE DOC.#
(note changes) chr/onco (83-5) Species: RAT Lab. Name:Hazleton Lab. Europe Study No:5191- 161/123R Date:Nov.86 (revised Mar.92)	no change	#03897.01 (add) 42343803 42343804 42343805 42364101	(replace with the following:) Chronic/onco feeding study - rat: Fenoxycarb was administered in the diet to 50 male and 50 female Crl:CD(SD)Br Sprague-Dawley derived rats at dose levels of 0, 200, 600 or 1800 ppm (approximate dose males - 0, 8.1, 24.7, 74.4 mg/kg/day; females - 0, 10.9, 33.1, 100.4 mg/kg/day) for 104 weeks. In addition 10/sex/group were sacrificed at 52 weeks. Systemic toxicity observed at 600 and 1800 ppm included non-neoplastic liver histopathology in males (including centrilobular hypertrophy, focal necrosis(1/50 controls; 14/50 mid and high doses), focal fibrosis (4/50 - controls, 15/50 - 600 ppm, 19/50 - 1800 ppm), focal cystic degeneration (13/50 - controls, 25/50 - 600 ppm, 32/50 - 1800 ppm), basophilic foci and pigmented macrophages) and increased liver enzymes including SGOT (100-150%), SGPT (>150%) and alkaline phosphatase (50-100%). In females there was centrilobular hypertrophy at 1800 ppm. At 1800 ppm in males and female, there was only a moderate increase in liver weight with a questionable increase at 600 ppm. The systemic LEL of 600 ppm is based on liver toxicity in males. The NOEL is 200 ppm. There was no evidence of carcinogenic potential. Dosing was adequate in males based on treatment related hepatic necrosis and fibrosis at 1800 ppm. The evidence in females is less strong, however signs including slight increases in liver enzymes and liver weight indicate that, while less sensitive than males, higher doses would result in similar toxicity as observed in males.		(add) minimum

VI. DATA GAPS:

83-2[5]	Carcinogenicity (Mouse)
85-1	Metabolism (low-and repeated-dose)

VII. ACTION TAKEN TO REMOVE DATA GAPS AND OBTAIN ADDITIONAL INFORMATION:

The sponsor is informed herein that the mouse carcinogenicity study (female) is a data gap. This will be presented for HED Cancer Peer Review Committee examination of the data of the mouse chronic/carcinogenicity study (MRID Nos. 403769202, 40972701, 43343809, 42343806, 42343807, 42343808). The metabolism study is also a data gap. Additional data on low-and repeated-dose metabolism studies are required.

VIII. REFERENCE DOSE (RfD):

The toxicological data base on fenoxycarb is currently inadequate to obtain permanent tolerances. Sufficient data are available to refer fenoxycarb to the RfD Committee for examination.

IX. PENDING REGULATORY ACTIONS:

There are no pending regulatory actions against this pesticide at this time that Toxicology Branch I is aware of.

X. TOXICOLOGICAL ISSUES:

1. Acute toxicity - There are no acute toxicity issues. Fenoxycarb toxicity category 4 for acute oral and dermal, category 3 for acute inhalation and irritation, and not a dermal sensitizer.

2. Developmental/reproduction - There are no developmental concerns. There is, however on NOEL in the reproduction study. The endpoint of concern is a small decrease in 21 day pup weight. The Sponsor has calculated a derived NOEL (DNOEL) using regression analysis for this endpoint. For risk assessment purposes The DNOEL of 40 ppm could be used or a safety factor of between 5 and 5 could be added to the LEL to account for no NOEL. This will be presented to the HED RfD committee.

3. Carcinogenicity - Fenoxycarb appears to be associated

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[5] The status of the study depends on the outcome of a Peer Review Committee examination of the data.

with lung tumors and possibly Harderian gland tumors in male mice. The dose levels in this study however, do not appear to be adequate in the female to evaluate carcinogenic potential. The HED Cancer Peer Review Committee (CPRC) will determine if the males need to be tested at higher dose levels. There is no treatment related increase in tumors in the rat. Fenoxycarb will be presented to the CPRC for final determination of carcinogenic potential.

It should be noted that there was a discrepancy between the "Toxicologic Evaluation of Fenoxycarb" (MRID 42343801) and the pathologists report as they relate to the NOEL and MTD of the mouse cancer study. TB1 initially used the low/mid dose for a NOEL/LEL as was described by Drs. Skripsky and Stevens in the evaluation (based on "liver lesions" in the mid dose) in determining that the study was conducted at adequately high dose levels. However, upon subsequent reevaluation of the pathologists report, it was determined that this was not supportable and that there were no treatment related effects in either male or female mice. In addition, the subchronic data did not support the high dose that was used in the mouse study.

4. Mutagenicity - There is no mutagenicity concern. This will be reevaluated by the CPRC.

5. Metabolism - Although there are no concerns at this time, there is a partial data gap for this endpoint.

XI. DATA REVIEWED (DERs attached):

A. The results of the acute inhalation toxicity study (MRID # 423438-02) are:

LC_{50} (males) > 4434 mg/l
LC_{50} (females) > 4434 mg/l
LC_{50} (Combined) > 4434 mg/l

Toxicity Category: III
Classification: Core-Acceptable

B. The results of the chronic feeding study in dogs (MRID # 423556-01) are:

NOEL = 25 mg/kg/day
LEL = 80 mg/kg/day (for male dogs based on significantly decreased absolute adrenal gland weight and decreased inorganic phosphorous

In addition, significant decreases in body weight gain were observed in 260 mg/kg/day males and females, decreased feed consumption in males and decreased inorganic phosphorous in females.

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Classification: Core-Guideline

Study Acceptability: The study satisfies the requirement for a Guideline Series 83-1 Chronic Feeding Study.

C. **The results of the mutagenicity study, chromosome analysis in human peripheral blood lymphocyte (MRID # 423438-10) were:**

Negative with and without metabolic activation at dose levels of 25, 50, 100 or 150 mg/ml.

D. The results of the 2-generation reproduction study (MRID Nos. 403769-03, 423438-12 and 423438-11) are:

Two generation reproduction study - rat: Fenoxycarb was administered in the diet to male and female Sprague-Dawley rats, at dose levels of 0, 200, 600 or 1800 ppm (approximately 0, 16, 47 and 140 mg/kg/day) for two generations.

Maternal toxicity was observed at 600 and 1800 ppm as liver effects, including increased absolute and relative organ weight. At 1800 ppm there was also increased incidences of slight focal necrosis and hypertrophy (0 % controls, 43-96 % high dose) however, low and mid dose livers were not examined histologically. **The systemic LEL and NOEL could not be determined since livers were not evaluated at all doses.**

Reproductive toxicity was observed at all three dose levels as a decrease in pup weight (decrement ranging from 2-21 % depending on dose and generation/litter. The registrant presented a DNOEL (derived NOEL) using analysis of variance and regression). The reported mean DNOELs for the F_1 and F_2 generations are 39±28.87 ppm and 83.53±13.66 ppm, respectively. At 600 and 1800 ppm there is delayed pinna unfolding and eye opening. **The reproductive LEL is 200 ppm based on decreased pup weight at day 21. The DNOEL of 40 ppm could be used or a safety factor of between 5 and 10 could be added to the LEL in order to account for no NOEL.**

Classification: Core-minimum This study satisfies the guideline requirement for a reproduction study (83-4) in rats

E. **The results of the combined chronic feeding/carcinogenicity study in mice are:**

Chronic/onco feeding study - mouse: Fenoxycarb was administered in the diet to 50 male and 50 female CD-1 mice at dose levels of 0, 30, 110 or

420 ppm for males (approximate dose 0, 6.0, 21.7 and 81.8 mg/kg/day) and 0, 20, 80 or 320 ppm for females (approximately 0, 4.8, 18.2 and 71.6 mg/kg/day) for 80 weeks. In addition 10/sex/dose were sacrificed at 52 weeks, and 10/sex at 0 and high dose were sacrificed at 58 weeks (52 weeks dosing and 6 weeks recovery period).

Systemic toxicity was not observed at any level. The systemic LEL was greater that 420 ppm and 320 ppm for males and females respectively. The NOEL was equal to or greater that the 420 ppm and 320 ppm for males and females respectively.

There was evidence of carcinogenic potential. Alveolar/bronchiolar tumors were increased in males in the 420 ppm group (14 % in controls vs. 40 % in HDT) and there was a possible increase in Harderian gland tumors in the male 420 ppm group (10 % in controls vs. 26 % in HDT). Dosing did not appear adequate for males or for females due to the absence of biologically relevant effects. The above issues will be referred to the HED Cancer Peer Review Committee.

Classification: Core-supplementary for carcinogenicity and for chronic feeding. This study does not satisfy the guideline requirement for a cancer study in female mice (83-2) (inadequate dose selection) or for a chronic study in mice (83-1). The Peer Review Committee will determine to need for an additional male study (inadequate dose selection). However, a mouse chronic study is not required.

F. The results of the combined chronic feeding/carcinogenicity study in rats are:

Chronic/onco feeding study - rat: Fenoxycarb was administered in the diet to 50 male and 50 female Crl:CD(SD)Br Sprague-Dawley derived rats at dose levels of 0, 200, 600 or 1800 ppm (approximate dose males - 0, 8.1, 24.7, 74.4 mg/kg/day; females - 0, 10.9, 33.1, 100.4 mg/kg/day) for 104 weeks. In addition 10/sex/group were sacrificed at 52 weeks.

Systemic toxicity observed at 600 and 1800 ppm included non-neoplastic liver histopathology in males (including centrilobular hypertrophy, focal necrosis(1/50 controls;14/50 mid and high doses), focal fibrosis (4/50 - controls, 15/50 - 600 ppm, 19/50 - 1800 ppm), focal cystic degeneration (13/50 - controls, 25/50 - 600 ppm, 32/50 - 1800 ppm), basophilic foci and pigmented macrophages) and increased liver enzymes including SGOT (100-150%), SGPT (>150%) and alkaline phosphatase (50-100%). In females there was

centrilobular hypertrophy at 1800 ppm. At 1800 ppm in males and female, there was only a moderate increase in liver weight with a questionable increase at 600 ppm. The systemic LEL of 600 ppm is based on liver toxicity in males. The NOEL is 200 ppm.

There was no evidence of carcinogenic potential. Dosing was adequate in males based on treatment related hepatic necrosis and fibrosis at 1800 ppm. The evidence in females is less strong, however signs including slight increases in liver enzymes and liver weight indicate that, while less sensitive than males, higher doses would result in similar toxicity as observed in males.

Classification: Core-minimum, This study satisfies the guideline requirement for a chronic/onco feeding study (83-5) in rats.

[Fenoxycarb] 80-Week Chronic/Onco Study - mouse(83-1,2b)

EPA Reviewer: William Greear, M.Ph.
Review Section 4, Toxicology Branch 1 (7509C)
EPA Secondary Reviewer: Marion Copley, D.V.M.
Review Section 4, Toxicology Branch 1 (7509C)

William B Greear, Date 12/21/93
Marion Copley, Date 12/21/93

SUPPLEMENTAL DATA EVALUATION RECORD
(Original DER DOC. # 008101)

STUDY TYPE: 80 Week chronic/onco - Mouse (83-1, 83-2))

TOX. CHEM. NO.: 652C P.C. CODE: 125301

DP Bar Code: D179471, D188212, D179484

MRID NO.: 1) 42343806; 2) 42343807; 3) 42343808; 4) 42343809; 5) 42364101 (original MRID 40376902 and 40972701)

TEST MATERIAL: Fenoxycarb

SYNONYMS: Ro 13-5223/000; CGA-114597 technical

STUDY NUMBER(S): 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, Fla. (original sponsor); Ciba-Geigy (current registrant)

TESTING FACILITY: Inveresk Research International, Musselburg, Scotland

TITLE OF REPORTS: 1) Fenoxycarb a supplement to a carcinogenicity study in mice original project no. 430624 IRI project no. 450719 EPA MRID numbers 40376902 and 40972701, 2) Ro 13-5223/000 (Fenoxycarb) re-examination of the lungs and Harderian glands: A supplement to a chronic toxicity study in mice original IRI project no. 430624 EPA MRID numbers 40376902 and 40972701, 3) Fenoxycarb a Supplement to an 80-week carcinogenicity study in mice original IRI project #430624 EPA MRID numbers 40376902 and 40972701, 4) Fenoxycarb technical pathology peer review of liver of female mice a supplement to a carcinogenicity study in mice original IRI project #430624 EPA MRID numbers 40376902 and 40972701, 5) Toxicological Evaluation of Fenoxycarb (CGA-114597 Technical).

AUTHOR(S): 1) PC Howroyd, DJ Everett; 2) Jerry Hardisty; 3) DJ Everett; 4) Jerry Hardisty; 5) T Skripsky, J Stevens (original study - DJ Everett, KA Scott, P Hudson, F MacNaughton)

REPORT ISSUED: 1 and 3) March 17, 1992; 2 and 4) Nov. 21, 1991; 5) June 2, 1982

(original study report date: March 1987)

EXECUTIVE SUMMARY:

Chronic/onco feeding study - mouse: Fenoxycarb was administered in the diet to 50 male and 50 female CD-1 mice at dose levels of 0, 30, 110 or 420 ppm for males (approximate dose 0, 6.0, 21.7 and 81.8 mg/kg/day) and 0, 20, 80 or 320 ppm for females (approximately 0, 4.8, 18.2 and 71.6 mg/kg/day) for 80 weeks. In addition 10/sex/dose were sacrificed at 52 weeks, and 10/sex at 0 and high dose were sacrificed at 58 weeks (52 weeks dosing and 6 weeks recovery period).

Systemic toxicity was not observed at any level. **The systemic LEL was greater that 420 ppm and 320 ppm for males and females respectively. The NOEL was equal to or greater that the 420 ppm and 320 ppm for males and females respectively.**

There was evidence of carcinogenic potential. Alveolar/bronchiolar tumors were increased in males in the 420 ppm group (14 % in controls vs. 40 % in HDT) and there was a possible increase in Harderian gland tumors in the male 420 ppm group (10 % in controls vs. 26 % in HDT). Dosing did not appear adequate for males or for females due to the absence of biologically relevant effects. The above issues will be referred to the HED Cancer Peer Review Committee.

This study is **core-supplementary** for carcinogenicity and for chronic feeding. This study does not satisfy the guideline requirement for a cancer study in female mice (83-2) (inadequate dose selection) or for a chronic study in mice (83-1). The Peer Review Committee will determine to need for an additional male study (inadequate dose selection). However, a mouse chronic study is not required.

Special Review Criteria (40 CFR 154.7) None

I. RESUBMITTED DATA CONSIDERED IN THIS NEW EVALUATION

Vol. 10 - "Fenoxycarb a Supplement to an 80-week carcinogenicity study in mice original IRI project #430624 EPA MRID numbers 40376902 and 40972701", MRID No. 423438-08, March 17,1992

Vol. 11 - "Ro 13-5223/000 (Fenoxycarb) re-examination of the lungs and harderian glands: A supplement to a chronic toxicity study in mice original IRI project no. 430624 EPA MRID numbers 40376902 and 40972701", MRID No. 423438-07, November 21,1991

Vol. 12 - "Fenoxycarb a supplement to a carcinogenicity study in mice original project no.

430624 IRI project no. 450719 EPA MRID numbers 40376902 and 40972701", MRID No. 423438-06, March 17, 1992

Vol. 13 - "Fenoxycarb technical pathology peer review of liver of female mice a supplement to a carcinogenicity study in mice original IRI project #430624 EPA MRID numbers 40376902 and 40972701", MRID No. 423438-09, November 21, 1991

"Toxicological evaluation of fenoxycarb (CGA-114597 technical), MRID no.42364101, June 17, 1992.

II. ISSUES

The original study submission was given the core classification of supplementary due to the following deficiencies:

1) A NOEL/LEL could not be determined because the liver, the apparent target organ, was not examined in all the low and mid dose animals.

2) It was not explained why the authors decided on making serial sections of the Harderian gland. It was also requested that the sponsor submit historical control data for this organ.

3) It was not apparent that lung tissues from all animals were examined, therefore it was requested that the sponsor verify the number of animals with lung tissues that were histologically examined in the male high dose group.

III. RESULTS AND DISCUSSION

A. ISSUES RELATED TO THE DEFICIENCIES IN THE ORIGINAL DER

1. Harderian Gland Tumors

In Vol. 10, the reason for performing serial sections on the harderian gland was provided by a letter dated October 21, 1991 from P.C. Howroyd to J. Steven as follows:

> "The serial sections of the Harderian gland were made and evaluated at the recommendation of the pathologist (Dr Francis J C Roe) who was requested to review the initial results by the Sponsors of the study. Dr Roe made this recommendation in the light of the higher incidence of tumours in this organ in males which had received the test compound than in Control males, reported from the evaluation of the original sections, particularly because many of the tumours concerned were very small and discovered only during microscopy."

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In the original report, the incidences of benign Harderian gland tumors were reported to be 1/50, 8/50, 5/50 and 8/50 in males in the 0, 30, 110 and 420 ppm groups, respectively. Upon reexamination of the original slides IRI and Dr. Roe concluded that the incidences were 7/50, 10/50, 7/50 and 13/50. After examining additional serial sections IRI and Dr. Roe agreed that the incidences of benign Harderian gland tumors in male mice were 7/50, 10/50, 7/50 and 13/49 in the 0, 30, 110 and 420 ppm groups, respectively. Table 1 reflects Dr. Roe's and IRI's final diagnosis.

TABLE 1 Harderian Gland - Primary Neoplasms (%) in Males[1]

LESION (No. examined) DOSE	0 ppm (50)	30 ppm (50)	100 ppm (50)	420 ppm (49)
Adenoma	7 (14.0)	9 (18.0)	6 (12.0)	13 (26.5)
Adenocarcinoma	0	1 (2.0)	1 (2.0)	0

[1] Results from the Original and Serial Sections Combined

In Vol. 11, J Hardisty reported that he had examined the slides and the additional serial sections. Dr. Hardisty concluded that the results of the evaluation of additional Harderian gland sections were valid. The results are provided in Table 2.

TABLE 2 Harderian Gland Tumors (%) in Male Mice[1]

LESION (No. examined) DOSE	0 ppm (50)	30 ppm (50)	100 ppm (50)	420 ppm (50)
Adenoma	5(10.0)	8 (16.0)	6 (12.0)	13 (26.0)
Adenocarcinoma	0	1 (2.0)	1 (2.0)	0

[1] Slides read by J. Hardisty

In Vol. 12, D.J. Everett provided the background incidences of Harderian gland tumors at IRI (see table 3).

TABLE 3 Historical Control Incidence of Harderian Gland Tumors from 8 Studies Conducted at IRI

Lesion	STUDY NUMBER							
	A	B	C	D	E	F	G	H
Benign	1/1[1]	0/0	0/0	0/0	6/100	0/0	1/1	0/0
Malignant	0/0	0/0	0/0	0/0	0/100	0/0	0/0	0/0

[1] # with tumor/# organs examined

Data extracted form Vol. 12 table 8, p. 51

Only the data from one study (E) is of any relevance due to the extremely low number of animals examined in the remainder of the studies. The incidence of benign Harderian gland tumors in males from study (E) is 6.0 %. In conclusion, the incidence of Harderian gland tumors in males in the 420 ppm group are greater when compared to controls. The data provided by IRI and Dr. Roe and Dr. Hardisty (table 2) are fairly similar. All groups (including the control group) in the Fenoxycarb study are greater than the 6.0 % observed in the one adequate historical control study (E). This may be because Harderian glands in study E may not have been serially sectioned.

2. Lung Tumors (alveolar/bronchiolar adenomas and carcinomas)

In the initial DER, the sponsor was requested to identify the number of males in the 420 ppm group with lung tumors that were histologically examined. The first reading of the slides are presented in table 4. The data on males demonstrated a statistically significant trend with increasing dose ($p<0.01$).

In Vol. 11, J. Hardisty of Experimental Pathology Laboratories, Inc. (EPL) reported the incidence of male mice with lung tumors (see table 5).

Dr. Hardisty concluded that there was an increased number of male mice with lung neoplasms in treated groups. However, he stated that a definitive interpretation of this observation was made difficult due to technical errors which occurred during the processing of additional lung sections. He stated that, "... Since the data generated from the additional lung sections is unreliable, only the data from the original sections as reported by the original pathologist should be used in the interpretation of the lung tumor response in this study." (see table 4).

TABLE 4 Alveolar/Bronchiolar Tumors in Mice (%)

DOSE (ppm)	0	30	110	420
MALES				
Adenoma only	5/50 (10)	7/50 (14)	7/50 (14)	13/50 (26)
Carcinoma only	2/50 (4)	6/50 (12)	6/50 (12)	7/50 (14)
Adenoma assoc. with carcinoma	0/50	1/50 (2)	1/50 (2)	0/50
Lung TBA	7/50 (14)	13/50 (26)	13/50 (26)	20/50 (40)
Females				
Adenoma only	8/49 (16)	0/10	0/7	5/50 (10)
Carcinoma only	1/49 (2)	0/10	0/7	2/50 (4)
Lung TBA	9/49 (18)	0/10	0/7	7/50 (14)

TBA - tumor bearing animals

TABLE 5 Incidence of Alveolar/Bronchiolar Tumors in Male Mice (%)

DOSE (ppm) (No. Lungs Examined)	0 (50)	30 (50)	110 (50)	420 (50)
Alveolar/Bronchiolar adenoma only	9 (18)	10 (20)	12 (24)	17 (34)
Alveolar/Bronchiolar carcinoma only	2 (4)	5 (10)	4 (8)	7 (14)
Both Alveolar/Bronchiolar adenoma and carcinoma	0	1 (2)	1 (2)	1 (2)
Lung TBA[1]	11 (22)	16 (32)	17 (34)	25 (50)

[1] TBA - tumor bearing animal

3. Liver Lesions

In the original DER, there were compound related liver lesions indicating localized perivascular lymphocytic infiltration, foci of pigmented macrophages, focal necrosis and focal angiectasis in females in the 320 ppm group (see table 6). The sponsor has

reevaluated slides from the control and high dose groups as well as previously unexamined livers from the low and mid dose groups. In this new evaluation (see table 7) the pathologist has replaced the term "angiectasis" with "erythrocytes in the hepatocytes" since "a characteristic feature of this finding is the presence of intra-cytoplasmic erythrocytes within hepatocytes adjacent to blood-filled areas. In addition, the term minor perivascular lymphocytic infiltrates has been included in "foci of inflammation". The author concluded that there were no notable differences in liver lesions among males in the control and treated groups. However, there was a slightly higher incidence of pigmented macrophages in the liver of females in the 320 ppm group (5/49; 10 %) compared to controls (0). However, the increase is not substantial and is probably of no biological significance. It was noted that there was an increase in relative liver weights in males in the 420 ppm group (4.7, 7.5, 5.2 and 6.3, control to high dose). However, this increase was slight and is probably of no biological significance. There was not a well defined dose-response relationship.

TABLE 6 Selected Liver Lesions in Female Mice (%)[1]

LESION	0 ppm	20 ppm	80 ppm	320 ppm
Localized perivascular lymphocytic infiltration	2/49 (4)	0/8	0/7	5/49 (10)
Foci of pigmented macrophages	0/48	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)

[1] table from original DER

TABLE 7 Selected Liver Lesions in Female Mice (%)[1]

LESION (no. examined)	0 ppm (50)	20 ppm (47)	80 ppm (50)	320 ppm (49)
Foci of inflammation	23	20	22	17
Foci of pigmented macrophages	0	0	0	5*
Foci of necrosis	1	1	0	5
Foci of erythrocytes in hepatocytes	13	13	20	14

[1] table from table 4 vol 12 of new submission

* $p \leq 0.05$

B. OTHER ISSUES NOT ADEQUATELY ADDRESSED IN THE ORIGINAL DER

Dosing was not adequate for males or for females due to the absence of adequate toxicity to assess carcinogenic potential. Effects on the livers were not considered to be significant. In a previous 90-day study with mice, the LEL was 300 mg/kg/day in males and females based on increased liver weight accompanied by fatty changes, glycogen depletion and increased multinucleated hepatocytes. The NOEL was 100 mg/kg/day. Although there was an increase in the mid dose females of erythrocytes in hepatocytes this was not apparent at the high dose and was not statistically significant. In addition, this lesion would not be adequate evidence of toxicity. In the Sponsor's Peer Review document it was concluded that "...Most pathologists consider the change to probably represent an unexplained tissue artifact and to be of no biological significance." This argument appears reasonable for this chemical.

C. DEFICIENCIES AND NEW ISSUES RAISED IN THE REVISED REPORT

1. It should be noted that T Skripsky and J Stevens, in the Toxicological Evaluation of Fenoxycarb, disagree with the Sponsor's Peer Review of the liver and indicate that the NOEL is 4 mg/kg/day (low dose) based on liver effects and the LEL is 15 mg/kg/day (mid dose). These conclusions do not appear to be reasonable in light of the evidence presented above.

IV Although the registrant has responded to the major concerns expressed in the original DER, this study is still classified as core-supplementary for both cancer (females for sure) and chronic toxicity. The classification is based primarily on the lack of adequate toxicity (males and females) to test for carcinogenic potential. In addition there are numerous errors and it is difficult to sort out the numerous readings. Since a chronic mouse toxicity study is not required this is not a data gap. However, the oncogenicity issue and dose selection issue will be presented to the HED Cancer Peer Review Committee. The Committee will determine whether the males have to be tested at higher doses since there appears to be evidence of carcinogenicity.

[Fenoxycarb] Reproduction Study (83-4)

EPA Reviewer: Marion Copley, D.V.M.
Review Section 4, Toxicology Branch 1 (7509C)
EPA Secondary Reviewer: William Greear, M.Ph.
Review Section 4, Toxicology Branch 1 (7509C)

Marion Copley, Date 12/29/93
William R. Greear Date 12/20/93

SUPPLEMENTAL DATA EVALUATION RECORD
(Original DER DOC. # 008101)

STUDY TYPE: Two-generation Reproduction - Rat (83-4)

TOX. CHEM. NO.: 652C P.C. CODE: 125301

DP Bar Code: D179471, D188212, D179484

MRID NO.: 42343811, 42343812 (original MRID 40376903)

TEST MATERIAL: Ro 13-5223/000

SYNONYMS: Fenoxycarb

STUDY NUMBER(S): 4623-161/124

SPONSOR: Hoffman-LaRoche and Co. (original sponsor); Ciba-Geigy (current registrant)

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

TITLE OF REPORT: 1) Amendment to Ro 13-5223/000: 2-generation oral (dietary administration) reproduction study in the rat); 2) A supplement to a 2-generation oral reproduction study in the rat original project #4223-161/124, EPA MRID Number 40376903

AUTHOR(S): 1) L.Barker; 2) L.G.Luempert (main study - L.Barker and M.Goodyer)

REPORT ISSUED: April 1992

EXECUTIVE SUMMARY:

Two generation reproduction study - rat: Fenoxycarb was administered in the diet to male and female Sprague-Dawley rats, at dose levels of 0, 200, 600 or 1800 ppm (approximately 0, 15, 47 and 140 mg/kg/day) for two generations.

Maternal toxicity was observed at 600 and 1800 ppm as liver effects, including increased absolute and relative organ weight. At 1800 ppm there was also increased incidences of slight focal necrosis and hypertrophy (0 % controls, 43-96 % high dose) however, low and mid dose livers were not examined histologically. **The systemic LEL and NOEL could not**

be determined since livers were not evaluated at all doses.

Reproductive toxicity was observed at all three dose levels as a decrease in pup weight (decrement ranging from 2-21 % depending on dose and generation/litter. The registrant presented a DNOEL (derived NOEL) using analysis of variance and regression). The reported mean DNOELs for the F_1 and F_2 generations are 39±28.87 ppm and 83.53±13.66 ppm, respectively. At 600 and 1800 ppm there is delayed pinna unfolding and eye opening. The reproductive LEL is 200 ppm based on decreased pup weight at day 21. The DNOEL of 40 ppm could be used or a safety factor of between 5 and 10 could be added to the LEL in order to account for no NOEL.

Classification: Core-minimum

This study satisfies the guideline requirement for a reproduction study (83-4) in rats

Special Review Criteria (40 CFR 154.7) None

I. ISSUES

The original study submission was given the core classification of supplementary due to the following deficiencies:

1) Gross lesions were not histologically examined.

2) Livers from low and mid dose parental animals 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.

Only these deficiencies will be discussed in this supplemental DER.

II. RESULTS AND DISCUSSION

1) Histologic evaluation of gross lesions was not addressed in the new submission; and 2) Histologic evaluation from the low and mid dose was not addressed in the new submission.

Although these should have been addressed, a new study would not be required because of these omissions. These systemic endpoints are not evidence of severe systemic toxicity and would be more clearly defined in the chronic rat study.

3) Individual data on physical developmental parameters (particularly pup weight, pinna unfolding and eye opening) were presented in appendix 1 of MRID 42343811. There was also a statistical analysis of these parameters. The original report suggested a possible dose related delay in pup weight (21 day), pinna unfolding and eye opening.

The new submission concluded that there was a delay in pup development as evidenced by decreased pup weight at 21 days in all three doses (see table 1).

TABLE 1 Decrease in 21 Day Mean Pup Weight (as % of controls)

DOSE (ppm)	F_{1a}	F_{1b}	F_{2a}	F_{2b}
200	8.5**	2.0	7.2	10.9**
600	7.3**	4.5	7.5**	12.9**
1800	11.3**	9.8**	12.2**	21.0**

Data extracted and calculated from tables 11, 12 of study
* $p \leq 0.05$, ** $p \leq 0.01$ (statistical pair-wise based on actual weight, not % decrement)

The supplemental report presented a statistical evaluation resulting in a DNOEL (derived NOEL) using analysis of variance and regression (see attachment for calculations). The reported mean DNOELs for the F_1 and F_2 generations are 39 ± 28.87 ppm and 83.53 ± 13.66 ppm, respectively. This is about 1/5 of the low dose of 200 ppm. The DNOEL of 40 ppm could be used or a factor of between 5 and 10 ctould be added tc the LEL to account for no NOEL.

Analysis of the pinna unfolding and eye opening were conducted by the registrant. They considered the time of first occurrence of the event and interval from first occurrence to all pups at normal range. The statistics of this evaluation are in the attachment. These two events appear to be treatment related in the 600 and 1800 ppm groups.

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 addressed in this response however this by itself would not result in downgrading the study to supplementary.

Since the registrant has responded to the major concerns expressed in the original DER, this study is now classified as core-minimum.

FENOXYCARB TOXR 010721

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Pages 31 through 35 are not included.

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 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.

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study report date: November 1986

EXECUTIVE SUMMARY:

Chronic/onco feeding study - rat: Fenoxycarb was administered in the diet to 50 male and 50 female Crl:CD(SD)Br Sprague-Dawley derived rats at dose levels of 0, 200, 600 or 1800 ppm (approximate dose males - 0, 8.1, 24.7, 74.4 mg/kg/day; females - 0, 10.9, 33.1, 100.4 mg/kg/day) for 104 weeks. In addition 10/sex/group were sacrificed at 52 weeks.

Systemic toxicity observed at 600 and 1800 ppm included non-neoplastic liver histopathology in males (including centrilobular hypertrophy, focal necrosis(1/50 controls;14/50 mid and high doses), focal fibrosis (4/50 - controls, 15/50 - 600 ppm, 19/50 - 1800 ppm), focal cystic degeneration (13/50 - controls, 25/50 - 600 ppm, 32/50 - 1800 ppm), basophilic foci and pigmented macrophages) and increased liver enzymes including SGOT (100-150%), SGPT (>150%) and alkaline phosphatase (50-100%). In females there was centrilobular hypertrophy at 1800 ppm. At 1800 ppm in males and female, there was only a moderate increase in liver weight with a questionable increase at 600 ppm. **The systemic LEL of 600 ppm is based on liver toxicity in males. The NOEL is 200 ppm.**

There was no evidence of carcinogenic potential. Dosing was adequate in males based on treatment related hepatic necrosis and fibrosis at 1800 ppm. The evidence in females is less strong, however signs including slight increases in liver enzymes and liver weight indicate that, while less sensitive than males, higher doses would result in similar toxicity as observed in males.

Classification: Core-minimum, This study satisfies the guideline requirement for a chronic/onco feeding study (83-5) in rats.

Special Review Criteria (40 CFR 154.7) None

I. ISSUES

The original study submission was given the core classification of supplementary due to the following deficiencies:

1) Lack of statistical analysis for many parameters, ie. body weight, food consumption, hematology, histopathology.

2) Lack of SGOT, SGPT and alkaline phosphatase for rats in the 200 ppm and 600 ppm

groups at 25, 51, and 78 weeks even though there were positive results at 1800 ppm.

3) No tissue accountability tables, therefore would not tell the actual number of tissues examined for each organ. This made it impossible to determine the actual percent incidence of lesions within groups of animals.

4) Individual pathology sheets did not have date of death for all rats.

5) There was no time-weighted average of daily compound intake.

6) Historical control data for pituitary tumors.

7) In addition to the above, it was also requested (in a separate memorandum to RD) that the sponsor: a) reexamine the pituitary slides since the incidence of pituitary carcinomas was unusually high; b) provide the criteria used in classifying pituitary proliferative lesions.

The above deficiencies as well as clarification of other areas of the original DER will be discussed in this supplemental DER.

II. RESULTS AND DISCUSSION

A. ISSUES RELATED TO THE DEFICIENCIES IN THE ORIGINAL REPORT

1. Statistical analysis was included in the replacement report and appeared adequate.

2. The lack of certain clinical chemistries and intermediate time points was not addressed, however this alone would not result in downgrading the study to supplementary.

3. Tissue accountability tables were presented in report tables 8.8-8.12 (pp 117-126) of the revised study report and appeared adequate.

4. Date of death for all rats was presented in a table in Appendix 1 (p 132) of the revised report.

5. The time-weighted average for compound intake is presented in table 1 below.

TABLE 1 Time-weighted average of compound intake (mg/kg/day)

DOSE (ppm)	MALES	FEMALES
200	8.1	10.9
600	24.7	33.1
1800	74.4	100.4

Table extracted from table 3.2 of the revised study report.

6. Historical control data was provided for thyroid and pituitary tumors. However since the concerns raised in the original DER have been satisfactorily addressed, the historical control data will not be discussed in the DER.

7. The registrant had liver and select pituitary and thyroid tissues reexamined by Jerry Hardisty, a veterinary pathologist at Experimental Pathology Laboratory (EPL).

a) Pituitary - The original pituitary tumor counts for males are in table 2 (denominators were not available in the original study report). It was noted in the original DER that although there was no increase in rats bearing pituitary tumors, there was an increase in pituitary carcinomas. In addition, the incidence of pituitary carcinomas appeared to be unusually high for the entire study.

TABLE 2 Pituitary Tumor Counts in Males (from the Original Study Report)

Dose (ppm)	0	200	600	1800
Adenoma	27	12	15	20
Carcinoma	1	2	2	6
Combined	28	14	17	26

Taken from the original DER, denominators not available.

Ciba had select slides, as noted below, reexamined (at the request of EPA) and the criteria used by Dr. Hardisty are attached to this DER. EPL examined all pituitary slides for males in the control and 1800 ppm groups. In addition pituitaries were also examined from rats in the 200 and 600 ppm groups for male rats killed in extremis or those with gross observations. Surrounding brain areas were also examined when there were pituitary carcinomas.

The results of the reexamination of pituitary slides by EPL are presented in table 3. The original study pathologist agreed that, although many of the tumors were originally classified as malignant, these would be considered adenomas by current criteria. These results indicate that there is no increase in pituitary tumors when current criteria are used. It should be noted that the total pituitary tumor bearing animals is approximately the same in both evaluations. Although not all tissues in the 200 and 600 ppm groups were reexamined by EPL, it does not change the conclusion that pituitary tumors are not increased by treatment with Fenoxycarb.

TABLE 3 Pituitary Lesion Counts[1] in Males (from reread by Dr. Hardisty - EPL)

GROUP (ppm) (No. Examined)	0 (49)	200 (22)	600 (23)	1800 (49)
Focal Hyperplasia, Pars Distalis	3	0	0	5
Adenoma, Pars Distalis	24	14	17	23
Adenoma, Pars Intermedia	0	0	0	1
Carcinoma, Pars Distalis	1	0	0	1

[1] Interim sacrifice are not included in the table. Only 1 adenoma was observed (control). Data extracted from p 11 of EPL's report

b) Thyroid - The original DER expressed some concern about a possible increase in C-cell hyperplasia (14, 0, 4, and 24) and follicular cysts (1, 1, 1, and 6) in the thyroid in 1800 ppm group males (denominators were not available in the original study report.

Ciba had select slides as noted below reexamined by Dr. Hardisty at EPL. EPL examined all thyroid slides for males in the control and 1800 ppm groups. In addition, thyroids were also examined from rats in the 200 and 600 ppm groups for male rats killed in extremis or those with gross observations. As can be seen in table 4, there is little increase in non-neoplastic thyroid changes using current criteria.

TABLE 4 Select Thyroid Histopathologic Changes in Males
Counts[1] in Males (from reread by Dr. Hardisty - EPL)

GROUP (ppm) (No. Examined)	0 (50)	200 (17)	600 (16)	1800 (50)
C-cell hyperplasia	20	2	5	25
Follicular cysts	0	2	0	4

[1] Interim sacrifice are not included in the table.
Data extracted from p 12 and 22 of EPL's report

c. Liver - The original DER expressed concern about a possible treatment-related increase in non-neoplastic pathology in both males and females (table 5) (denominators were not available in the original study report).

TABLE 5 Select Liver Lesions (taken from original study report)

	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
Histiocytes	0	0	2	4	0	0	0	0

Data taken from the original DER, denominators not available.

Ciba had all male liver slides from all groups reexamined by Dr. Hardisty at EPL. According to the pathology report by EPL, livers from all 50 animals per group were available for reading. There was no treatment related increase in liver neoplasia. Select non-neoplastic observations are in table 6. There was a treatment related effect in the liver at 600 and 1800 ppm including centrilobular hypertrophy, focal necrosis, focal fibrosis, focal cystic degeneration, basophilic foci and pigmented macrophages. Although there appears to be a slight increase in focal cystic degeneration at 200 ppm as well, this is the only effect observed at this dose. It is unlikely that this marginal effect is biologically relevant at 200 ppm .

TABLE 6 Select Liver Histopathologic Changes in Males
Counts[1] in Males (from reread by Dr. Hardisty - EPL)

52 WEEK INTERIM KILL				
GROUP (ppm) (No. examined)	0 (10)	200 (10)	600 (10)	1800 (10)
Centrilobular hepatocellular hypertrophy	0	0	2	6
Focal necrosis	0	1	3	5
Focal fibrosis	0	1	0	3
104 WEEK TERMINAL KILL (AND SPORADIC DEATHS)				
(No. examined)	(50)	(50)	(50)	(50)
Centrilobular hepatocellular hypertrophy	0	0	9**	18**
Focal necrosis	1	3	14**	14**
Focal fibrosis	4	5	15**	19**
Focal cystic degeneration	13	20	25*	32**
Basophilic cell focus	3	1	7	11*
Pigmented macrophages	4	3	9	16**

Data extracted from EPL report, p 14 (statistics taken from talbe 3, p. 13 of Tox. Eval. Rpt.
* $p \leq 0.05$ (1-tail); ** $p \leq 0.01$ (1-tail): These statistics were conducted on data with the interim sacrifiec animals included (N=60)

B. OTHER ISSUES NOT ADEQUATELY ADDRESSED IN THE ORIGINAL DER

1. Liver histopathology in females. Liver slides were not read by EPL. The only effect noted in the study report as being treatment related in females is hypertrophy (0/50, 0/50, 0/50, 10/49).

2. Liver weight changes were noted as treatment related in males and females in the original DER but were not supported with data. This increase was only moderate, with the most severe increase only 32 % over controls in the high dose females. Data are presented in table 7. There is an increase at both 1 and 2 years at the 1800 ppm and possibly at 600 ppm.

TABLE 7 Liver weight data at terminal sacrifice relative to body weight (%)

DOSE (ppm)	0	200	600	1800
MALES				
1 yr	2.388	2.209	2.774	2.687*
Term	2.157	2.063	2.431	2.292
FEMALES				
1 yr	2.461	2.524	2.656	3.130**
Term	2.221	2.209	2.505*	2.941**

Data extracted form original report table 7, p 71-2
* $p \leq 0.05$; ** $p \leq 0.01$

3. Clinical chemistries indicative of liver toxicity were not supported by data in the originall DER. The study did not include evaluation of these parameters in the 200 and 600 ppm groups at the interim time points. As can be seen in table 8 there is a treatment related increase in SGOT, SGPT and alkaline phosphatase in males at 1800 ppm. The increase in 1800 ppm females at term is not statistically significant. Although the increases are similar for females at earlier time points, several of these increases at 1800 ppm reach statistical significance at $p \leq 0.05$. This indicates that the females, while less sensitive than males to liver toxicity, do have some evidence of toxicity.

TABLE 8 Select Clinical Chemistries at 104 Weeks

DOSE (ppm)	0	200	600	1800
MALES				
SGOT	78	90(15%)	197**(152%)	153*(96%)
SGPT	29	36(24%)	82**(183%)	73**(152%)
Alk.Phos.	136	163(20%)	202(49%)	286**(110%)
FEMALES				
SGOT	85	79	107(26%)	104(22%)

SGPT	37	34	41	34
Alk.Phos.	72	74	94(30%)	104(44%)

Data extracted form original report table 5, p 73
* $p \leq 0.05$; ** $p \leq 0.01$

4. Although the original DER notes anemia in the 1800 ppm females it appears that this may be a spurious result since there is no statistical significance, it only occurs at term, and is the result of extremely low values in two rats, one of which has evidence of other problems.

5. Adequate dose testing in females - There was no evidence of adequate toxicity at the high dose in the females. Although toxicity was minimal at 1800 ppm there was evidence that the toxicity profile in females is similar to, but less severe than the males. Repeating this study in females at higher doses would probably be unwarranted.

C. DEFICIENCIES AND NEW ISSUES RAISED IN THE REVISED REPORT

1. It is unclear why organ weight data is presented differently for males and females in the revised report.

2. Relative and absolute organ weight data are not presented for each organ.

3. There were not always references in the text as to which tables had the supporting data to values and effects described in the results section.

The above deficiencies however, would not result in classifying the study as supplementary.

III Since the registrant has responded to the major concerns expressed in the original DER, this study is now classified as core-minimum for both cancer and chronic toxicity.

FENOXYCARB TOXR 010721

Page_____ is not included in this copy.

Pages 44 through 45 are not included.

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 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.

010721

FINAL

DATA EVALUATION REPORT

FENOXYCARB TECHNICAL

Study Type: Acute Inhalation Toxicity (81-3)

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Principal Reviewer Vera Brankovan Date Feb 11, 1993
Vera Brankovan, Ph.D.

Independent Reviewer William L. McLellan Date Feb. 10, 1993
William McLellan, Ph.D.

QA/QC Manager Sharon A. Segal Date 2/11/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-41
Clement Number: 126
Project Officer: Caroline Gordon

010721

EPA Reviewer and
Section Head: Marion Copley, DVM
Review Section , Toxicology Branch/HED

Signature: Marion Copley
Date: 2/23/93

DATA EVALUATION REPORT

STUDY TYPE: Acute inhalation toxicity - rat (81-3)

EPA IDENTIFICATION NUMBERS

Tox Chem. No.: 652C

MRID No.: 423438-02

PC Number: 125301

TEST MATERIAL: Fenoxycarb technical

SYNONYM(S): CGA 114597 technical

SPONSOR: CIBA-Geigy Limited, Plant Protection Division, Basel, Switzerland

STUDY NUMBER: 911362

TESTING FACILITY: Short-term Toxicology, CIBA-Geigy Limited, Stein, Switzerland

TITLE OF REPORT: Acute Inhalation Toxicity in the Rat

AUTHOR(S): H.R. Hartmann

STUDY COMPLETED: January 22, 1992

CONCLUSIONS: Acute inhalation LC_{50} in males: greater than 4.434 mg/L
Acute inhalation LC_{50} in females: greater than 4.434 mg/L
Acute inhalation LC_{50} in sexes combined: greater than 4.434 mg/L

Only one exposure level was used in this study. This maximum atainable concentration was considered a limit test.

CORE CLASSIFICATION: Core Acceptable Data. This study meets the requirements set forth under EPA Guideline Series 81-3 for an acute inhalation toxicity study in rats.

TOXICITY CATEGORY: III

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A. MATERIALS

Test Compound

Test material:	**CGA 114597 technical**
Lot number:	**139044**
Active ingredient:	**Not reported**
Purity:	**97.6%**
Physical description:	**White-brownish solid**
Storage condition:	Not reported
Stability:	Not reported
Concentration levels:	4.434 mg/L of air
Dosing volume:	2 L/min
Vehicle:	Ethanol
Controls:	10 rats (5/sex)

Test Animals

Species:	Rats
Strain:	(RII/1 x RII/2)F_1
Source:	CIBA-GEIGY Limited, Animal Production, Stein, Switzerland
Sex:	Males and females
Age:	Not reported
Weight:	Males 204-220 g; females 195-205 on day 0
No. animals/dose:	10 rats, (5/sex)

Environmental/housing conditions: Temperature 22°C ± 3°C
Humidity 45% - 65%
15 air changes per hour

B. TEST PERFORMANCE

Inhalation chamber: A cylindrical stainless steel exposure chamber fitted with nose-only exposure tubes was used. The internal volume of the chamber was <1 liter.

Dose preparation/Generation of test atmpsphere: The solid test aerosol (dust) could not be generated from the test material with the available equipment. Therefore, the test aerosol was made from a 10% solution of the CGA 114597 technical in ethanol after heating the test material to 60°C overnight in a drying kiln. Thus, the highest concentration obtainable was 4.434 mg/L. The aerosol was generated in two pneumatic nebulizers operating at pressures of 100 and 120 kPa. The air flow rate was 32 L/minute. A glass cyclone was used to remove coarse particles from the aerosol. The control animals were exposed to 61.879 mg/L of ethanol under same conditions but at a different time (not concurrently).

Analytical determinations: The concentration of the test material in the aerosol in the chamber was determined from five 1-L samples collected during the exposure period. Analytical results are summarized in Table 1.

Chamber conditions: Temperature: 22.5°C ± 0.2°C
Humidity: 49%-51%
Oxygen content: 21% ± 0%
No. air changes per hour were not reported, but the air flow through the chamber was 32 L/minute.

Exposure conditions: Animals were exposed to the aerosol for 4 hours after a 10-minute equilibrium period. The exposures were by nose only. The chamber clearing time immediately following air or test material exposures was not reported.

Observation period: 14 days

Observation frequency: During the 4-hour exposure and immediately after exposure; thereafter, daily

Body weight interval: Immediately prior to exposure, day 7, and day 14

Gross pathology: YES x ; NO _____

Histopathology: YES _____; NO x

C. RESULTS

Mortality: No animals died at the exposure concentration of 4.434 mg/L of CGA 114597 technical.

Clinical observations: The results of the study indicate that there were no differences between exposed male and female rats. The signs of toxicity observed included slight dyspnea, slight piloerection, slight hunched posture, and weight loss. Both exposed males and exposed females appeared normal by day 4. The signs of toxicity of a lesser degree were present in the control groups on the day following the exposure.

Body weights: A significant decrease in body weight gain was observed in animals exposed to 4.434 mg/L on day 7. The body weights of males returned to control levels by day 14, while the exposed females exibited a significantly higher weight gain compared to control females. A summary of mean body weights (g) for exposed and control males and females is presented Table 2.

Gross Necropsy: The authors stated that no exposure-related deviations from normal morphology were observed.

D. REVIEWERS COMMENTS

EPA guidelines specify that at least three concentrations should be tested in an acute inhalation study. This study had only one exposure group. The group exposed to test material and the ethanol- exposed control group were tested 1 month apart. However, since there were no deaths it is unlikely that the conclusion of the study would change if it were reported.

Other reporting deficiencies included the following: the number of air changes per hour were not reported; the recording times for air flow measurements were not reported; and the percent of test material particles in the aerosol with diameters ≤1.1 μm was only reported graphically.

These deviations from EPA guidelines, are not expected to alter the conclusion that this study is in Toxicity Category III. Therefore, it is classified as Core Acceptable Data.

E. COMPLIANCE

- A signed Statement of No Data Confidentiality Claims, dated April 8, 1992, was provided.
- A signed Statement of EPA GLPs, dated April 8, 1992, was provided.
- A signed Statement of Quality Assurance, dated January 27, 1992, was provided.

Table 1: Summary of Analytical Exposure Data[a]

Mean Exposure Concentration[b] mg/L	Nominal Concentration mg/L	MMAD[c] (μm)	Percentage of Particles[d] $\leq$1.1 μm
4.434 $\pm$ 0.162	6.321	0.9 $\pm$ 2.6[e]	64
		1.2 $\pm$ 3.4[f]	72

[a] Data taken from study No. 911362, Table 1, p.19
[b] Mean(s) $\pm$ standard deviation(s) of five samples
[c] Mass median aerodynamic diameter $\pm$ geometric standard deviation
[d] Estimate based on percent of particles $\leq$1.1 μm given in a graph by the study authors
[e] The lowest MMAD recorded during exposure
[f] The highest MMAD recorded during exposure

Table 2. Mean Body Weights in Male and Female Rats[a]

Test material concentration (mg/L)	Sex	Day 0	Day 7	Day 14
0	Males	221	268	306
	Females	202	221	231
4.434	Males	212	249	290
	Females	200	207	227

[a] Data taken from study No. 911362, Table 3, p 18

010721

FINAL

DATA EVALUATION REPORT

FENOXYCARB

Study Title:
Chronic Toxicity Study in Dogs

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer: Vera Brankovan — Date 5/25/93
Vera Brankovan, Ph.D.

Independent Reviewer: John Liccione — Date 5/25/93
John Liccione, Ph.D.

QA/QC Manager: Sharon Segal — Date 5/25/93
Sharon Segal, Ph.D.

handwritten Corrections by HED Reviewer
MC.
7/21/93

Contract Number: 68D10075
Work Assignment Number: 2-41
Clement Number: 127
Project Officer: Caroline C. Gordon

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010721

Guideline Series 83-1b: Chronic Feeding Study in Dogs

EPA Reviewer: William Greear, MPH. Signature: William B. Greear +
Review Section IV, Toxicology Branch I, Date: 6/2/93
Health Effects Division (H7509C)

EPA Section Head: Marion Copley, DVM Signature: Marion Copley
Reviewe Section IV, Toxicology Branch I, Date: 7/21/93
Health Effects Division (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Chronic toxicity study in dogs (83-1b)

TEST MATERIAL: Ethyl[2-(p-phenoxyphenoxy)ethyl]carbamate

PC Code: 125301

Tox Chem. Number: 652C

MRID Number: 423556-01

SYNONYMS: Fenoxycarb; Ro 13-5223/000

STUDY NUMBER: B-153'778

SPONSOR: Agricultural Division, CIBA-GEIGY Corporation, Post Office Box 18300, Greensboro, North Carolina 27419

TESTING FACILITY: F. Hoffmann-LaRoche & Co. Ltd., CH-4002 Basle, Switzerland

TITLE OF REPORT: Chronic Toxicity Study Following Oral Administration of Ro-5223/000 (fenoxycarb), an Insect Growth Regulator, to Dogs for a Period of One Year

AUTHOR: P. Keller-Rupp

REPORT ISSUED: June 30, 1988

CONCLUSIONS: Fenoxycarb was given orally by capsule to groups of four beagle dogs/sex for 52 weeks at dose levels of 0, 25, 80, or 260 mg/kg/day.

NOEL = 25 mg/kg/day
LEL = 80 mg/kg/day for male dogs based on significantly decreased absolute adrenal gland weight and decreased inorganic phosphorus.

Statistically significant ($p<0.05$) decrease in body weight gain was observed in 260 mg/kg/day males and females; decreased feed consumption in males, and decreased inorganic phosphorus in females.

CORE CLASSIFICATION: Core Guideline Data. This study meets the requirements set forth under Guideline Series 83-1b for a chronic toxicity study in dogs.

* with noted corrections in pen.

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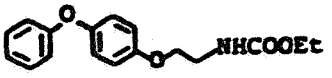
A. MATERIALS

1. Test Article Description

Name: Ethyl[2-(p-phenoxyphenoxy)ethyl]carbamate

Structural formula: 

Batch number: 2

Purity: 96.6%

Physical property: White powder

Stability: Reported to be stable for several years

Storage conditions: Room temperature

2. Dose Preparation

Test material was administered by gelatin capsules.

3. Animals

Species: Dog (*Canis familiaris*)

Strain: Beagle

Age: Males, 36.6 ± 0.9 weeks at start of study; females, 38.5 ± 0.6 weeks at start of study

Weight at initiation: Males, 9.2–13.5 kg; females, 8.8–13.2 kg

Source: Institute of Biological and Medical Research, CH-4414 Fullinsdorf, Switzerland

Animal assignment: Animals were acclimated to laboratory conditions for 3 weeks and were assigned by sex to the following test groups using a randomization procedure performed by ballot:

Test Group	Dose Level (mg/kg/day)	Number of Animals	
		Males	Females
1 Control	0	4	4
2 Low-dose (LDT)	25	4	4
3 Mid-dose (MDT)	80	4	4
4 High-dose (HDT)	260	4	4

The differences in initial body weights between animals in the four groups were not statistically significant.

Environmental conditions: Animals were housed 4/sex per cage. Temperature and relative humidity were controlled at 18 ± 2°C and 55 ± 10%, respectively. A 12-hour dark/light cycle was maintained.

Food and water consumption: Animals received food (NAFAG standard dog cubes No.930) and tap water ad libitum. When available, dogs received calf bones weekly, but at least once monthly.

Rationale for dose selection: No rationale for dose selection was provided.

Dosing procedure: Since the test material was administered in gelatin capsules, all the animals received a constant dose (mg/kg/day) orally throughout the 52 weeks of study. No information was provided on the preparation of capsules or their storage. Dogs in the control group received empty gelatin capsules in their diets.

Results: The test material (Batch #2) was analyzed for stability during weeks 6, 25, and 52. The stability was defined as stable in a 2-year rat feeding study (Hazleton Report #5191-161/123). The analytical concentrations of the test material in the diets were comparable to the nominal (expected) concentrations. Diets were prepared from the same batch over a 2-year period. The test material was evaluated for purity during weeks 6, 25, and 52 and was found to be 95.1%, 95.0%, and 95.0% pure, respectively.

4. Statistics

The data were processed to obtain group mean values and standard deviation (SD). This was followed by the Kruskal-Wallis-Anova test, Mann-Whitney test, Dunn test, and U-test. Dunn test was used for multiple comparisons of control values versus all treated groups. The results were expressed as mean ranks and were reported only when the comparisons were statistically significant.

5. Compliance

- Signed statements of No Data Confidentiality Claim, dated October 18, 1988 and April 2, 1992, were provided.
- Signed statements of Compliance with GLPs, dated June 30, 1988 and April 1, 1992, were provided.
- A signed Quality Assurance Statement, dated August 19, 1988, was provided.

B. METHODS AND RESULTS

1. General Observations

Animals were observed daily for mortality and clinical signs of toxicity. Detailed physical examinations were performed weekly. The dogs were inspected for their general state of health, behavior, vivacity, signs of injury, signs of sickness and abnormality, appearance of the skin and fur, skin turgor, discharge from eye and nose, and for the nature of excretes and soiled body regions (anus, genitals).

Results: No compound-related mortalities or clinical signs were observed. Various transient symptoms were observed but were not considered to be related to dose.

Body Weights and Food Consumption

Body Weights: Body weights were recorded on day -14, -6, 0 (first day of treatment), day 1, day 2, and weekly thereafter throughout the study.

Results: Table 1 summarizes data on mean body weights. Mean body weights did not differ significantly throughout the study in females fed 25, 80, or 260 mg/kg/day of fenoxycarb when compared to those of controls. Mean body weights in high-dose males were significantly lower (41%) than those of controls throughout the study, except for weeks 1, 3, and 7. Mean body weight gains are summarized in Table 2. Stagnation in growth rate was noted in the high-dose males and females. Mean body weight gains for high-dose males and females were lower that those of controls at 0-13, 1-26, and 0-52 weeks. Overall body weight gain (52 weeks) was 38%, 44%, and 87% lower than controls in males receiving 25, 80, and 260 mg/kg/day, respectively. In the 260-mg/kg/day males the decreased body weight gain was statistically significant ($p<0.05$) for 0-26 and 1-52 week interval. Overall body weight gains (52 weeks) were 9% and 94% lower than controls in females receiving 25 and 260 mg/kg/day, respectively, while females receiving 80 mg/kg/day had an 19% increase in body weight gain. Statistically significant ($p<0.05$) decrease in body weight gain was observed in 260-mg/kg/day females for the 0-13 week period.

Food consumption: Food consumption data were recorded once or twice per week throughout the study. However, no [illegible] food intake data were provided except for mean values based on the total daily food intake per four dogs.

Results: Food consumption was reduced in males in the 260 mg/kg/day group when compared to controls.

3. Ophthalmoscopic Examination

Ophthalmoscopic examinations were performed on all animals before initiation of the study and during week 52 using a Keeler Dualite ophthalmoscope.

Results: No compound-related lesions were observed in any of the treated dogs.

4. Clinical Pathology

(a) Hematology

The dogs were fasted for 15 hours prior to sample collection. The blood was collected from the jugular vein of all animals prior to study initiation and during weeks 2, 6, 13, 26, 39, and 52 for general chemistry (into heparinized vials), for electrophoresis, sodium and potassium levels (without

TABLE 1. Mean Body Weights (kg ± SD) at Selected Intervals in Dogs Fed Fenoxycarb for 52 Weeks[a,b]

Dose (mg/kg/day)	Week 0 (%)	13 (%)	26 (%)	52 (%)
		Males		
0	12.6±1.0	14.6±1.2*	17.1±0.9*	19.7±1.5*
25	10.9±0.7 (87)	13.0±2.1 (89)	14.2±2.9 (83)	15.3±4.1 (78)
80	12.1±1.3 (95)	13.6±2.3 (93)	14.8±3.3 (87)	15.9±4.1 (81)
260	10.8±1.3 (86)	11.4±1.4*(78)	11.8±1.4*(69)	11.7±1.4*(59)
		Females		
0	9.3±0.4	10.6±0.5	11.4±1.4	12.5±1.6
25	10.5±1.9 (113)	11.2±2.2 (106)	12.2±3.4 (107)	13.4±4.5 (107)
80	11.3±1.1 (122)	12.6±1.0 (119)	13.0±1.3 (114)	15.1±1.9 (121)
260	10.7±1.2 (115)	10.4±1.0 (98)	11.2±1.7 (98)	10.9±1.4 (87)

[a]Data were extracted from Study No. B-153'778, Tables 1, 3, 5, 9 (males) and Tables 11, 13, 15, 19 (females)

[b]The number in parenthesis represents % control

*Statistically significant mean rank comparison differences of Dunn-test (multiple comparisons; control versus all treated groups)

TABLE 2. Mean Body Weight Gains (kg ± SD) in Dogs Fed Fenoxycarb for 52 Weeks[a,b]

Dose (mg/kg/day)	Week 0–13 (%)	0–26 (%)	0–52 (%)
		Males	
0	2.0 ± 0.6	4.5 ± 0.9	7.1 ± 2.3
25	2.1 ± 1.5 (105)	3.3 ± 2.5 (73)	4.4 ± 3.7 (62)
80	1.5 ± 1.1 (75)	2.7 ± 2.1 (60)	4.0 ± 3.0 (56)
260	0.6 ± 0.5 (30)	1.0 ± 0.5* (22)	0.9 ± 0.8* (13)
		Females	
0	1.3 ± 0.4	2.1 ± 1.2	3.2 ± 1.3
25	0.7 ± 0.4 (54)	1.7 ± 1.7 (81)	2.9 ± 2.9 (91)
80	1.3 ± 0.5 (100)	1.7 ± 0.9 (81)	3.8 ± 0.2 (119)
260	-0.3 ± 0.7* (-23)	0.5 ± 1.2 (24)	0.2 ± 1.4 (6)

[a]Calculated by the reviewers
[b]The number in parenthesis represents % control

*$p<0.05$

anticoagulant), and for hematology (into EDTA vials). The parameters checked (X) below were determined:

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
Red cell distribution width (RDW)
X Platelet count*
X Reticulocyte count (RETIC)
Red cell morphology
X Lymphocyte count (LYMP)
X Eosinophil count (EOSN)
X Atypical lymphocyte count (ATYP)
Mean platelet volume (MVP)
X Immature WBC
X Polymorphonuclear neutrophils (SEG)
X Nucleated red blood cells (NRBC)
X Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB concentration (MCHC)
Segmented neutrophil count (N-SEG)
X Mean corpuscular volume (MCV)
X Prothrombin time (PT)
X Basophil count (BASO)
X Monocyte count (MONO)
X Band leucocyte (BAND)
Heinz bodies
X Plasma cells (PLASM)

*Recommended by Subdivision F (1984) Guidelines

Results: No dose-related changes in any of the evaluated hematological end points were observed; however, there were considerable individual variations.

(b) Blood (Clinical) Chemistry

Electrolytes

X Calcium*
Chloride*
Magnesium
X Phosphorus*
X Potassium*
X Sodium*

Enzymes

X Alkaline phosphatase (ALP)
X Cholinesterase
Creatine phosphokinase
Lactic acid dehydrogenase
X Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)*
X Gamma glutamyltransferase (GGT)

Other

X Albumin*
X Albumin/globulin ratio
X Blood creatinine*
X Blood urea nitrogen*
X Cholesterol (total)*
X Globulins
X Glucose*
X Total bilirubin*
Direct bilirubin
X Total protein*
X Triglycerides

*Recommended by Subdivision F (November 1984) Guidelines

Results: There was a dose-related decrease in plasma levels of inorganic phosphorus (P) in males at weeks 26, 39, and 52, and in females at weeks 2, 26, 39 and 52. However, this decrease was statistically significant only at week 52: in males (Table 3) fed

TABLE 3. Selected Mean Clinical Chemistry Values in Male Dogs Fed Fenoxycarb for 52 Weeks[a,b]

Dose (mg/kg/day)	ALP (μkat/L)[c]	P (mmol/L)	Tobil (μmol/L)
Week 0			
0	1.44	1.70	1.44
25	1.47 (102)	1.75 (103)	1.57 (109)
80	1.32 (92)	1.81 (106)	1.51 (105)
260	1.65 (115)	1.94 (114)	1.64 (114)
Week 26			
0	0.70	1.46	1.81
25	0.71 (101)	1.33 (91)	1.67 (92)
80	0.58 (83)	1.24 (85)	1.80 (99)
260	1.39*(199)	1.06*(73)	1.80 (99)
Week 39			
0	0.54	1.31	1.00
25	0.72 (133)	1.24 (95)	0.93 (93)
80	0.48 (89)	1.09 (83)	1.19 (119)
260	1.11*(206)	0.99 (76)	1.68*(168)
Week 52			
0	0.53	1.23	0.93
25	0.62 (117)	0.93 (76)	0.81 (87)
80	0.47 (89)	0.84*(68)	1.14 (123)
260	1.30 (245)	0.67*(54)	1.69*(182)

[a]Data were extracted from Study No. B-153'778, Table 287, 288
[b]Data expressed as means (% control)
[c]1 μkat/L = 60 U/L (Enzyme activity in international units (U)

*$p<0.05$

TABLE 4. Selected Mean Clinical Chemistry Values in Female Dogs Fed Fenoxycarb for 52 Weeks[a,b]

Dose (mg/kg/day)	ALP (μkat/L)[c]	P (mmol/L)
Week 0		
0	2.22	1.60
25	1.50 (67.6)	1.57 (98)
80	1.32 (59.5)	1.55 (96.9)
260	1.53 (68.9)	1.65 (103)
Week 2		
0	1.98	1.40
25	1.04 (52.5)	1.32 (94.3)
80	1.06 (53.5)	1.30 (92.9)
260	1.42 (71.7)	1.25 (89.3)
Week 26		
0	1.23	1.26
25	0.67*(54.5)	1.04 (82.5)
80	0.65*(52.8)	1.25 (99.2)
260	1.36 (110.6)	1.14 (90.5)
Week 39		
0	0.98	1.28
25	0.69 (70.4)	1.15 (89.8)
80	0.52*(53.1)	1.11 (86.7)
260	1.16 (118.4)	0.96 (75.0)
Week 52		
0	0.89	1.09
25	0.60 (67.4)	0.92 (84.4)
80	0.45*(50.6)	0.71 (65.1)
260	1.16 (130.3)	0.54*(49.5)

[a]Data were extracted from Study No. B-153'778, Table 288
[b]Data expressed as means (% control)
[c]1 μkat/L = 60 U/L (Enzyme activity in international units (U)

*p<0.05

80 and 260 mg/kg/day and in females (Table 4) fed 260 mg/kg/day. Although the biological significance of this dose-related decrease in P is not clear, it may be an indication of malnutrition.

Statistically significant changes in the levels of alkaline phosphatase (ALP) were observed in male dogs (weeks 26 and 39) fed 260 mg/kg/day. The increase in ALP value in the high dose-males at 52 weeks was not statistically significant when compared to the levels in untreated dogs. The ALP levels were also increased in female dogs (weeks 26, 39 and 52) fed 80 mg/kg/day, and in females (week 26) fed 25 mg/kg/day. These changes may be due to the treatment and related to a significant increase in relative liver weights observed in 260 mg/kg/day male and female dogs. However, histopathological analysis of the liver did not corroborate these findings, the decrease in the ALP values was not seen in the 260 mg/kg/day females, and there was no dose-response for ALP in either male or female dogs.

Statistically significant ($p<0.05$) increase in levels of total bilirubin (Tobil) were observed in male dogs fed 260 mg/kg/day (weeks 39 and 52). These changes may be related to the significant increase in relative liver weight observed in 260 mg/kg/day males.

(c) Urinalysis

Urine was collected by catheterization of the bladder and analyzed at weeks 5, 25, and 50. The samples were inspected for the parameters checked (X) bellow:

X Appearance*	X Sediment (microscopic)	X Bilirubin*
Volume*	X Protein*	X Blood*
X Specific gravity*	X Glucose*	X Nitrite
X pH*	X Ketones*	X Urobilinogen

*Recommended by Subdivision F (November 1984) Guidelines

Results: The minor differences observed in the urinalysis data from treated dogs were no different from those observed in the controls.

5. Sacrifice and Pathology

All animals were subjected to gross pathological examination. The animals were weighed at term, anesthetized with 5-10 mL of phenobarbitone, exsanguinated by incision of the axillary blood vessels, and necropsied. The pituitary was weighed after fixation in 4% buffered formalin. Tissue samples from the following checked (X) organs were examined microscopically after fixation in 4% phosphate buffered formol. The following checked (XX) organs were also weighed:

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Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue	X Aorta*	XX Brain* (3 levels)
X Salivary glands*	XX Heart*	X Peripheral nerve* (sciatic nerve)
X Esophagus*	X Bone marrow*	X Spinal cord* (three levels)
X Stomach*	X Lymph nodes*	X Pituitary*
X Duodenum*	X Spleen*	X Eyes* (Optic nerve)
X Jejunum*	X Thymus*	
X Ileum*		Glandular
X Cecum*	Urogenital	
X Colon*		XX Adrenals*
X Rectum*	XX Kidneys*	Lacrimal gland
XX Liver*	X Urinary bladder*	X Mammary gland
X Gallbladder*	XX Testes*	XX Thyroids*
X Pancreas*	X Epididymides	X Parathyroids*
	X Prostate*	Harderian glands
Respiratory	X Seminal vesicle	
	X Ovaries*	
X Trachea*	XX Uterus*	
X Lungs*		

Other

X Bone (sternum and femur)*
X Skeletal muscle*
X Skin*
X All gross lesions and masses*

*Recommended by Subdivision F (November 1984) Guidelines

(a) Organ Weights

No compound-related effects were observed in absolute or relative organ weights in the low- and intermediate-dose groups. Changes in organ weights were observed in the high-dose (260 mg/kg/day) groups (Table 5). Both male and female dogs had a statistically significant ($p<0.05$) increase in relative liver weights. Relative liver weight in high-dose male and female dogs was 26% and 57% higher, respectively, than control relative liver weight. Absolute brain weight (males) and kidney weight (females) were significantly higher in dogs fed 260 mg/kg/day. The changes in absolute brain weight and in relative liver weight may have been treatment-related, but lack of histopathology indicates that these changes were probably not adverse. There was a significant dose-related decrease in absolute adrenal weight in male dogs fed 80 and 260 mg/kg/day of fenoxycarb. These changes may have also been treatment-related. However, the lack of histopathological findings in the adrenals may be an indication that there were no adverse adrenal effects related to treatment.

(b) Macroscopic Pathology

No compound related lesions were observed in either sex.

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TABLE 5. Selected Mean Organ Weights in Dogs Fed Fenoxycarb for 52 Weeks[a,b]

Dose (mg/kg)	Organ Weight	Brain	Liver	Kidney	Adrenals
		Males			
0	Absolute (g)	80.448	414.925	72.215	1.3500
	Relative (g/100 g)	0.419	2.156	0.378	0.0070
25	Absolute (g)	82.770 (103)	358.775 (86.5)	61.808 (85.6)	1.0425 (77)
	Relative (g/100 g)	0.570 (136)	2.395 (111)	0.430 (114)	0.0072 (102.9)
80	Absolute (g)	78.710 (98)	414.825 (99.9)	71.168 (98.5)	1.0800*(80)
	Relative (g/100 g)	0.512 (122)	2.561 (119)	0.454 (120)	0.0070 (100)
260	Absolute (g)	71.545*(89)	311.000 (75)	64.853 (89.8)	0.8850*(65.6)
	Relative (g/100 g)	0.630 (150)	2.715*(126)	0.565 (149.5)	0.0078 (111)
		Females			
0	Absolute (g)	73.465	236.098	44.718	1.2625
	Relative (g/100 g)	0.615	1.931	0.368	0.0107
25	Absolute (g)	73.370 (99.9)	327.668 (139)	53.390 (119.4)	1.2150 (96)
	Relative (g/100 g)	0.590 (95.9)	2.521 (131)	0.410 (111)	0.0095 (88.8)
80	Absolute (g)	79.780 (109)	345.260 (146)	53.738 (120)	1.2450 (89)
	Relative (g/100 g)	0.547 (89)	2.347 (121.5)	0.364 (98.9)	0.0085 (79)
260	Absolute (g)	72.985 (99)	327.983 (139)	48.105 (107.6)	1.3525 (107)
	Relative (g/100 g)	0.703 (114)	3.033*(157)	0.444*(120.6)	0.0128 (120)

[a]Data were extracted from Study No. B-153'778, Tables 301-304 (males) and Tables 305-308 (females)

[b]The number in parenthesis represents % control

*$p<0.05$

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(c) **Microscopic Pathology**

No compound-related histological changes were observed in any of the examined tissues. Slight morphological changes in the pituitary gland were present in treated female dogs, while treated male dogs had focal, isolated lymphohistiocytic infiltrates in the lungs. The presence of the lymphohistiocytic infiltrates was the most common finding in the liver, esophagus, and salivary glands of treated and control animals.

D. STUDY AUTHOR'S CONCLUSION

Fenoxycarb was given orally by capsule to groups of four beagle dogs/sex for 52 weeks at dose levels of 0, 25, 80, or 260 mg/kg/day. No adverse effects were observed regarding the general condition of the animals, hematology parameters, urinalysis data, ophthalmoscopic findings, or macroscopic and microscopic observations.

Decreased plasma levels of inorganic phosphorus were seen at week 52 in males receiving 80 mg/kg/day. Minor signs of systemic toxicity were observed in both sexes at 260 mg/kg/day and were manifested as stagnation of body weight gain (both sexes), decreased plasma concentration of inorganic phosphorus at week 52 (in males only), increased relative liver weights (in both males and females), and decreased absolute adrenal weights (in males only). These effects were probably due to the reduced food intake and adaptation to the liver overload with the test compound.

The authors determined the NOEL for chronic systemic toxicity to be 25 mg/kg/day based on clinical condition, body weight development, food consumption, laboratory results and organ weights.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS

The data reporting was acceptable, and the summary means that were validated were supported by the individual animal data. The primary effect observed in this study was the decrease in body weight gains in high-dose animals compared to those of controls. This marked decrease in body weight gains in high-dose animals was consistent throughout the study. In the 260-mg/kg/day males the decreased body weight gain was statistically significant ($p<0.05$) for 0-26 and 0-52 week interval. In 260-mg/kg/day females, statistically significant ($p<0.05$) decrease in body weight gain was observed for the 0-13 week period.

The reviewers agree with the NOEL value for systemic toxicity of 25 mg/kg/day for both males and females.

The reviewers agree with a LEL value of 80 mg/kg/day for chronic systemic toxicity. The proposed LEL value is based on a significant decreases in phosphorus and inorganic absolute adrenal gland weight in males at 80 mg/kg/day.

F. CLASSIFICATION: Core Guideline Data.

010721

FINAL

DATA EVALUATION REPORT

FENOXYCARB TECHNICAL

Study Type: Mutagenicity: Mammalian Cells in Culture Cytogenetic Assay in Human Lymphocytes

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

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QA/QC Manager	Sharon Segal, Ph.D.	Date 5/6/93

Contract Number: 68D10075
Work Assignment Number: 2-41.1
Clement Number: 128
Project Officer: Caroline Gordon

010721

GUIDELINE SERIES 84: MUTAGENICITY
MAMMALIAN CELLS IN CULTURE CYTOGENETICS

EPA Reviewer: Irving Mauer, Ph.D. Signature:
Immediate Office, Toxicology Branch I Date: 05 May 93
Health Effects Division (H-7509C)
EPA Section Head: Marion Copley, DVM, DABT Signature: Marion Copley
EPA Review Section IV, Toxicology Branch I Date: 5/14/93
Health Effects Division (H-7509C)

DATA EVALUATION REPORT

CHEMICAL: Insect growth regulator Ro 13-5223/000

Tox Chem. No.: 652C

PC Code: 125301

STUDY TYPE: In vitro mammalian cytogenetics chromosome aberration assay in human lymphocytes

MRID Number: 423438-10

SYNONYMS: Fenoxycarb technical; ethyl [2-(p-phenoxyphenoxy)ethyl] carbamate

SPONSOR: Agricultural Division, Ciba-Geigy Corporation, Greensboro, NC

TESTING FACILITY: Hoffman-La Roche & Co., Ltd., Basle, Switzerland

TITLE OF REPORT: Chromosome Analysis in Human Peripheral Blood Lymphocytes Treated In Vitro with the Insect Growth Regulator Ro 13-5223/000 in Absence and in Presence of a Metabolic Activation System

AUTHOR: J. Dresp

STUDY NUMBERS: Laboratory Study No. 128 M 88; Report No. B-153,586

REPORT ISSUED: February 21, 1989

CONCLUSIONS-EXECUTIVE SUMMARY:

Insect growth regulator Ro 13-5223/000 was reported to be negative for inducing chromosome aberrations in human lymphocytes at doses of 25 µg/mL -S9 and 25 or 50 µg/mL +S9. Severe cytotoxicity was noted at doses ≥50 µg/mL -S9 and ≥100 µg/mL +S9; in addition, the mitotic index was suppressed (≈44% of controls) at 50 µg/mL +S9. However, the study is unacceptable because of several study deficiencies (see Section D, Reviewers' Discussion/Conclusions).

Classification: Unacceptable

This study does not satisfy the requirements for FIFRA Test Guideline 84-2 for in vitro cytogenetic mutagenicity data.

A. MATERIALS:

1. Test Material: Ro 13-5223/000

Description: White granules
Identification numbers: Lot number 2; reference number 29.6.88
Purity: Not reported
Receipt date: Not reported
Stability: Not reported
Contaminants: None listed
Solvent used: Dimethyl sulfoxide (DMSO)
Other comments: The test material was stored at room temperature. The frequency of dosing solution preparation was not reported, and analytical determinations were not performed on dosing solutions.

2. Control Materials:

Negative: Untreated cells in Ham's F10 medium supplemented with 2.5% fetal bovine serum (FBS), L-glutamine, and antibiotics (F10-2.5).

Solvent/final concentration: DMSO/50 µL per culture

Positive:

Nonactivation: Bleomycin sulfate (BS) was prepared in 0.9% NaCl to yield a final concentration of 11.4 µg/mL.

Activation: Cyclophosphamide (CP) was prepared in distilled water to yield a final concentration of 15.0 µg/mL.

3. Activation: S9 derived from male Sprague-Dawley (weight range 167-191 g)

x Aroclor 1254	x induced	x rat	x liver
_____ phenobarbital	_____ noninduced	_____ mouse	_____ lung
_____ none		_____ hamster	_____ other
_____ other:		_____ other	

The S9 homogenate was prepared by the performing laboratory using four animals. The protein concentration of the pooled S9 homogenate was determined to be 39.3 mg/mL. The S9 mix was prepared as follows:

Component	Amount/10 mL
Sodium orthophosphate buffer (0.2 M, pH 7.4)	5.0 mL
Glucose-6-phosphate	15.2 mg
NADP	31.5 mg
$MgCl_2$ (0.4 M)	0.2 mL
H_2O (distilled)	3.8 mL
S9 homogenate	1.0 mL (10%)

4. Test Compound Concentrations Used:[1] Cells were exposed to four dose levels (25, 50, 100, and 150 µg/mL +/- S9). Metaphases recovered from 25 µg/mL -S9 and 25 and 50 µg/mL +S9 were scored for chromosomal aberrations. Duplicate cultures were prepared per dose, per condition.

5. Test Cells: Human lymphocytes were obtained from a 37-year-old male; no further information on the donor was provided. Lymphocyte cultures were initiated in Ham's F10 medium supplemented with 12.5% FBS (F10-12.5); phytohemagglutinin (PHA) was added at a final concentration of 0.13 mL/culture. Cultures were incubated for 24 hours at 37°C prior to treatment.

   Properly maintained? Yes.
   Cell line or strain periodically checked for mycoplasma contamination? Not reported.
   Cell line or strain periodically check for karyotype stability? Not reported.

B. TEST PERFORMANCE:

1. Cell Treatment: Cells were exposed to the nonactivated test compound, negative, solvent or positive control for: 2 hours; cells were exposed to the S9-activated test compound or positive control for: 2 hours.

2. Cytogenetic Assay:

   (a) Treatment: Twenty-four hours after PHA-stimulation, replicate cultures were exposed to the selected test material doses or the positive controls (BS -S9 or CP +S9) in either the presence or absence of S9 activation. Negative and solvent control cultures were included only in the nonactivated phase of testing. At the end of the 2-hour treatment, cells were washed twice, resuspended in Ham's F10-2.5 containing 0.13 mL PHA/culture and 35 µL of 3.3×10^{-5} M BrdU and reincubated for 22 hours. Colcemid (final concentration 0.15 µg/mL) was added to the cultures 2 hours prior to cell harvest at 48 hours post-initiation.

[1]The concentrations used in the cytogenetic assay were based on the findings of a previous study in which nonactivated doses of 0.4-4.0 µg/mL (24-hour treatment) and S9-activated concentrations of 1.0-10 µg/mL (2-hour treatment) did not cause appreciable cytotoxicity.

Metaphase cells were collected, swollen in 0.56% KCl, recentrifuged and fixed in methanol:acetic acid (3:1). Cells were resuspended and dropped onto slides; slides were air-dried, stained with bisbenzimide, irradiated with UV for 90 minutes, stained with 4-5% Giemsa, dried, mounted in Eukitt and coded.

(b) Metaphase analysis: At least 200 metaphase cells in the treatment, negative and solvent control groups (100 cells/culture) and at least 100 metaphase cells in the positive control groups (50 cells/culture) were scored for chromosomal aberrations. The mitotic index (MI) was determined for each treatment, negative, solvent and positive control group.

3. Statistical Methods: The percentage of cells with chromosome aberrations (excluding gaps) was evaluated for statistical significance ($p<0.05$ and 0.01) using Fisher's exact test. Data from the negative and solvent control groups were pooled if no statistical differences between the two control groups were calculated, using Fisher's exact test.

4. Evaluation Criteria: No criteria were provided to establish the validity of the assay, a positive response, or the biological significance of the results.

C. REPORTED RESULTS: The study author stated that an earlier experiment (Study Number 52 M 82), conducted with nonactivated concentrations of the test material ranging from 0.4 to 4.0 µg/mL (with a 24-hour cell treatment) and S9-activated concentrations ranging from 1.0 to 10 µg/mL (2-hour cell treatment), was criticized by an unidentified source "for not evaluating dose levels which caused cytotoxic effects." Summarized data from the rejected study were included in the study report (see Attachment 1). Based on these considerations, the currently reviewed study was conducted with dose ranges of 25-150 µg/mL +/- S9 (2-hour cell treatment for both nonactivated and S9-activated conditions). Results from the nonactivated and S9-activated cytogenetic assays with Ro 13-5223/000 are presented in Table 1. Concentrations ≥50 µg/mL -S9 and ≥100 µg/mL +S9 were severely cytotoxic and were, therefore, not scored for chromosomal aberrations. At 50 µg/mL +S9, the MI was markedly reduced (≈44% of control). There were no appreciable increases in the frequency of structural aberrations at the dose levels scored (i.e., 25 µg/mL -S9 and 25 and 50 µg/mL +S9).

By contrast, the response induced by the nonactivated positive control (11.4 µg/mL BS) was consistent with the reported frequency of structural aberrations in human lymphocytes exposed to an equivalent concentration of BS[2]. However, the performance of the S9-activated control (15.0 µg/mL CP) was relatively poor, with aberrations observed in 4% of the cells,

[2]Dresp, J., Schmid, E., and Bauchinger, M. (1978). The cytogenetic effect of bleomycin on human peripheral lymphocytes in vitro and in vivo. Mutat Res 56:341-353.

Table 1. Results from the In Vitro Cytogenetic Assay in Human Lymphocytes Treated with Ro 13-5223/000

Substance	Dose/mL	S9 Activation	No. of Cells Scored	Mitotic Index (%)	Total No. of Aberrations[a]	Aberrations per Cell	Cells with Aberrations[a] (%)	Biologically Significant Aberrations (No/Type)[b]
Pooled Negative Controls[c]								
Medium and Dimethyl sulfoxide	--	-	400	3.6	4	0.01	1.0	2 CHRI; 1 AC; 1 MIN
Positive Control								
Bleomycin sulfate	11.4 µg	-	200	2.5	52	0.26	14.5*	3 CHRI; 18 AC; 2 MIN; 26 DIC; 3 ATYP
Cyclophosphamide	15.0 µg	+	200	2.1	9	0.05	4.0*	1 CHRI; 1 EX; 6 AC; 1 DIC
Test Material								
Ro 13-5223/000	25.0 µg	-	200	2.7	0	0.00	0.0	--
	25.0 µg	+	200	2.6	2	0.01	1.0	1 AC; 1 DIC
	50.0 µg	+	200	1.6	5	0.03	2.5	3 AC; 1 DIC; 1 ATYP

[a]Gaps excluded
[b]Abbreviations used:

EX = Chromatid exchange; CHRI = Chromosomal break (one or both chromatids); AC = Acentric fragment
MIN = Minute; DIC = Dicentric chromosome; ATYP = Atypical monocentric chromosome

[c]S9-activated negative and/or solvent control groups were not included; however, historical negative control data from 24 experiments were provided. The overall percentage of cells with aberrations for S9-activated negative control cultures was 1.6% (range 0.4-3.0%).
[d]Higher doses (50, 100, and 150 µg/mL -S9; 100 and 150 µg/mL +S9) were severely cytotoxic.

*Significantly ($p<0.01$) higher than summarized (negative and solvent) controls, by Fisher's exact test

Note: Data were extracted from the study report, pp. 25 and 27.

which was only slightly higher than the historical range of background structural aberrations reported by the performing laboratory (0-3%).

Based on the overall results, the study authors concluded that Ro 13-5223/000 was not clastogenic in this in vitro cytogenetic assay.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We assess that the study is unacceptable for the following reasons:

(1) No explanation was provided for decreasing the exposure time for the nonactivated assay from 24 hours (as used in the rejected study) to 2 hours. It is clear that levels ≥50 µg/mL -S9 were cytotoxic; however, in order to facilitate comparison between the results of the two assays, the inclusion of dose levels overlapping those used in the rejected study would have been prudent. In lieu of using such a dosing regimen, a rationale for the shortened exposure period should have been provided.

(2) There are also concerns that the PHA-stimulation of the lymphocytes may have been less-than-optimal. By convention, human lymphocytes are generally stimulated for 44-48 hours prior to chemical treatment to ensure that cells in all stages of the cell cycle are treated and analyzed. However, in this study, lymphocytes were allowed a 24-hour stimulation period prior to treatment. Although the data from the nonactivated positive control (11.4 µg/mL BS) showed clear and significant clastogenic effects, it was of note that all of the induced aberrations were of the chromosome-type, suggesting that the lymphocytes were probably in G_1 at the time of exposure. When S or G_2 cells are exposed, the damage is manifested primarily as chromatid-type aberrations. The lower than expected MIs for the nonactivated negative and solvent controls, in conjunction with the poor performance of the S9-activated positive control (15.0 µg/mL CP), tend to support our concerns that an inadequate number of cells in G_2, the stage that is most sensitive to chemical insult[3], were available for treatment.

(3) Lymphocytes used in the study were derived from a single donor. It is strongly recommended that in vitro human lymphocyte cytogenetic assays be performed with lymphocytes collected from different donors (i.e., each culture at each experimental point should be from separate donors, or the entire experiment should be repeated with new donor lymphocytes).

(4) Information on the purity of the test material was missing.

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[3]Preston, R.J., Au, W., Bender, M.A., Brewen, J.G., Carrano, A.V., Heddle, J.A., McFee, A.F., Wolff, S., and Wassom, J.S. (1981). Mammalian in vivo and in vitro cytogenetic assays: A report of the Gene-Tox program. Mutat Res 87:143-188.

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLPs? Yes. (A quality assurance statement, indicating only that the final report had been reviewed, was signed and dated March 2, 1989.)

CORE CLASSIFICATION: Unacceptable. The study does not satisfy the requirements for FIFRA Test Guideline 84-2 for in vitro cytogenetic mutagenicity data.