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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MAR 3 1995

MEMORANDUM

SUBJECT: Peer Review of Fenoxycarb

Tox Chem No. 652C
PC Code. 125301

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Attached are Sections C, D, E, and F for incorporation into the Peer review Document on Fenoxycarb.

The issues of concern are 1) lung tumors and Harderian gland tumors in male mice, 2) the adequacy of dosing in male and female mice and 3) the adequacy of dosing in female rats.

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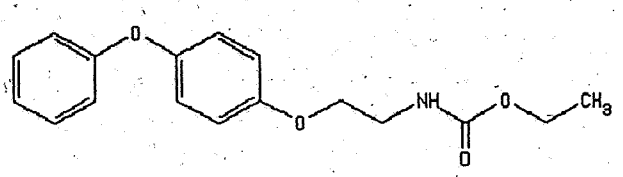
A. and B. Not part of this document - To be completed by the Peer Review Committee.

C. Background Information

Fenoxycarb is an insecticide (insect growth regulator). Its chemical name is ethyl (2-[4-phenoxyphenoxy] ethyl) carbamate. (Other names include RO-13,5233; carbamic acid, [2-4(-phenoxyphenoxy) ethyl-, ethyl ester; 2-(phenoxyphenoxy) ethylcarbamic acid, ethyl ester; ACR 2984F and ACR 2913 Insert Growth Regulator. Its proprietary names are INSEGAR, LOGIC, TORUS, PICTYL and TACTIC. Its chemical structure contains a diphenyl ether group and is shown 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physical and chemical properties of fenoxycarb are described in the Registration Standard for Fenoxycarb (EPA, 1985; unpublished).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 PC Code Number is 125301 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.

D. Evaluation of Carcinogenic Evidence

1. Mouse Chronic Feeding/Carcinogenicity Study (TXR DOC. #s 008101 and 010721)

References:

Everett, D.J., Scott, K.A., Hudson, P. and MacNaughton, F., "80 Week Carcinogenicity/Toxicity Study in Mice," March, 1987, Study No.: Research Report No. B-104'819; Inveresk Research International Report No. 3390/IRI Project No. 430624, Testing Facility: Inveresk Research International, Musselberg, Scotland. MRID Nos. 40376902 and 40972701.

Howroyd, P.C. and Everett, D.J., "Fenoxycarb A Supplement to a Carcinogenicity Study in Mice Original Project No. 430624; EPA MRID Nos.: 40376902 and 40927201," March 17, 1992, MRID No. 42343806.

Hardisty, Jerry, "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 Nos. 40376902 and 40972701," December 11, 1991, MRID No. 42343807.

Everett, D.J., "Fenoxycarb A Supplement to a Carcinogenicity Study in Mice Original Project No. 430624 IRI Project No. 450719 EPA MRID Nos. 40376902 and 40972701," March 17, 1992, MRID No. 42343808.

Hardisty, Jerry, "Fenoxycarb Technical Pathology Peer Review of Liver of Female Mice A Supplement to a Carcinogenicity Study in Mice Original IRI Project No. 430624 EPA MRID Nos. 40376902 and 40972701," November 21, 1991, MRID No. 42343809.

Skripsky, T. and Stevens, J., "Toxicological Evaluation of Fenoxycarb (CGA-114597 Technical,)" June 2, 1992, MRID No. 42364101.

a. Experimental Design

Fenoxycarb (Purity not stated) 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).

b. Discussion of Tumor Data

(1) Harderian Gland Tumors

In the original report, the incidences of benign Harderian gland tumors in single histological sections 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. After examining additional serial sections, IRI and Dr. Francis J.L. 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)	0 ppm (50)	30 ppm (50)	110 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-see MRID No. 40376902 p.120.

At the request of EPA, Ciba-Geigy had J. Hardisty of the Experimental Pathology Laboratory examine the slides and the additional serial sections of the Harderian gland. The results are provided in Table 2.

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

LESION (No. examined)	0 ppm (50)	30 ppm (50)	110 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 see MRID No. 42343807, p.15.

As can be seen, there is little difference between the IRI and Dr. Hardistry's reading of the slides. Statistical analysis of the data was conducted by L. Brunsman using the data present in the original submission (see memorandum dated December 16, 1992). The results are provided in Table 3.

TABLE 3. Male Harderian Gland Tumor Rates+ and Peto Prevalence Test Results[1]

Lesion	0 ppm	30 ppm	110 ppm	420 ppm
Adenoma (%)	7/50(14)[a]	9/50 (18)	6/50(12)	13/46(28)
p =	0.028*	0.324	---	0.047*
Adenocarcinomas (%)	0/42(0)	1/45(2)[b]	1/43(2)	0/37(0)
p =	---	0.167	0.162	---
Combined (%)	7/50(14)	10/50(20)	7/50(14)	13/46(28)
p =	0.041*	0.241	---	0.047*

[1] Taken from the memorandum of L. Brunsman, dated Dec 16, 1992.
+ Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor.
[a] First adenoma observed at week 55, dose 0 ppm.
[b] First adenocarcinoma observed at week 81, dose 30 ppm.
NOTE: Significance of trend denoted at control
Significance of pair-wise comparison with control denoted at dose level
If *, the $p < 0.05$. If **, then $p < 0.01$.

Male mice had significant dose-related increasing trends in Harderian Gland adenomas and combined Harderian Gland adenomas and/or adenocarcinomas. Male mice also had significant differences in the pair-wise comparison of controls with the 420 ppm group for Harderian Gland adenomas and combined Harderian Gland adenomas and/or adenocarcinomas (due to adenomas).

J.D. Everett provided the background incidences of Harderian gland tumors at IRI (see Table 4).

TABLE 4. Historical Control Incidence of Harderian Gland Tumors from 8 Studies Conducted at IRI[1]

Lesion	STUDY NUMBER							
	A	B	C	D	E	F	G	H
Benign	1/1[2]	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] Data extracted from MRID No. 423438-08 table 8, p. 51.
[2] # with tumor/# organs examined

Only data from one study (E) are of any relevance due to the extremely low number of animals examined in the remainder of the studies. Benign Hardarian gland tumors in all male 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.

In conclusion, the incidence of Harderian gland tumors in males in the 420 ppm treated group is greater than concurrent controls.

(2) Lung Tumors (Alveolar/Bronchiolar Adenomas and Carcinomas)

The first reading of the slides are presented in table 5. The data on males demonstrated a statistically significant trend with increasing dose ($p<0.01$).

TABLE 5. Alveolar/Bronchiolar Tumors in Mice (%)[1]

Lesion	0 ppm	30 ppm	110 ppm	420 ppm
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)

1 Data extracted from tables 34 and 35, MRID No. 40376902, pp. 111, 140.
TBA - tumor bearing animals

In MRID No. 42343807, J. Hardisty, of Experimental Pathology Laboratories, Inc. (EPL), reread the slides of male mice for lung tumors. He concluded that there was an increased number of male mice with lung neoplasms in treated groups (Lung TBA:7/50, 13/50, 13/50, 20/50). 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 5).

Statistical analysis, conducted by L. Brunsman using the data present in the original submission (see memorandum of December 16, 1992) are provided in Table 6.

TABLE 6: Male Alveolar/Bronchiolar Tumor Rates+ and Peto Prevalence Test Results (p Values)[1]

Lesion	0 ppm	30 ppm	100 ppm	420 ppm
Adenoma (%)	5/60(8)	7/60(12)	7/60(10)	13/60[a](22)
p =	0.006**	0.312	0.282	0.014*
Carcinomas (%)	2/49(4)	6/50(12)	6/50(12)	7/49(14)[b]
p =	0.163	0.055	0.065	0.041
Combined (%)	7/60(12)	13/60(22)	13/60(22)	20/60(33)
p =	0.004**	0.072	0.067	0.002**

[1] Taken from memorandum of L. Brunsman, dated Dec 12, 1992.
+ Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor.
[a] First adenoma observed at week 28, dose 420 ppm.
[b] First carcinoma observed at week 59, dose 420 ppm.
NOTE: Significance of trend denoted at control
Significance of pair-wise comparison with control denoted at dose level
If *, the $p < 0.05$. If **, then $p < 0.01$.

Male mice had significant increasing trends alveolar/bronchiolar adenomas ($p < 0.01$), combined alveolar/bronchiolar adenomas and/or carcinomas. The male mice also had significant differences in the pair-wise comparisons of the control with 420 ppm dose group or alveolar/bronchiolar adenomas ($p < 0.050$ and combined alveolar/bronchiolar adenomas and/or carcinomas ($p<0.01$).

c. Non-Neoplastic Lesions

Liver Lesions - There are 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). 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 since there was not a well defined dose-response relationship.

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 pigmented macrophages	0	0	0	5*
Foci of necrosis	1	1	0	5

[1] Extracted from table 4 of IRI Project No. 450719, p. 36, MRID No. 42343808.
* $p \leq 0.05$

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Dosing was not adequate for either 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 females based on increased liver weight (21.7%) accompanied by fatty changes, glycogen depletion and increased multinucleated hepatocytes. The NOEL was 100 mg/kg/day. Although there was an increase in the 300 mg/kg/day females of erythrocytes in hepatocytes this was not apparent at 900 mg/kg/day and was not statistically significant. In addition, this lesion would not be adequate evidence of toxicity. In the Sponsor's Pathology 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.

2. Rat Chronic Feeding/Carcinogenicity Study (TXR #s 004569 and 010721)

Reference

Goodyer, M.J., "Ro 13-5223/000: 104-Week Oral (Dietary Administration) Carcinogenicity and Toxicity Study in the Rat with a 52-Week Interim Kill," March, 1986, Study No.: Hazleton Report No. 5191-161/123, Testing facility: Hazleton Laboratories Europe, Ltd., North Yorkshire, England, MRID No. 40376901.

Goodyer, M.J., "Ro 13-5223/000: 104-Week Oral (Dietary Administration) Carcinogenicity and Toxicity Study in the Rat with a 52-Week Interim Kill: Hazleton Report No. 5191-161/123 (Replaces Report No. 5191-161/123 MRID No. 40376901)," March, 1992, MRID No. 42343803.

Hardisty, J., "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. 5191-191/123 EPA MRID No. 40376901," November 21, 1991. MRID No. 42343804.

Stevens, J.T., "Historical Control Data From 18 Studies Conducted at Hazleton Laboratories Europe With Animal Termination Dates Between 1983-1988- Thyroid and Pituitary Tumor Data," Not Dated, MRID No. 42543805.

Skripsky, T., and Stevens, J., "Toxicological Evaluation of Fenoxycarb (CGA-114597 Technical): Emphasis on the Re-examination of Chronic Rodent and Two Generation Reproduction Studies," June 17, 1992, MRID No. 42364101.

a. Experimental Design

Fenoxycarb (96.6%) 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.

b. Discussion of Tumor Data

There was no evidence of carcinogenic potential.

c. Non-Neoplastic Lesions

Liver - **Male** - Select non-neoplastic observations are listed in table 8. 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 (see table 8).

TABLE 8. Select Liver Histopathologic Changes in Males (from reread by Dr. Hardisty - EPL)[1]

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**

[1] Data extracted from EPL report, p. 14, MRID No. 42343804; (statistics taken from table 3, p. 13 of MRID No. 42364101.
* $p \leq 0.05$ (1-tail); ** $p \leq 0.01$ (1-tail): These statistics were conducted on data with the interim sacrifice animals included N=60)

As can be seen in table 9 there is a treatment related increase in SGOT, SGPT and alkaline phosphatase in males at 1800 ppm. The study did not include evaluation of these parameters in the 200 and 600 ppm groups at the interim time points.

TABLE 9. Select Clinical Chemistries at 104 Weeks[1]

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%)*

[1]Data extracted form original report table 5, p. 64, MRID No. 40376901.
* $p \leq 0.05$; ** $p \leq 0.01$

Females - The only histologic treatment related effect noted in the study report in females is hypertrophy (0/50, 0/50, 0/50, 10/49). Increased liver weight was noted as treatment related. This increase was only moderate, with the most severe increase only 32 % over controls in the high dose females. Data are presented in table 10. There is an increase at both 1 and 2 years at 1800 ppm and possibly at 600 ppm. The increase in SGOT, SGPT and alkaline phosphatase in the 1800 ppm group females at term is not statistically significant. These increases are similar for females at earlier time points at 1800 ppm where several 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 10. Female Rat Liver Weight Data Relative to Body Weight[1]

DOSE (ppm)	0	200	600	1800
1 yr	2.461	2.524	2.656	3.130**
Term	2.221	2.209	2.505*	2.941**

[1] Data extracted from original report table 7, pp. 71-2, MRID No. 40376901.
* $p \leq 0.05$; ** $p \leq 0.01$

d. Adequacy of Dosing

Dosing was adequate for males in the high-dose group as evidenced by liver toxicity. There were increases in serum enzymes: SGOT, SGPT and alkaline phosphatase, and increased liver pathology: centrilobular hepatocellular hypertrophy, focal necrosis, focal fibrosis, focal cystic degeneration, basophilic cell focus and segmented macrophages. There was no evidence of adequate toxicity in females in the high-dose group. However, the 1800 ppm dose probably approached an adequate dose level for the following reasons. Toxicity was minimal at 1800 ppm, however, there was evidence that the toxicity profile in females is similar to, but less severe than the males. Females exhibited hypertrophy of the liver, increased alkaline phosphatase and increased liver weights.

E. Additional Toxicology Data on Fenoxycarb

1. Metabolism

Ninety-eight percent of an oral dose (high-dose) of 3000 mg/kg to rats of ^{14}C-fenoxycarb ring-labeled was recovered; 50% in the feces, 42 to 47% in the urine, 0.09% in CO_2 and 0.08% in tissues within 96 hours. Eighty-three percent of the radioactivity in the feces was the parent compound whereas 0.8% of urine radioactivity was the parent compound. Residues were present primarily in the liver, fat, kidney and muscle. Male (27%) and female (25%) urinary metabolites were identified. The major metabolites usually occurred as the sulfate or glucuronic conjugates and were identified as Ro 43-4756, Ro 17-3192, Ro 16-8797 and Ro 43-4764 (2.5 %) (males only). A total of eighteen urinary metabolites were identified. At a dose of 50 mg/kg in rats, most radioactivity was excreted in urine and feces (60 to 80%) in 24 hours and 90 to 92% by 96 hours post-dosing. The metabolic pathway from parent to Ro 17-3193 involves several hydroxylation, oxidation and condensation reactions (see Attachment #1). In a biliary excretion study where rats received 50 mg/kg of fenoxycarb, 37 and 63% were eliminated in the bile of males and females, respectively. Repeated low-dose (50 mg/kg) studies indicated that the highest residues were found in the liver. The material bioaccumulates in fat and metabolism was increased at low doses and with the administration of repeat doses (see MRID Nos. 40376904 and 41241401). Dogs were administered 50, 150 or 500 mg/kg day for 26 weeks. Samples of tissues were obtained at days 1 and 19. Residues in fat ranged from 9.7 to 30.2 ppm, residues in plasma ranged from 0.5 to 2.0 ppm and residues in liver ranged from 0.32 to 0.5 ppm on day 19 (see ACC No. 071780).

2. Mutagenicity

Fenoxycarb has been tested in several mutagenicity studies. Acceptable tests fulfill all three categories for mutagenicity testing, e.g. gene mutation, structural chromosomal aberration and other genotoxic effects. The following studies have been conducted (see Table 15).

Table 15. Mutagenicity Studies on Fenoxycarb

Study	Status
Gene Mutation	
Ames - (Salmonella strains TA98, TA100, TA1535, TA1537, TA1538) Tested at up to 400 µg/disk (Spot test) and 300 µg/plate with and without metabolic activation (ACC No. 247925, Study No. B-96153, Date: 3/17/81. NEGATIVE	Acceptable TXR Doc. No. 002215
CHO-HGPRT Tested at up to 25 µg/ml with and without metabolic activation (ACC No., Study No., Date. not provided) NEGATIVE	Acceptable TXR Doc. No. 002215
CH V 79 Tested at up to 100 mg/ml with and without activation (MRID No. 00071850, Study No. B-96728, Date: 6/11/82) NEGATIVE	Acceptable TXR Doc. No. 002215
Structural Chromosomal Aberration	
In Vitro Chromosomal aberrations (Human Lymphocytes) Tested at up to 25 µg/ml without S9 and up to 100 µg/ml with S9. (MRID No. 42343810, Study No. 128-M-88, Date 2/21/89) NEGATIVE	Unacceptable TXR Doc. No. 010721
Micronucleus-mouse Tested at up to 5000 mg/kg (MRID No. 00130373, Study No. B-96679, Date 7/20/82) NEGATIVE	Acceptable TXR Doc. No. 004178
In Vitro Chromosomal Aberrations (Human Lymphocytes) Tested at levels up to 4.0 µg/ml without activation and 10 µg/ml with activation Reported by sponsor, not reviewed due to serious omissions (MRID No. 4272010-05, Study No. B-96681, Date: 8/11/82). Reported to be negative.	Not reviewed TXR Doc. No. not assigned
Other Genotoxic Effects	
Recombination (Conversion - S. cerevisiae D-7 Tested at up to 0.40 mg/ml (MRID No. 00130371, Study No. B-95594, Date: 6/7/82) NEGATIVE	Acceptable TXR Doc. No. 002215

3. Developmental Toxicity

Developmental toxicity was observed in **rabbits** in the 300 mg/kg day (high-dose) group in two studies, one in which rabbits were dosed with 0, 30, 100 or 300 mg/kg/day fenoxycarb and in a second, subsequent study where rabbits were dosed at 0 or 200 mg/kg/day. In the high dose group there was a slightly increased incidence of spina bifida of the sacral region (3 fetuses in 3/20 litters vs. 0 in either control group, total 53 litters) and possibly increased incidence of hypoplastic tail (4 fetuses in 3/20 litters vs. 1 per control group, or 2/53 litters). The LEL and NOEL for developmental toxicity are 300 and 200 mg/kg/day, respectively (MRID No. 00153125, Study No. B-104700). Maternal toxicity was observed at 200 and 300 mg/kg/day as reduced body weight gain during treatment (24% and 20% less than controls, respectively). The LEL and NOEL for maternal toxicity are 200 and 100 mg/kg/day, respectively. In a **rat developmental toxicity study**, neither maternal toxicity nor developmental toxicity were observed at the highest dose tested of 500 mg/kg/day (MRID No. 00131346, Study No. B-104875).

4. Structure-Activity Correlations

Fenoxycarb is a urethan derivative N-substituted with a phenoxyphenoxyethyl group (Figure 1). Urethan[1] is a known carcinogen in numerous species and is an active initiator of skin tumorigenesis. It produces lung tumors in a multitude of mouse strains and produces Harderian gland tumors in several (3) different strains of mice. N-Substitution would most likely decrease this activity. If N-dealkalation should occur, urethan could potentially be regenerated. Fenoxycarb has Ro43-4764 (2.5 % recovered in urine - males only) and Ro43-4765 (trace in urine) as two of it's metabolites indicating that urethan regeneration is possible. The tumor sites with Fenoxycarb are consistent with those associated with urethan.

Fenoxycarb is also structurally related to the diphenyl ether pesticides[2] Hoelon, Oxyfluorfen, Fomesafen, Lactofen, Acifluorfen, Nitrofen and Verdict. The structures of these

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[1] Chemical Induction of Cancer - Structural Bases and Biological Mechanism (Vol IIIA, Aliphatic Carcinogens) by J. Arcos, Y.T. Woo and M. Argus, pp 400-507 (1982).

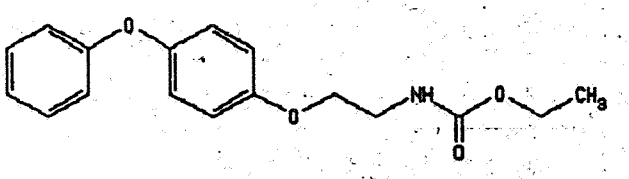
[2] This SAR was discussed in detail in the Carcinogenicity Peer Review memorandum on Hoelon (see memorandum of W. Dykstra and E. Rinde, 5/26/93).

compounds are shown in Figure 1. It should be noted however, that Fenoxycarb would be less potent since it lacks the chlorine and branching side chains present in these chemicals[3].

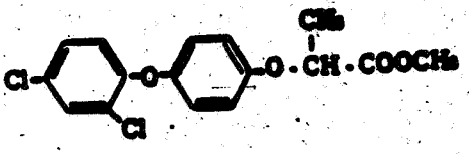
[3] Carcinogenicity and Pesticides - Principles, Issues, and relationships, Edited by N. Ragsdale and R. Menzer, pp 184-5 (1989).

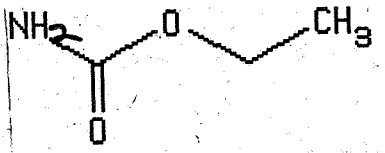
Figure 1: Structures of Diphenyl Ether Analogues

Fenoxycarb



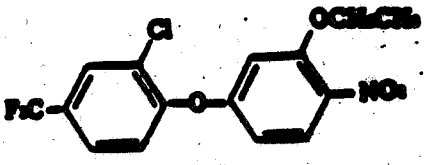
Hoelon



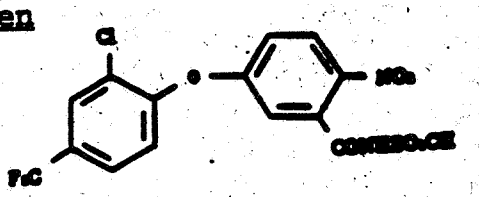


URETHAN

Oxyfluorfen



Fomesafen



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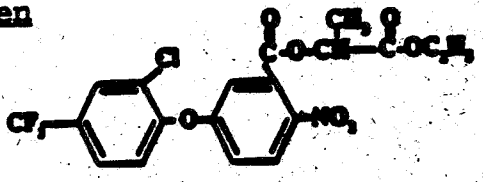

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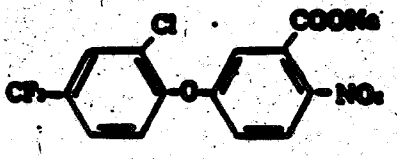
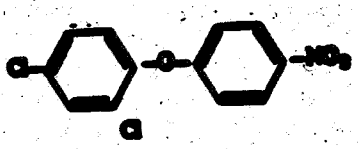
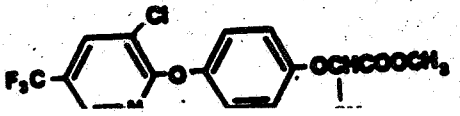


Nitrofen



Verdict®



5. Acute, Subchronic and Chronic Toxicity

a. Acute Toxicity

The acute oral LD_{50} for fenoxycarb is greater than 10,000 mg/kg in rats (Toxicity Category IV). The acute dermal LD_{50} is greater that 2 g/kg (Toxicity Category IV). The inhalation LC_{50} is greater than 4.434 mg/l (Toxicity Category III). Fenoxycarb produces mild erythema of the conjunctive of the eyes (Toxicity Category III). No dermal irritation was observed when a 40% solution of fenoxycarb in corn oil was placed on the backs of rabbits at a level of 2000 mg/kg (Toxicity Category IV). Fenoxycarb is not a skin sensitizer.

b. Subchronic Toxicity

(1) Oral Toxicity

In a **90-day feeding study in rats**, the rats exhibited toxicity at all three dose levels tested: 80, 250 or 800 mg/kg/day. At 80 mg/kg/day, there were increases in absolute and relative liver weights. At 250 mg/kg/day there were increases in absolute and relative thyroid weights, alopecia, cholesterol and decreases in male body weight, erythrocytes, hemoglobin and hematocrit in females and increased follicular activity in the thyroid, hepatocyte hypertrophy and decreased glycogen in the liver. At 800 mg/kg/day there was an increase in the incidence of "soiled tail" and diuresis. The NOEL was less than or equal to 80 mg/kg/day. The LEL was 750 mg/kg/day. (MRID No. 00131802, Study No. B-104779). A **13-week feeding study in mice** was conducted at dose levels of 100, 300 or 900 mg/kg/day. The absolute and relative weight of the liver was increased in females at 300 and 900 mg/kg/day. At 300 and 900 mg/kg/day there were increase in fatty changes, glycogen depletion and increased multinucleated hepatocytes. The NOEL was 100 mg/kg/day and the LEL was 300 mg/kg/day (MRID No. 00131345, Study No. B-104802). A **6-month oral toxicity study in dogs** was conducted at dose levels of 50, 150 or 500 mg/kg/day. The only effect observed was a decrease in body weight gain at 500 mg/kg/day. The NOEL was 150 mg/kg/day and the LEL was 500 mg/kg/day (MRID No. 00132221, Study No. B-104927).

(2) Dermal toxicity

A **21-day dermal toxicity study was conducted in rats** at dose levels of 20, 200 or 2000 mg/kg/day. Increases

in absolute and relative liver weights and slight liver hypertrophy were observed in the 2000 mg/kg/day group. The NOEL was 200 mg/kg/day and the LEL was 2000 mg/kg/day (MRID No. 00146601, Study No. 4552-161/157).

(3) Inhalation toxicity

A 21-day inhalation toxicity study was conducted in rats at dose levels of 0.01, 0.1 or 1.13 mg/l for 6 hours/day, 5 days/week. Decreased body weight gain in males and increased absolute liver weights in females were observed at 1.13 mg/l (MRID No. 40355801, Study No. 085500).

c. Chronic toxicity

A 1-year chronic toxicity study in dogs was conducted at dose levels of 25, 80 or 260 mg/kg/day. At 80 mg/kg/day decreased absolute adrenal gland weight and decreased inorganic phosphoric were observed in males. In addition, at 260 mg/kg/day there were decreased body weight gains and decreased food consumption in males. At this level inorganic phosphorus was decreased in females. The NOEL was 25 mg/kg/day and the LEL was 80 mg/kg/day (MRID No. 42355601, Study No. B-153'778). The results of the two year rat chronic toxicity/carcinogenicity study and 80-week mouse chronic toxicity/carcinogenicity study have been summarized in Section D.

In a **two generation reproduction study in rats** maternal toxicity was observed at 600 and 1800 ppm (approximately 47 and 140 mg/kg/day, respectively) and liver effects, including increased absolute and relative organ weights. At 1800 ppm there was also an increased incidence 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/systemic toxicity was observed at 1800 ppm as a decrease in pup weight (decrement ranging from 10-21% depending on generation/ litter). The reproductive/systemic LEL is 1800 ppm and the NOEL is 600 ppm (MRID Nos. 40376903, 42343812 and 42364101, Study No. 4223-161/124).

F. Weight of Evidence Considerations

The Committee is asked to consider the following facts regarding the toxicology data on fenoxycarb in a weight-of-the-evidence determination of carcinogenic potential:

1. Fenoxycarb was associated with a statistically significant increase in Harderian gland tumors in male mice in the high-dose group.

2. Fenoxycarb was associated with a statistically significant increase in lung bronchiolar/alveolar tumors in male mice in the high-dose group.

3. Dosing was not adequate for male or female mice due to the absence of adequate toxicity to assess carcinogenic potential. Doses in the main study were not supported by a 90-day study.

4. Fenoxycarb was not associated with increased incidences of neoplasm in Crl:CD(SD)Br Sprague-Dawley derived rats dietary levels up to 1800 ppm. Dosing was considered to be adequate for males in the high-dose group base on liver toxicity: centrilobular hepatocellular hypertrophy, focal necrosis, focal fibrosis, focal cystic degeneration, basophilic cell focus and pigmented macrophage. Liver toxicity was minimal in females, i.e. hepatocellular hypertrophy, increased liver weights and increased alkaline phosphatase. There was no evidence of adequate toxicity in females in the high dose group.

5. Fenoxycarb was not genotoxic in several mutagenicity assays.

6. Fenoxycarb is structurally related to urethane a known carcinogen.

G. Not in this document (to be prepared by the Peer Review Committee)

ATTACHMENTS

Attachment 1. Metabolic Pathway for Fenoxycarb

FIGURE 1. METABOLIC PATHWAY OF FENOXYCARB IN THE RAT

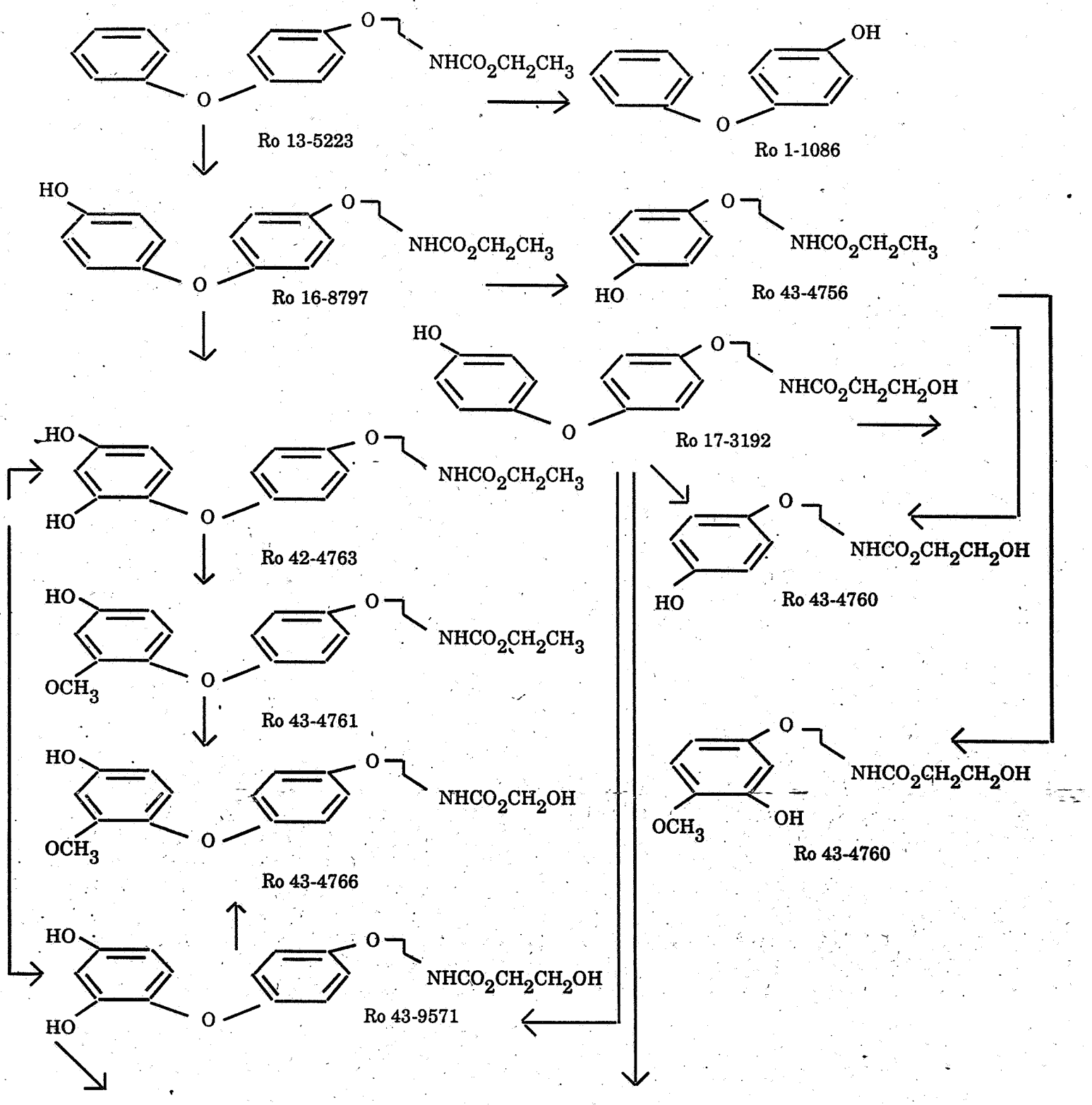


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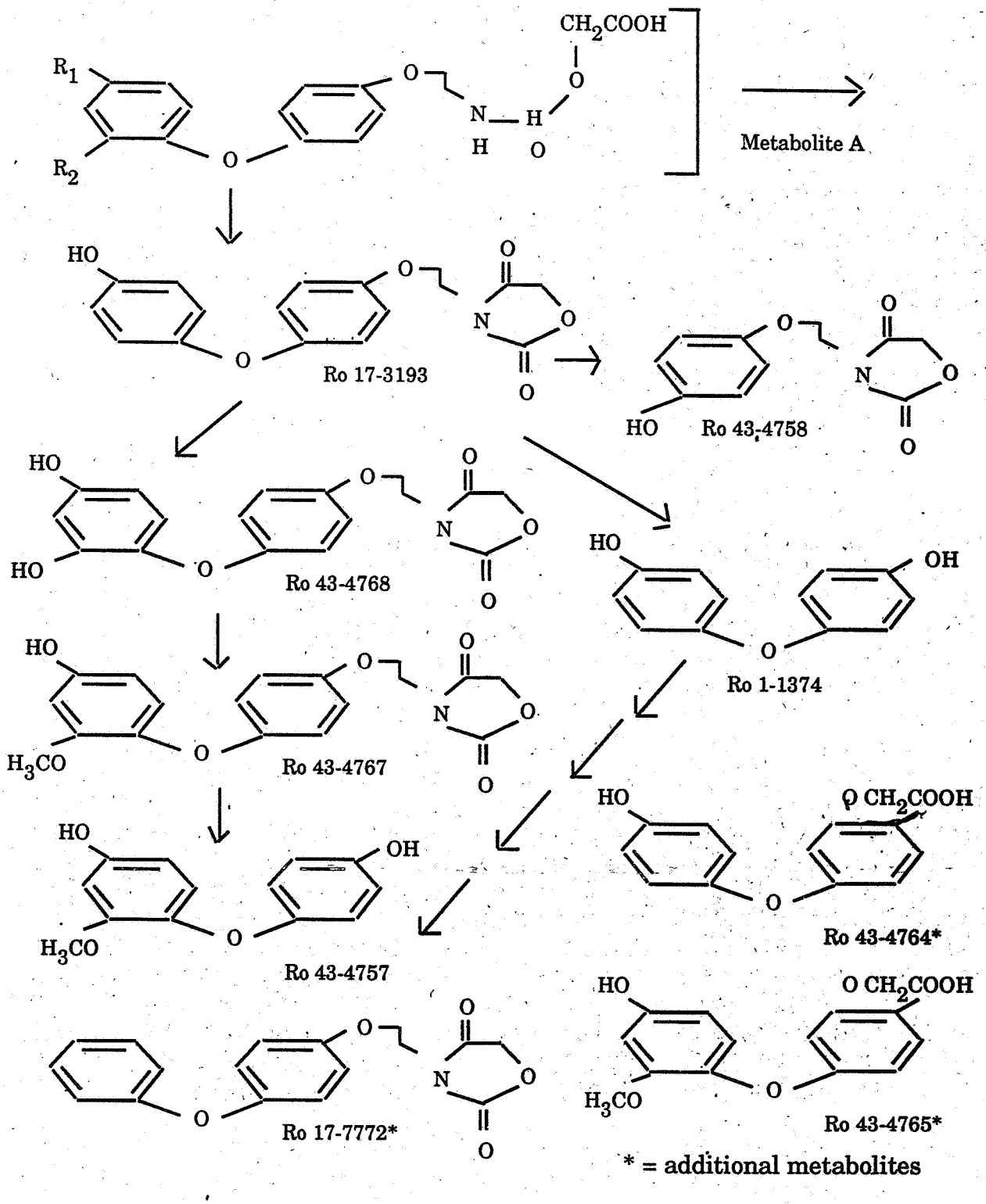
FIGURE 1: METABOLIC PATHWAY OF FENOXYCARB IN THE RAT (Continued)



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Attachment 2. DER of the Mouse 80-Week Chronic/Carcinogenicity Study (With Upgrade)

Attachment #2

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

EPA Reviewer: William Greear, M.Ph. William B. Greear, Date 12/21/93
Review Section 4, Toxicology Branch 1 (7509C)
EPA Secondary Reviewer: Marion Copley, D.V.M. Marion Copley, Date 12/21/93
Review Section 4, Toxicology Branch 1 (7509C)

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."

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 DOSE (No. examined)	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 DOSE (No. examined)	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).

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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.

008101

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

DATA EVALUATION REPORT

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

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

Test Material: Fenoxycarb

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

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

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

Testing Facility: Inveresk Research International
Musselburg, Scotland

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

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

Report Issued: March 1987

Conclusions:

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

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

Carcinogenicity

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

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

Carcinogenicity: Classification is pending the outcome of the Peer Review Committee Meeting

A. Materials:

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

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

B. Study Design:

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

Chronic Toxicity Study

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

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

Carcinogenicity Study

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

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

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

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

2. Diet Preparation - A 2000 ppm premix was prepared by mixing the test material with the untreated diet. The formulated diets were then prepared by mixing the premix with the untreated diet for 20 min. Fresh diets were prepared weekly up to week 14 and then were prepared every 2 weeks. Analysis of the test diets was periodically conducted over a 73 week period; however, the methods were not described.

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

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

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

C. Methods and Results

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

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

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

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

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

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

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

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

   Mean Compound Intake (mg/kg/day)

   Carcinogenicity Study

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

   Chronic Toxicity Study

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

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

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

a. Hematology

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

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

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

b. Clinical Chemistry

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

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

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

Selected Group Mean Clinical Chemistry Data

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

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

Selected Group Mean Clinical Chemistry Data (cont'd)

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

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

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

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

Results - The results of the urinalysis were unremarkable.

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

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

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

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

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

1) The types of lesion observed.

2) The number of animals showing the lesion.

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

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

c. Microscopic Pathology

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

Selected Liver Lesions in Female Mice

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

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

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

Alveolar/Bronchiolar Tumors in Mice

Males
Dose (ppm)

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

Females
Dose (ppm)

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

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

Incidence of Lung Tumors in Males[1]

Dose Level (ppm)

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

[1] Includes first and second set of slides.

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

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

Incidence of Harderian Gland Tumors in Male Mice

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

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

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

D. Discussion

The study consisted of a carcinogenicity study of 80 weeks in duration utilizing three dosage levels (males: 30, 110, and 420 ppm; females: 20, 80, and 320 ppm) and a chronic toxicity study of 52 weeks plus a 6-week recovery phase for a control and a high-dose group. There were no clinical signs of toxicity reported and mortality was similar for control and treated animals. Test material intake for the low-, mid-, and high-dose groups was 5.3, 19.3, and 73.9 mg/kg/day for males and 4.4, 16.9, and 72.2 mg/kg/day for females in the carcinogenicity study. In the chronic toxicity study, test material intake for the low-, mid-, and high-dose groups was 5.0, 21.7, and 81.8 mg/kg/day for males and 4.8, 18.2, and 71.6 mg/kg/day for females. Treatment did not affect

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

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

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

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

Attachment

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

	Group 1	Group 2	Group 3	Group 4
Lung tumors				
Worst grade = 4		66 99	147	153
Worst grade = 3	10 28	54 57 62 68	113 129 132 134 148	154 157 187 195 196 200
Worst grade = 2	5 14	52 92	116 150	152 160 172
Worst grade = 1	8 20 41	67 71 78 88 94	102 119 141 142 144	151 164 167 175 176 177 179 186 189 193

Attachment 3. DER of the Rat 2-Year Chronic/Carcinogenicity Study (With Upgrade)

Attachment # 3

[Fenoxycarb] 2-yr Chronic/onco Study (83-5)

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 12/20/93
William B. Greear, Date 12/21/93

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

STUDY TYPE: Two-year Chronic/onco - Rat (83-5)

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

DP Bar Code: D179471, D188212, D179484

MRID NO.: 1) 42343803; 2) 42343804; 3) 42343805; 4) 42364101 (original MRID 40376901)

TEST MATERIAL: Fenoxycarb

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

STUDY NUMBER(S): 5191-161/123R (original study number 5191-161/123)

SPONSOR: Maag Agrochemicals/Research and Development/HLR Sciences, Inc. Vero Beach, Fla. (original sponsor); Ciba-Geigy (current registrant)

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

TITLE OF REPORT: 1) 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 study # 5191-191/[1[1]]23 MRID 40376901; 2) 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. 5191-191/123 EPA MRID number 40376901; 3) Historical control data from 18 studies conducted at Hazleton Laboratories Europe with animal termination dates between 1983-1988 - thyroid and pituitary tumor data; 4) Toxicological evaluation of Fenoxycarb (CGA-114597 technical): Emphasis on the re-examination of chronic rodent and two-generation reproduction studies.

AUTHOR(S): 1) M.J.Goodyer; 2) J.Hardisty; 3) J.T.Stevens; 4) T.Skripsky and J.Stevens (main study - M.Goodyer)

REPORT ISSUED: 1) March 1992; 2) Nov. 21, 1991; 3) not dated; 4) June 17, 1992(original

[1] Original study number was incorrectly noted in this title, should be 123 not 23

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

(5C)

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.

(52)

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 .

(55)

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.

55

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.

[redacted] 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.

(56)

Proliferative Lesions of the Pituitary Gland

Focal Hyperplasia

- Focal increase in the number of cells of the same type
- Poorly delineated and blends with adjacent normal tissue
- No compression at borders
- Vascular pattern usually normal
- Arrangement of cells may be slightly altered
- Cells may be normal or hypertrophied

Adenoma

- Well-delineated circumscribed mass of cells
- Some compression of adjacent normal tissue
- Altered vascular pattern; angiectasis often present
- Arrangement of cells is altered
- Cellular hypertrophy may be present
- Cellular atypia and pleomorphism may be present

Carcinoma

- Unequivocal invasion of pars nervosa, brain, or other surrounding tissues

Proliferative lesions in the thyroid gland involved both follicular cells and C-cells and were classified as either hyperplasia, adenoma or carcinoma. The criteria used for the classification of proliferative lesions in the thyroid glands are those established by the National Toxicology Program[2] and are summarized below:

Proliferative Lesions of Thyroid Follicular Epithelium

Focal Follicular Cell Hyperplasia:

- Increased cellularity (focal with simple papillary infoldings of the follicular epithelium)
- Cells hypertrophied but generally uniform in morphology

Follicular Cell Adenoma:

- Discrete and well-demarcated mass; generally not encapsulated
- Compression of adjacent tissue
- Growth pattern that varies from normal (complex papillary or follicular)
- Cells well differentiated but abnormal in size and staining quality
- Cell nuclei abnormal in size and chromatin content (e.g., small and hyperchromatic or large with prominent nucleoli)
- No invasion of capsule, adjacent tissue, or metastases

Follicular Cell Carcinoma:

- Obvious mass without well-demarcated boundaries
- Disorganized or varied growth pattern
- Growth in solid clusters or sheets
- Anaplasia; cellular pleomorphism and atypia
- Neoplastic cells associated with scirrhous reaction
- Invasion of capsule, adjacent tissue, or metastases

Proliferative Lesions of Thyroid C-cells

C-cell Hyperplasia:

- Increased numbers of C-cells involving most follicles within the plane of section when diffuse
- Small nodular accumulation of C-cells that partially displaces the follicular epithelium of an individual follicle when focal
- Lesion less than five normal follicles in diameter
- Cellular morphology is normal or there may be minimal to mild hypertrophy

C-Cell Adenoma:

- Discrete mass of C-cells
- Usually larger than five normal follicles in diameter
- Displacement and compression of surrounding follicles
- Minimal to mild atypia

C-cell Carcinoma:

- Invasion into capsule or adjacent tissue
- Metastases to regional lymph nodes or lungs
- Cellular anaplasia

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

DATA EVALUATION REPORT 008101

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

TOX Chem No.: 652C

MRID No.: 40376901

Test Material: Fenoxycarb

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

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

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

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

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

Author: M.J. Goodyer

Report Issued: November 1986

Conclusions:

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

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

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

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

Classifications: Supplementary

Justification of Classification:

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

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

A. Materials:

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

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

B. Study Design:

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

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

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

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

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

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

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

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

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

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

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

C. Methods and Results:

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

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

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

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

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

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

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

Group (ppm)	Week						
	0	16	32	48	64	80	104
Control	169.2	512.9	592.2	658.5	694.7	706.9	736.6
200	172.4	495.7	577.5	650.0	676.6	688.6	707.4
600	169.8	506.9	590.3	663.4	699.9	719.9	747.8
1800	166.1	476.0	554.7	612.5	653.3	668.7	711.2

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

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

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

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

Mean Compound Intake (mg/kg/day)

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

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

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

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

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

The CHECKED(X) parameters were determined.

a. Hematology

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

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

b. Clinical Chemistry

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

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

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

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

The group mean data are summarized in the table below:

Selected Group Mean Clinical Chemistry Data

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

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

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

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

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

Results - Unremarkable.

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

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

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

b. Gross Pathology - Unremarkable.

c. Microscopic Pathology

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

Selected Lesions of the Lung

	Males				Females			
ose (ppm)	0	200	600	1800	0	200	600	1800
oamy histiocytes	6	6	6	12	11	3	11	31
ranuloma	0	0	0	4	1	0	1	5

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

Selected Liver Lesions

	Males				Females			
ose (ppm)	0	200	600	1800	0	200	600	1800
icrocystic degeneration	13	19	23	28	0	1	1	3
ocal necrosis	1	6	18	19	2	2	6	0
ibrosis	0	3	3	12	0	0	0	6
ypertrophy	0	0	8	22	0	0	0	10
igmented histiocytes	0	0	2	4	0	0	0	0

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

Pituitary Neoplasms

	Males				Females			
ose (ppm)	0	200	600	1800	0	200	600	1800
denoma	27	12	15	20	32	13	25	35
arcinoma	1	2	2	6	14	14	10	9

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

D. Discussion:

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

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

E. Deficiencies:

The study suffers from several deficiencies. Many of the parameters that were measured were not statistically analyzed. Examples of this are no statistical analysis of body weight, food consumption, hematology values and the results of the histopathology examination. In the clinical chemistry examination, no determinations were made for SGOT, SGPT, and alkaline phosphatase for rats in the 200 and 600 ppm groups at 25, 51, and 73 weeks even though positive results were obtained for the 1800 ppm group. Tissue accountability tables are absent, therefore, it is impossible to determine how many animals had a complete set of tissues examined. It is unknown how many sets of tissues (or partial sets were lost to autolysis, cannibalism, etc. Most important, it is impossible to determine the actual percent incidence of lesions within groups of animals. Also, conspicuously missing from the individual pathology sheets is the date of death of the animal which would be of use in analyzing the data. The sponsor should provide information on the time-weighted average daily intake of the test material. Historical control data are required for the pituitary tumors as noted above. This should present the data by study for 2+ years on either side of this present study. the data should be from the same laboratory, using the same strain of rat and be for the same duration. The Tumors should be listed for the malignant Tumors, benign Tumors and pituitary Tumor bearing animals (sexes separate).

Attachment 4. Qualitative Risk Assessment Document

Attachment #4

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

DEC 16 1992

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

SUBJECT: Fenoxycarb Qualitative Risk Assessment
Charles River Crl:CD(SD)BR Sprague-Dawley Rat
and Charles River CD-1 Mouse Dietary Studies

Caswell No. 652C

TO: William B. Greear, Toxicologist
Review Section IV
Toxicology Branch I
Health Effects Division (H7509C)

FROM: Lori L. Brunsman, Statistician
Statistics Section
Science Analysis Branch
Health Effects Division (H7509C)

Lori L. Brunsman 12/16/92

THROUGH: Bernice Fisher, Biostatistician
Statistics Section
Science Analysis Branch
Health Effects Division (H7509C)

for B. Fisher 12/16/92

Summary

The qualitative risk assessment of Fenoxycarb was based upon chronic toxicity/oncogenicity studies conducted in Charles River Crl:CD(SD)BR Sprague-Dawley rats and Charles River CD-1 mice. The rats were fed 0, 200, 600, or 1800 ppm of Fenoxycarb for 105 weeks. Each rat dose group consisted of 60 animals per sex. The male mice were fed 0, 30, 110, or 420 ppm of Fenoxycarb for 81 weeks. The female mice were fed 0, 20, 80, or 320 ppm of Fenoxycarb for 81 weeks. Each mouse dose group consisted of 60 animals per sex.

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Fenoxycarb in either male or female rats.

Male rats had significant dose-related increasing trends in pituitary carcinomas. There were no significant differences in the pair-wise comparisons of the controls with the dosed groups.

No compound-related tumors were observed in female rats.

The statistical evaluation of mortality indicated a significant increasing trend in male mice. There were no significant differences in the pair-wise comparisons of the controls with the dosed groups. The female mice indicated no significant incremental changes with increasing doses of Fenoxycarb.

Male mice had significant dose-related increasing trends in alveolar/bronchiolar adenomas, combined alveolar/bronchiolar adenomas and/or carcinomas, harderian gland adenomas, and combined harderian gland adenomas and/or adenocarcinomas. The male mice also had significant differences in the pair-wise comparisons of the controls with the 420 ppm dose group for alveolar/bronchiolar adenomas, combined alveolar/bronchiolar adenomas and/or carcinomas, harderian gland adenomas, and combined harderian gland adenomas and/or carcinomas.

No compound-related tumors were observed in female mice.

Background

A 105-week chronic toxicity/oncogenicity study in Charles River Crl:CD(SD)BR Sprague-Dawley rats was conducted by Hazleton Laboratories Europe, Ltd., North Yorkshire, England, for Maag Agrochemicals, Vero Beach, Florida, issued November, 1986 (Report No. 5191-161/123; MRID No. 403769-01).

The study design allocated groups of 60 rats per sex to dose levels of 0, 200, 600, and 1800 ppm of Fenoxycarb. Ten animals per sex per dose were designated for interim sacrifice at week 53.

An 80-week chronic toxicity/oncogenicity study in Charles River CD-1 mice was conducted by Inveresk Research International, Musselburg, Scotland, for Maag Agrochemicals, Vero Beach, Florida, issued March, 1987 (Research Report No. B-104'819; IRI Report No. 3390; IRI Project No. 430624; MRID Nos. 403769-02 and 409727-01).

The study design allocated groups of 60 mice per sex to each dose level. Dose levels for male mice were 0, 30, 110, and 420 ppm of Fenoxycarb. Dose levels for female mice were 0, 20, 80, and 320 ppm of Fenoxycarb. Ten animals per sex per dose were designated for interim sacrifice at week 53.

Survival Analysis

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Fenoxycarb in male or female rats. See Tables 1 and 2 for test results.

In male mice there was a statistically significant increasing trend ($p < 0.05$) for mortality with incremental doses of Fenoxycarb. There were no significant differences in the pair-wise

comparisons of the controls with the dosed groups. The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Fenoxycarb in female mice. See Tables 3 and 4 for test results.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analysis

Male rats had significant increasing trends in pituitary carcinomas ($p < 0.05$). There were no significant differences in the pair-wise comparisons of the controls with the dosed groups. This statistical analysis of tumor rates was based upon the Cochran-Armitage trend test and the Fisher's Exact test for pair-wise comparisons since there was no significant statistical evidence of differential mortality with increasing doses of Fenoxycarb (Table 5).

No compound-related tumors were observed in female rats.

Male mice had significant increasing trends in alveolar/bronchiolar adenomas ($p < 0.01$), combined alveolar/bronchiolar adenomas and/or carcinomas ($p < 0.01$), harderian gland adenomas ($p < 0.05$), and combined harderian gland adenomas and/or adenocarcinomas ($p < 0.05$). The male mice also had significant differences in the pair-wise comparisons of the controls with the 420 ppm dose group for alveolar/bronchiolar adenomas ($p < 0.05$), combined alveolar/bronchiolar adenomas and/or carcinomas ($p < 0.01$), harderian gland adenomas ($p < 0.05$), and combined harderian gland adenomas and/or carcinomas ($p < 0.05$). This statistical analysis of tumor rates was based upon Peto's prevalence test since there was differential mortality with increasing doses of Fenoxycarb in male mice (Tables 6 and 7).

No compound-related tumors were observed in female mice.

Table 1. Fenoxycarb - Charles River Crl:CD(SD)BR Rat Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-26	27-52	53[i]	53-78	79-105[f]	Total
0	0/60	0/60	10/60	1/50	11/49	12/50 (24)
200	1/60	0/59	10/59	2/49	14/47	17/50 (34)
600	0/60	2/60	9/58	6/49	9/43	17/51 (33)
1800	0/60	0/60	10/60	4/50	9/46	13/50 (26)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Fenoxycarb - Charles River Crl:CD(SD)BR Rat Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-26	27-52	53[i]	53-78	79-106[f]	Total
0	0/60	0/60	10/60	3/50	9/47	12/50 (24)
200	0/60	0/60	10/60	3/50	8/47	11/50 (22)
600	0/60	1/60	10/59	3/49	17/46	21/50 (42)
1800	0/60	1/60	10/59	4/49	13/45	18/50 (36)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 3. Fenoxycarb - Charles River CD-1 Mouse Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-26	27-52	53[i]	53-78	79-81[f]	Total
0	0/60	1/60	9/59	6/50	2/44	9/51* (18)
30	0/60	1/60	9/59	3/50	2/47	6/51 (12)
110	0/60	0/60	10/60	5/50	2/45	7/50 (14)
420	0/60	2/60	9/58	8/49	3/41	13/51 (25)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 81.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. Fenoxycarb - Charles River CD-1 Mouse Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-26	27-52	53[i]	53-78	79-81[f]	Total
0	1/60	2/59	10/57	4/47	2/43	9/50 (18)
20	2/60	3/58	10/55	4/45	2/41	11/50 (22)
80	0/60	4/59[a]	8/55	4/47	0/43	8/51 (16)
320	0/60	4/60	10/56	2/46	1/44	7/50 (14)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[a]One accidental death at week 35.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 81.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 5. Fenoxycarb - Charles River Crl:CD(SD)BR Rat Study

Male Pituitary Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors:	0	200	600	1800
Adenomas (%)	27[a]/60 (45)	12/59 (20)	15/58 (26)	20/60 (33)
p =	0.419[n]	0.004[**n]	0.024[*n]	0.131[n]
Carcinomas (%)	1/60 (2)	2/59 (3)	2/58 (3)	6[b]/60 (10)
p =	0.010[*]	0.494	0.487	0.057
Combined (%)	28/60 (47)	14/59 (24)	17/58 (29)	26/60 (43)
p =	0.203[n]	0.007[**n]	0.040[*n]	0.427[n]

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[n]Negative trend or negative change from control.

[a]First adenoma observed at week 53, dose 0 ppm.

[b]First carcinoma observed at week 61, dose 1800 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 6. Fenoxycarb - Charles River CD-1 Mouse Study

Male Alveolar/Bronchiolar Tumor Rates[+] and
Peto Prevalence Test Results (p values)

	Dose (ppm)			
Tumors:	0	30	110	420
Adenomas (%)	5/60 (8)	7/60 (12)	7/60 (12)	13[a]/60 (22)
p =	0.006**	0.312	0.282	0.014*
Carcinomas (%)	2/49 (4)	6/50 (12)	6/50 (12)	7[b]/49 (14)
p =	0.163	0.055	0.063	0.041
Combined (%)	7/60 (12)	13/60 (22)	13/60 (22)	20/60 (33)
p =	0.004**	0.072	0.067	0.002**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor.

[a]First adenoma observed at week 28, dose 420 ppm.

[b]First carcinoma observed at week 59, dose 420 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 7. Fenoxycarb - Charles River CD-1 Mouse Study

Male Harderian Gland Tumor Rates[+] and
Peto Prevalence Test Results (p values)

	Dose (ppm)			
Tumors:	0	30	110	420
Adenomas	7[a]/50	9/50	6/50	13/46
(%)	(14)	(18)	(12)	(28)
p =	0.028*	0.324	-	0.047*
Adenocarcinomas	0/42	1[b]/45	1/43	0/37
(%)	(0)	(2)	(2)	(0)
p =	-	0.167	0.162	-
Combined	7/50	10/50	7/50	13/46
(%)	(14)	(20)	(14)	(28)
p =	0.041*	0.241	-	0.047*

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor.

[n]Negative change from control.

[a]First adenoma observed at week 55, dose 0 ppm.

[b]First adenocarcinoma observed at week 81, dose 30 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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Attachment 5. One-Liners

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: 06/13/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ 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

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P.C. CODE 125301- N-[2-(p-Phenoxyphenoxy)ethyl]carbamic acid FILE LAST PRINTED: 06/13/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
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)	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 macropahges, focal necrosis and focal angietasis? 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% (Fenxoycarb)	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
83-1(b) Feeding-1 year Species: dog Hoffman LaRoche, Switz. B-153-778; 06/30/88	Fenoxycarb 96.6%	423556-01	NOEL = 25 mg/kg/day. LOEL = 80 mg/kg/day (based on decrease in adrenal weight and decreased inorganic phosphorus. In addition, at 260 mg/kg/d there was a decrease in body wt. gain, decr. feed consumption.		Guideline 010721
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 010870 011020
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, 30, 100, and 300 mg/kg/day. Teratogenic NOEL > 300 mg/kg (HDT) Maternal NOEL = 100 mg/kg. Maternal LEL = 300 mg/kg (reduced body weight gain). Fetotoxic NOEL > 300 mg/kg (HDT).		Minimum 004319

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P.C. CODE 125301- N-[2-(p-Phenoxyphenoxy)ethyl]carbamic acid FILE LAST PRINTED: 06/13/94

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%	403769-03 423438-11	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. Maternal toxicity was observed at 600 and 1800 ppm as liver effects, including incr. absolute and relative organ weight. At 1800 ppm there was also incr. incidences of slight focal necrosis and hypertrophy (0% controls, 43-96% high dose) however, low & mid dose livers were not examined histologically. The systemic LEL and NOEL could not be determined since livers were not evaluated at all doses. Reprod. Tox. was observed at all three dose levels as a decrease in pup weight (decrement ranging from 2-21% depending on dose & generation/ litter. The registrant presented a DNOEL (derived NOEL) using analysis of variance and regression). The reported mean DNOELs for the F1 and f2 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 Reprod. LEL = 200 ppm based on decr. pup wt. 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.		Supplementary 008101 Minimum 010721
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

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P.C. CODE 125301- N-[2-(p-Phenoxyphenoxy)ethyl]carbamic acid FILE LAST PRINTED: 06/13/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
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 Cr1:CD(SD)BR strain.		Guideline 004621
Inhalation-21 day Species: rat Res. and Consulting Co.; Switz 085500; 6/17/87	Fenoxycarb 96.6%	40355801	Levels tested: 0.0, 0.01, 0.10, and 1.13 mg/l for 6 hrs/day/5 days/week for 3 weeks. NOEL = 0.10 mg/l , LEL = 1.13 mg/l (decreased body weight gain in males and increased absolute liver weight in females)		Guideline 006897
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-micronucleus assay Species: mice Hoffman LaRoche, Switz. B-96-679; 7/20/82	RO-13-5223 Tech in peanut oil	071856	Does not produce micronuclei in mouse PCEs at 5000 mg/kg (HDT)		Supplementary 004178 Acceptable 004178
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
84-2(b) Mutagenic-chromosome aberr. Species: human lymphocytes Hoffman LaRoche 128-M-88; 02/21/89	Fenoxycarb tech. (% a.i. not stated).	423438-10	Reportedly negative fo inducing chromosome aberrations in human lymphocytes cultured in vitro exposed with/without activation to 25 ug/mL/-S9, and 50-100 ug/mL/+S9. Major deficiencies exist.		Unacceptable 010721

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P.C. CODE 125301- N-[2-(p-Phenoxyphenoxy)ethyl]carbamic acid FILE LAST PRINTED: 06/13/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
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: dog Hoffman LaRoche 54 A 82; 3/14/83	RO-13-5223 Tech.	071780	Dosage at 50, 150 and 500 mg/kg/day. Elimination of parent compound 19 days after oral administration at 50 mg/kg/day for 26 weeks: fat 97% eliminated. Plasma 84% eliminated liver 81% eliminated. Higher dosages showed higher elimination rates.		Supplementary 004178
85-1 Metabolism Species: rat MAAG 041/2368; 11/2/81	RO-13-5223 Tech.	247925 071856	Only one level tested - 50 mg/kg (14C labeled in the dioxyphenyl ring). Most radioactivity excreted in urine and feces (60-80%) in 24 hours and 90-92% by 96 hours. Organs did not show persistent residues. Identification of metabolites not presented.		Supplementary 002215
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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P.C. CODE 125301- N-[2-(p-Phenoxyphenoxy)ethyl]carbamic acid FILE LAST PRINTED: 06/13/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
86-1 Dom. animal safety env. exp. Species: dogs & cats Fementa Res. Cen.; #2229 9/7/90	Fenoxycarb 1%; Permethrin .15%;Pip. butox .50%; Caswell 613 1.0%; Caswell 025A 0.1%; Casw 400, 0.2%	416374-01	Groups of cats & dogs (each consisting of 1 adult male, 1 adult female, 3 mlae & 3 female kitens/puppies) were sprayed with the proposed formulation or a 4X conc. of its active ingredients or the vehicle (nonactive) components on days 0, 7 & 14 of a 21 day study. For dogs, individual applications (of either the vehicle, 1X or 4X formulations) ranged from 11.12 to 25.76 grams; for cats the corresponding values were 3.25 to 17.6 gms. In terms of the active ingred. Fenoxycarb single doses ranged from 0.0018 to 0.0100 g/kg at 1X, and from 0.0067 to 0.0415 g/kg at 4X. Possible symptoms observed only in a few dogs exposed to 1X & 4X formulations (and only in periods immediately after spraying): slight serous ocular discharge, panting, slight erythema on the lower abdomen. For cats only depression (highest level recorded defined as 'moderately depressed, lies down mostly, will stand') appeared to be correlated with exposure to the actives (observed only in a few kittens of the 1X & 4X groups on days 0-2, 7 & 14). Occurrence of matted hair in 4X cats & kittens, along with observation of 'oily' hair, particularly for a few days after spraying on day 14, sugests grooming behavior differences. While no significant adverse effects in cats and/or dogs were observed as a result of normal use-application of the proposed product, a point of toxicological concern is with 'inerts' in this formulation. Application of the 4X concentrate resulted in an exposure to 'inerts' equivalent to only that occurring with a 1X exposure. No information provided as to rate of delivery of this product (from a pum-sprayer). Comment in report (p. 13) as to 'the inherent inaccuracy of spray application' is also a point of concern. Not acceptable without additional information.		Unacceptable 008238

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
86-1 Dom. animal safety env. exp. Species: cat (kittens) 3/6/91 2239	Fenoxycarb .1%; Allethrin .1%; Permethrin .15%; Piperonyl but .5%; cas 613 1%;Cas 400 .2%; other 97%		Six kittens (14-17 weeks old, weighing between 2.6 & 3.8 lbs) were sprayed 4 times with the formulation, with sufficient time between spraying for he formulation to dry. Total time elapsed between 1st and 4th spray for any one kitten was no more than 2 hrs & 15 min. Individual single applications ranged from 3.02 to 6.52 gms; cumulative applications ranged from 13.02 to 24.59 gms. One kitten (subsequently diagnosed to have a respiratory tract infection) was slightly depressed following the 4th spraying. The minimum rectal temperatures observed in 5/6 kittens (exception was the kitten with the infection) were observed on the day following spraying, but were still within normal range. A 'chalky' hair coat appearance was observed in 4/6 kittens following the 4th spraying, but was no longer detectable the second day after treatment. No significant toxicological effects were observed in any of the kittens; this study, with the previously reviewed studies, demonstrates that there is a reasonably adequate margin of safety (4X) associated with the normal use of this product in kittens. Acceptable when combined with previously reviewed material.		Acceptable 008304
86-1 Dom. animal safety env. exp. Species: dog Kansas State Univ. 11/14/89	Pyrethrins 0.14%; Tetramethrin 0.063%; Pip but. 1%; Fenoxycarb 0.15%; N-octyl bicylohep.. 1.00%	422439-01	Groups of 4M, 4F dogs received a single 1X, 3X, or 10X normal-use application of the product. There was a control group consisting of 3M and 3F which were sprayed with a placebo formulation. Following spraying, animals were observed for 14 days. There were no symptoms of toxicity, even in the 10X group, & there were no indications of any effects on such parameters as body weight, food consumption, hematology, clinical chemistry or urinalysis.		Acceptable 010222
Cholinesterase Species: housefly	RO-13-5223 Tech	247925	The carbamate Ro13-5223 did not cause any synaptic disturbance at the AChE locus at highest in vitro conc. tested, 2.5 x 10-4 M		Minimum 002215
81-1 Acute oral LD50 Species: rat	RO-13-5223 Tech.	247925	LD 50 > 16,800 mg/kg.	4	Guideline 002215

PENDING REGISTRATION INFORMATION IS NOT INCLUDED

[redacted]

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-1 Acute oral LD50 Species: rat	RO-13-5223 10.3% a.i. in [redacted] INERT INGREDIENT INFORMATION IS NOT INCLUDED	247925	LD 50 > 10,000 mg/kg.		Guideline 002215
81-1 Acute oral LD50 Species: mice	RO-13-5223 Tech.	247925	LD 50 > 8000 mg/kg.		Guideline 002215
81-1 Acute oral LD50 Species: rat	RO-13-5223 Tech.	247925	LD 50 > 10,000 mg/kg. 2/5 females died. Splenic hemopoesis.		Guideline 002215
81-1 Acute oral LD50 Species: rat Food and Drug Research Lab 7876B; 12/16/83	Raid Fogger plus (formulation 0.6% fenoxycarb)	261392	LD 50 > 5.0 g/kg. Decreased activity, ataxia, salivation, rales, nasal discharge and diarrhea.	4	Guideline 005549
81-1 Acute oral LD50 Species: rat Res. and Consulting Co.; Switz 017796; 5/2/83	Fenoxycarb 25% WP	414989-02	LD50 > 5,000 mg/kg (0 deaths). Dsoe level: 5000 mg/kg; strain WIST, SPF Han. Dose by gavage.	4	Guideline 008263
81-1 Acute oral LD50 Species: rat 04/10/86	Torus 2E (24.6% Fenoxycarb)	400865-01	LD50 (M&F) > 5.0 g/kg	4	Guideline 009116
81-2 Acute Dermal LD50 Species: rat Hoffman LaRoche, Switz. B-97341; 5/5/82	Formulation ACR 5023 (10.% in [redacted] INERT INGREDIENT INFORMATION IS NOT INCLUDED	071856	LD 50 = > 5000 mg/kg. Dyspnea, curved body position, ruffled fur, sedation, and diarrhea. No deaths.	3	Guideline 004178
81-2 Acute Dermal LD50 Species: rat Huntingdon Res. Centre, Eng. B-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

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-2 Acute Dermal LD50 Species: rabbit Food and Drug Research Lab 7876B; 12/22/83	Raid Fogger plus (formulation 0.6% fenoxycarb)	261392	LD 50 > 2.0 g/kg. Dry, flaking skin, soft stools and anorexia.	3	Guideline 005549
81-2 Acute Dermal LD50 Species: rat Res. and Consulting Co.; Switz 017807; 6/15/83	Fenoxycarb 25% WP.	414989-02	LD50 > 2000 mg/kg (0 deaths). Dsoe level: 2000 mg/kg to Wist, SPF Han.	3	Guideline 008263
81-2 Acute Dermal LD50 Species: rabbit 02/18/86	Torus 2E (24.6% Fenoxycarb)	400865-02	LD50 (M&F) > 2000 mg/kg	3	Guideline 009116
81-3 Acute inhalation LC50 Species: rat Res. and Consulting Co.; Switz 3/16/82	RO-13-5223 10.3% a.i. in [redacted] INERT INGREDIENT INFORMATION IS NOT INCLUDED	247925	LC 50 > 3.05 mg/L of formulation. Levels tested, 2.221 and 3.052 mg/L.	3	Supplementary 002215 Minimum 004178
81-3 Acute inhalation LC50 Species: rat Huntingdon Res. Centre, Eng.	RO-13-5223 Dust 0.26 g/m3 ..32.5%; respirable & aerosol 0.48% g/m3 94.5% respirable	247925	Highest concentration of dust obtainable for dust and aerosol with the equipment employed. Too low concentration to assess hazard by inhalation alone. At concentration tested (4 hours) no significant effects observed during 14 days.		Supplementary 002215 Minimum 004178
81-3 Acute inhalation LC50 Species: rat Food and Drug Research Lab 8349; 5/20/85	Raid Fogger plus (formulation 0.6% fenoxycarb)	261392	LC50 = 6.7 mg/L; slope = 15 (males), 4.8 (females). Alopecia, decreased tivity, labored breathing, nasal discharge, salivation, tremors. Body wt .decrease in males. Reddened lungs. Corneal opacity at top dose.	3	Minimum 005549
81-3 Acute inhalation LC50 Species: rat Food and Drug Research Lab 7876; 10/15/84	Raid Fogger plus (formulation 0.6% fenoxycarb)	261392	Four Sprague-Dawley rats (1/5 males, 3/5 females) died within 15 days after a 4-hour, whole -body exposure to 5.1 mg/L (analytical concentration). Labored breathing, decreased activity, and (in those succumbing) , tremors, ataxia, and diarrhea. Reddened nasal passages and lungs in one two animals.		Supplementary 005549

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-3 Acute inhalation LC50 Species: rat Res. and Consulting Co.; Switz 017818; 6/15/83	Fenoxycarb 25% WP	414989-02	LC50 > 3481 mg/m3 (0 deaths). Dose level: 3481 mg/m3. Strain: Wist, SPF Han. (Inhalation).	3	Minimum 008263
81-3 Acute inhalation LC50 Species: rat 05/12/86	Torus 2E (24.6% Fenoxycarb)	400865-03	LC50 (M) = 2.538 mg/L. LC50 (F) = 2.254 mg/L. LC50 (combined) = 2.450 mg/L	3	Guideline 009116
81-3 Acute inhalation LC50 Species: rat Ciba-Geigy Corp. Inc. 011362; 01/22/92	Fenoxycarb tech. 97.6%; Lot# 139044	423438-02	LC50 > 4,434 mg/m3 (4.434 mg/L) in male & females. Dose levels: 4,434 mg/m3 by inhalation to strain (RII/1 x RII/2) F1. No deaths occurred; slight dyspnea, slight piloerection, slight hunched posture & weight loss were observed.	3	Acceptable 010721
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
81-4 Primary eye irritation Species: rabbit 2/12/82	RO-13-5223 Formulation (10.3% w/w in [redacted] INERT INGREDIENT INFORMATION IS NOT INCLUDED	247925	Mild and transitory redness in first hour.	4	Minimum 002215
81-4 Primary eye irritation Species: rabbit Food and Drug Research Lab 7876B; 12/13/83	Raid Fogger plus (formulation 0.6% fenoxycarb)	261392	Irritation clearing in 7 days or less.	3	Guideline 004449
81-4 Primary eye irritation Species: rabbit Biosearch Inc. 90-7011A-1; 6/11/90	Insegar 25% WP	416559-01	Produces mild to moderate irritation; reversible within 7 days.	3	Guideline 008253
81-4 Primary eye irritation Species: rabbit Res. and Consulting Co.; Switz 094983; 9/21/87	Fenoxycarb 25% WP	414989-02	Slight irritation, reversible in 72 hrs. #animals: 3. Strain NZW KFM-SPF.	3	Acceptable 008263

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81-4 Primary eye irritation Species: rabbit 09/26/85	Torus 2E (24.6% Fenoxycarb)	400865-04	At 100% and 30%, corneal opacity & irritation through 72 hrs. At 10%, only redness (low grade); (should have continued to 21 days).		Supplementary 009116
81-4 Primary eye irritation Species: rabbit American Standards Biosci Corp 88-347; 06/24/88	Torus 2E (24.6% Fenoxycarb)	408245-01	Corneal involvement through day 21, iris involvement and conjunctival irritation through day 14.	1	Guideline 009116
81-5 Primary dermal irritation Species: rat 11/15/79	RO-13-5223 40% a.i. in corn oil	247925	PIS = 0.0 at 2000 mg/kg.	4	Minimum 002215
81-5 Primary dermal irritation Species: rat 11/15/79	RO-13-5223 Formulation 10.3%	247925	PIS = 0.0 at 1000, 3000, and 5000 mg/kg.	4	Minimum 002215
81-5 Primary dermal irritation Species: rabbit Food and Drug Research Lab 7876B; 2/15/84	Raid Fogger plus (formulation 0.6% fenoxycarb)	261392	PIS = 3.4: Moderately irritating.	3	Guideline 005549
81-5 Primary dermal irritation Species: rabbit Res. and Consulting Co.; Switz 095038; 9/16/87	Fenoxycarb 25% WP	414989-02	No irritation at 30% dilution in water and 100%. # animals: 3. Strain: NZW KFM-SPF.	4	Acceptable 008263
81-5 Primary dermal irritation Species: rabbit 08/26/85	Torus 2E (24.6% Fenoxycarb)	400865-05	Slight irritation; P.I. Index = 0.82.	4	Guideline 009116
81-6 Dermal sensitization Species: guinea pig Hoffman LaRoche 041/0576; 11/15/79	Fenoxycarb	247925	0.025 mls of 100, 30, 10 and 3% a.i. applied to one flank for 21 days. Challenge doses at 21 and 35 days produced no allergic reactions 24 and 48 hours post challenge.		Guideline 002215

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81-6 Dermal sensitization Species: guines pig Hoffman LaRoche 2330a; 3/18/82	Formulation ACR 5023 (10.3% in [redacted] INERT INGREDIENT INFORMATION IS NOT INCLUDED	071779	Not sensitizing at 0.1 ml in the guinea pig.		Guideline 004178
81-6 Dermal sensitization Species: guinea pig Hoffman LaRoche 2330; 1/4/83	Formulation ACR 5023 (10.0% in [redacted] INERT INGREDIENT INFORMATION IS NOT INCLUDED	671850	Not sensitizing in guinea pig at 0.1 ml.		Guideline 004178
81-6 Dermal sensitization Species: guinea pig Food and Drug Research Lab 8349; 1/7/85	Raid Fogger plus (formulation 0.6% fenoxycarb)	261392	Negative for dermal sensitization when applied neat to female guinea pigs by modified Buehler test.		Guideline 005549
81-6 Dermal sensitization Species: guinea pig Biosearch Inc. 90-7011A-2; 7/12/90	Insegar 25% WP	416559-02	Not a sensitizer.		Guideline 008253
81-6 Dermal sensitization Species: guinea pig Hoffman LaRoche 2514 a and b; 2/17/83	RO 13-5223/037 25% WP (Fenoxycarb)	414989-02	No sensitization occurred.		Unacceptable 008263
81-6 Dermal sensitization Species: guinea pig 03/13/86	Torus 2E (24.6% Fenoxycarb)	400865-06	No dermal sensitization elecited by Torus 2E.		Guideline 009116
Acute intraperitoneal LD50 Species: rat	Fenoxycarb tech	247925	LD50 = 9220 mg/kg	4	Guideline 002215

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