



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of Fenoxycarb

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THROUGH: Stephanie R. Irene Ph.D. *Stephanie R. Irene 3/28/96*
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The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on May 10, 1995 to discuss and evaluate the weight-of-the-evidence on fenoxycarb with particular reference to its carcinogenic potential. The CPRC concluded that fenoxycarb should be classified as Group B2 - probable human carcinogen. This classification was based on statistically significant increases in lung adenomas, carcinomas and combined adenoma/carcinoma - and in adenomas of the Harderian gland in male CD-1 mice. Urethan, a possible metabolite of fenoxycarb, is associated with tumors at these same sites, and others, in multiple species and strains. The CPRC recommended that for the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk, based on the combined incidence of adenoma/carcinoma in the lungs of male mice.

SUMMARY

Administration of fenoxycarb in the diet to CD-1 mice resulted in statistically significant increases in lung bronchiolar/alveolar adenomas, carcinomas and combined adenoma/carcinoma at the highest dose (420 ppm), with statistically significant positive trends for the adenomas and combined adenoma/carcinoma in male mice. There were also statistically significant increases in adenomas of the Harderian gland in male mice at the highest dose, with a statistically significant positive trend. There were no apparent increases in tumor incidences in female mice at doses up to 320 ppm. The CPRC determined that the highest dose was not adequate for fully assessing the carcinogenic potential of fenoxycarb in either sex, due to the absence of significant toxicity. However, the CPRC agreed that another study in the mouse at higher doses was not necessary, since there are adequate data for performing Risk Characterization, based on the lung tumors in the mouse¹.

There was no apparent increase in tumor incidences in either sex when fenoxycarb was administered in the diet to Sprague-Dawley rats. The CPRC determined that the highest dose (1800 ppm) in the rats was only marginally adequate, based on minimal liver toxicity, and that the rats could have tolerated a higher dose.

Fenoxycarb does not appear to show evidence of genotoxicity, however a data gap for the structural chromosomal aberration category was identified. Fenoxycarb is structurally related to chemicals of the diphenyl ether class and to urethan. The analogy to the diphenyl ethers was not considered a major contributing factor to fenoxycarb's activity. On the other hand, urethan, which may be generated metabolically from fenoxycarb, is associated with tumors of the Harderian gland and lung tumors (the same sites as fenoxycarb) and other tumor types in many species.

The classification of Group B2 was based on the increases of tumors of the lung (carcinomas and adenomas) and Harderian gland (adenomas) in male mice, even at a dose that was not adequate; concern for urethan, a possible metabolite, which is associated with the same tumor types, and others, in many species; a rat study considered to be only marginally adequate, and the absence of an adequate genotoxicity assay in the structural chromosomal category (urethan has shown activity in this assay).

¹The Registrant, however, did repeat the mouse study, of its own volition.

A. Individuals in Attendance at the meetings:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Stephanie Irene

Stephanie Irene

William Burnam

Wm Burnam

Karl Baetcke

Karl A. Baetcke

Marcia Van Gemert

retired

Kerry Dearfield

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Marion Copley

Marion Copley

Hugh Pettigrew

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Esther Rinde

Esther Rinde

Yin Tak Woo

Yin Tak Woo

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Marion Copley²

Marion Copley

William Greear³

William B. Greear 3/12/96

Lori Brunzman

Hugh Pettigrew for Lori Brunzman

Michael Stedham for
Lucas Brennecke⁴
(PAI/ORNL)

John W. Brennecke

²Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

³Tox reviewer; not present at this meeting.

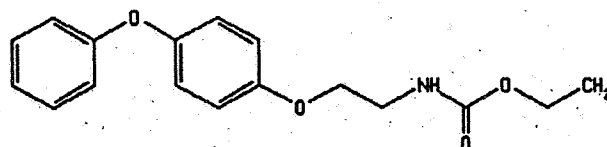
⁴Signature indicates concurrence with pathology report.

B. Material Reviewed

The material available for review consisted of DER's, one-liners, data from the literature and other data summaries prepared and/or supplied by William Greear, and tables and statistical analysis by Lori Brunsman. The material reviewed is attached to the file copy of this report.

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 Insect 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

Tox Chem No.: 652C

PC Code: 125301

CAS Registry Number: 72490-01-8.

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.

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. 42354101.

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 Males¹

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 Mice¹

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. Hardisty's reading of the slides. Statistical analysis of the data was conducted by L. Brunzman using the data present in the original submission (memorandum dated December 16, 1992). The results are provided in Table 3.

TABLE 3. Male Harderian Gland Tumor Rates+ and Peto Prevalence Test Results¹

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. Brunzman, 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 IRI¹

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 Harderian 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 # 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 (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 (%) ^a	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 =	.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 (the denominators include the 10 mice sacrifices at 1 year since they were considered at risk).

^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 for 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 the 420 ppm dose group for alveolar/bronchiolar adenomas, carcinomas (both $p < 0.050$ 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

¹Taken from table 4 of IRI Project No. 450719, p.36, MRID #42343808

* p_{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.

Although the dosing was not considered adequate additional testing in the mouse is not required. There are tumors in the males and additional testing in the females is not expected to alter the carcinogenic classification of fenoxycarb.

2. 18-Month Carcinogenicity Study in the Mouse Recent 6a2 submission⁵.

Groups of 60 mice [Tif: MAGf (SPF)] were fed diets containing fenoxycarb at concentrations of 0, 10, 50, or 2000 ppm (1.1, 5.75, 55.4, or 222 mg/kg/day for males and 1.04, 5.33, 51.5 or 201 mg/kg/day for females) for 18 months.

Preliminary review of this study indicates there were significant increases in the incidences of adenomas, carcinomas and combined adenoma/carcinoma of the lungs in both sexes of mice at 500 and 2000 ppm for males, and at 2000 ppm for female mice. There were also significant increases in hepatocellular carcinomas and combined adenoma/carcinoma at 500 and 2000 ppm in male mice only.

3. 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

⁵This repeat mouse study was not requested or required by the Agency.

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. These changes, however are not excessive. 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)

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 Weeks¹

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%)*

¹Data extracted from 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 Weight¹

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

Males in the high-dose group evidenced only minimal 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. The CPRC determined that the highest dose (1800 ppm) in the rats was only marginally adequate, based on minimal liver toxicity, and that the rats could have tolerated a higher dose.

E. Additional Toxicology Data on Fenoxycarb

1. Metabolism

Ninety-eight percent of an oral dose (high-dose) of 3000 mg/kg to rats of ¹⁴C-fenoxycarb ring-labeled was recovered; 50% in the feces, 42 to 47% in the urine, 0.09% in CO₂ 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 Figure 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). No metabolism tests were conducted with mice.

FIGURE 1. METABOLIC PATHWAY OF FENOXYCARB
IN THE RAT

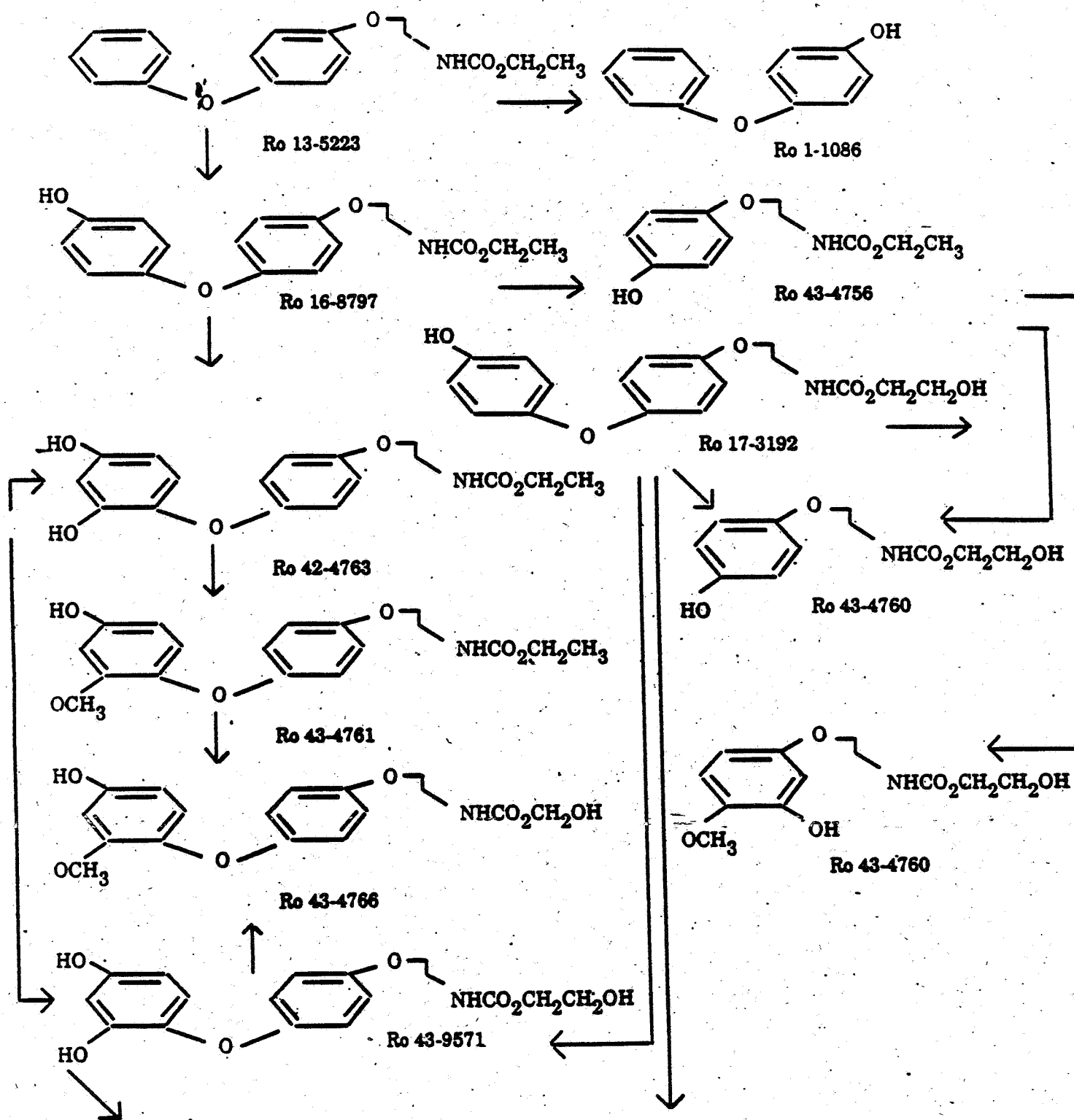
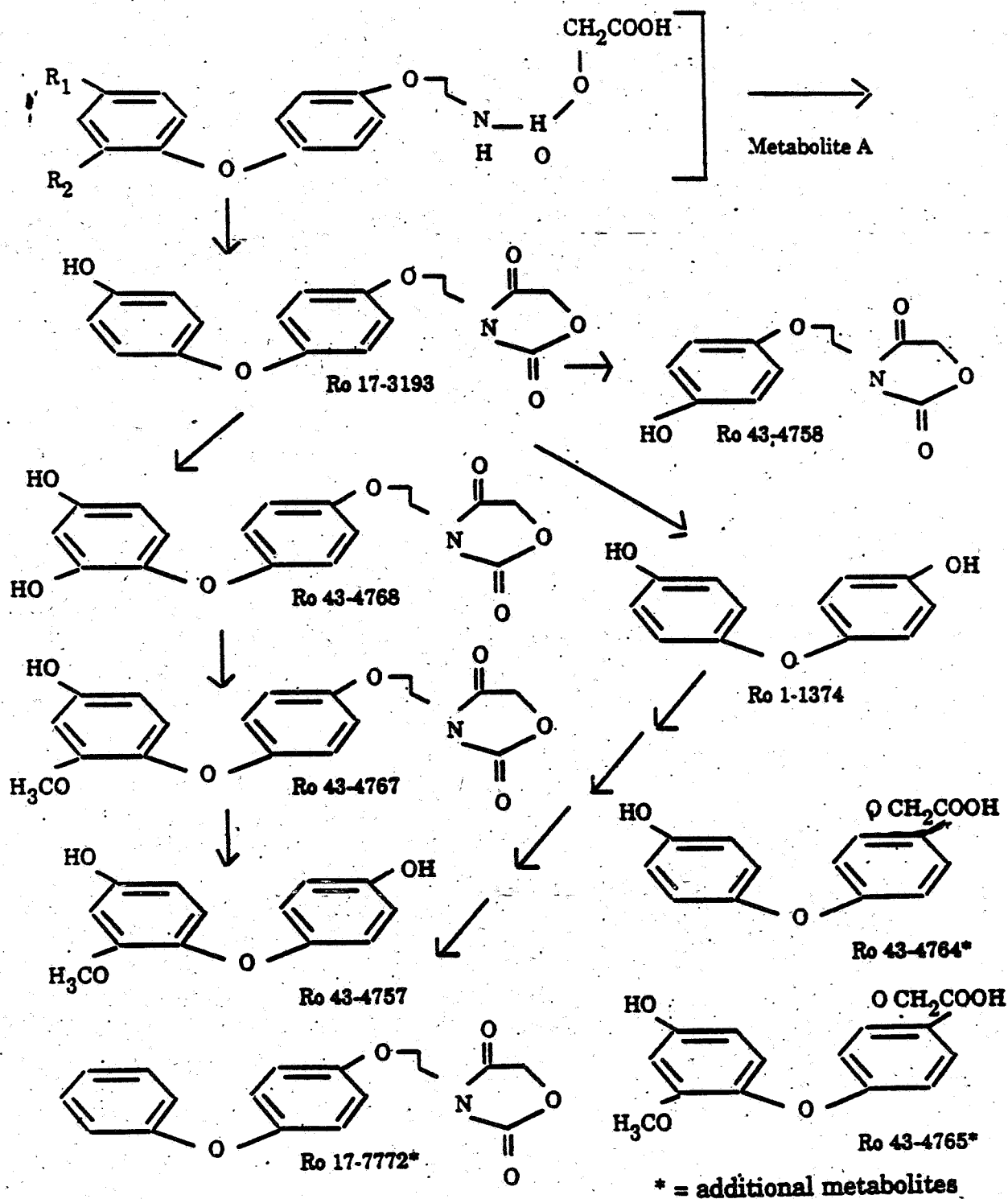


FIGURE 1: METABOLIC PATHWAY OF FENOXYCARB
IN THE RAT (Continued)



2. Mutagenicity

Fenoxycarb has been tested in several mutagenicity studies. Acceptable tests fulfill only two of the three categories for mutagenicity testing, gene mutation, and other genotoxic effects. Studies which have been conducted are shown in Table 11.

A new study is required for the structural chromosomal aberrations category. The HED Carcinogenicity Peer Review Committee recommends that this be filled with a new micronucleus test.

Although there is a data gap for structural chromosomal aberrations based on submitted data, the other data do not indicate a concern. However, urethan has been shown to be genotoxic and this supports a possible concern and the recommendation for additional testing.

Table 11. Mutagenicity Studies on Fenoxycarb

Study	Status
Gene Mutation	
Ames - (<i>Salmonella</i> strains TA98, TA100, TA1535, TA1537, TA1538) Tested at up to 2400 µg/disk (Spot test) and 300 µg/plate with and without metabolic activation (quantitative test) (ACC No. 247925, Study No. B-96153, Date: 3/17/81. NEGATIVE	Acceptable TXR Doc. No. 002215
V79-HGPRT Tested at up to 25 µg/ml with and without metabolic activation (ACC No., Study No., Date. not provided) NEGATIVE CH V79 (replicate of above study) Tested at up to 100 µg/ml with and without activation (MRID No. 00071850, Study No. B-96728, Date: 6/11/82) - NEGATIVE	Unacceptable Used 8-azaguanine as selective agent (unappropriate) TXR Doc. No. 002215
Structural Chromosomal Aberration	
<u>In Vitro</u> 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
<u>In Vitro</u> 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	Unacceptable (unacceptable protocol) TXR Doc. No. 004178, new document unknown Doc. No. as yet
Other Genotoxic Effects	
Recombination (Conversion - <i>S. cerevisiae</i> 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. Structure-Activity Correlations

Fenoxycarb is a urethan derivative N-substituted with a phenoxyphenoxyethyl group (Figure 2). Urethan^{6,7} is a known carcinogen in several species and is an active initiator of skin tumorigenesis. It produces lung tumors in a number 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-dealkylation should occur, urethan could potentially be regenerated. Fenoxycarb has Ro43-4764 (2.5 % recovered in urine - male rats only) and Ro43-4765 (trace in urine) as two of its metabolites indicating that urethan regeneration is possible. The tumor sites with fenoxycarb are consistent with those associated with urethan. It should be noted that fenoxycarb is negative for tumorigenicity in rats.

Fenoxycarb is also structurally related to the diphenyl ether pesticides⁸ Hoelon, Oxyfluorfen, Fomesafen, Lactofen, Acifluorfen, Nitrofen and Verdict. The structures of these compounds are shown in Figure 2. It should be noted however, that the structure-activity relationship analogy of Fenoxycarb to these pesticides is somewhat weak. The carcinogenic potential of the diphenyl ether moiety of Fenoxycarb is expected to be lower than that of these other pesticides, because it lacks the chlorine ring substitution and/or branched alkyl sidechains associated with most carcinogenic diphenyl ether pesticides⁹. In addition, the carcinogenicity profile for the diphenyl ether pesticides is different with the primary target for tumors being the liver.

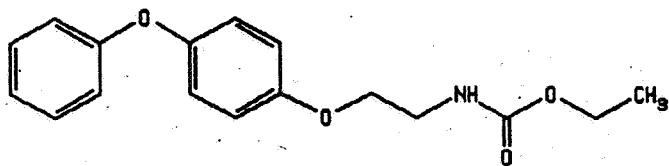
⁶ Chemical Induction of Cancer - Structural Bases and Biological Mechanism (Vol IIIA, Aliphatic Carcinogens) by J. Arcos, Y.T. Woo and M. Argus, pp 400-507 (1982).

⁷ See Appendix for discussion of the carcinogenic potential of urethan (also written as urethane).

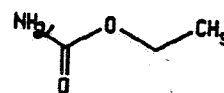
⁸ This SAR was discussed in detail in the Carcinogenicity Peer Review memorandum on Hoelon (see memorandum of W. Dykstra and E. Rinde, 5/26/93).

⁹ Carcinogenicity and Pesticides - Principles, Issues, and relationships, Edited by N. Ragsdale and R. Menzer, pp 184-5 (1989).

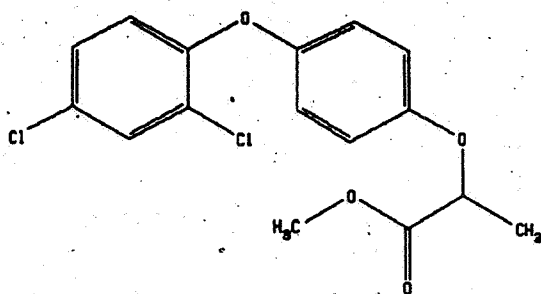
Figure 2: Structures of Diphenyl Ether Analogues



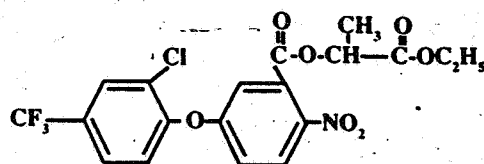
FENOXYCARB



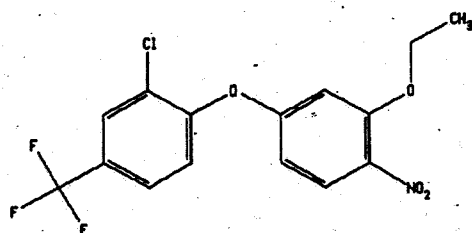
URETHAN



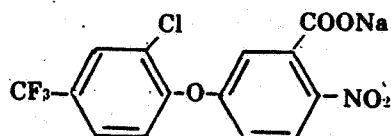
HOELON (DICLOFOP-ME)



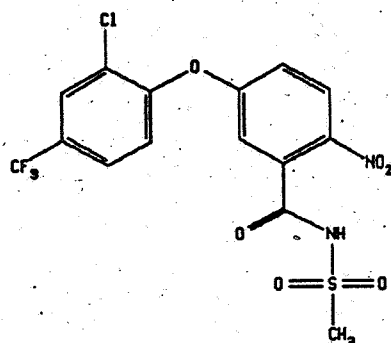
LACTOFEN



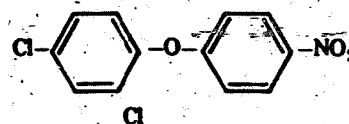
OXYFLUORFEN



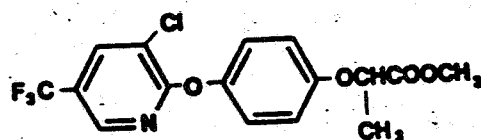
ACIFLUORFEN



FOMESAFEN



NITROFEN



VERDICT (HALOXYFOP-ME)

4. Subchronic and Chronic Toxicity

a. Oral Subchronic 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 250 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).

b. 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.

F. Weight of Evidence Considerations

The Committee was 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 (420 ppm).
2. Fenoxycarb was associated with a statistically significant increase in lung bronchiolar/alveolar tumors (contribution by both adenomas and carcinomas) 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. Preliminary review of a recent 6a2 submission of a new 18-Month study in [Tif: MAGf (SPF)] mice at doses up to 2000 ppm indicated significant increases in lung adenoma/carcinoma in both sexes as well as significant increases in hepatocellular adenoma/carcinoma in male mice. The lung tumors are consistent with the earlier mouse study.
5. Fenoxycarb was not associated with increased incidences of neoplasms in Crl:CD(SD)Br Sprague-Dawley derived rats at dietary levels up to 1800 ppm. The CPRC considered dosing to be only marginally adequate for both sexes in the high-dose group based on minimal liver toxicity. It was postulated by the CPRC that the rat may have been positive for carcinogenicity if tested at higher doses.
6. Fenoxycarb was not genotoxic in several mutagenicity assays. However, there is no adequate study to satisfy the structural chromosomal aberrations category. An adequate micronucleus test is recommended (urethan is positive in the micronucleus assay).
7. Fenoxycarb is structurally related to urethan (see appendix for discussion of urethan's carcinogenic potential) a known carcinogen associated with the same tumor types as fenoxycarb.
8. Urethan is potentially a metabolite of fenoxycarb in male rats (not females) but metabolism has not been tested in mice, the positive species.
9. The HED Cancer Peer Review Committee determined that, if urethan were to be formally presented to the Committee for evaluation, it would most likely be given the classification of B2 (probable human carcinogen).

G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity.

The CPRC agreed that fenoxycarb should be classified as a Group B2 - probable human carcinogen. This decision was based on increases of tumors of the lung (carcinomas and adenomas) and Harderian gland (adenomas) in male mice, even at a dose that was not adequate; concern for urethan, a possible metabolite, which is associated with the same tumor types, and others, in many species; a rat study considered to be only marginally adequate, and the absence of an adequate genotoxicity assay in the structural chromosomal category (urethan has shown activity in this assay).

The CPRC recommended that for the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk, based on the combined adenoma/carcinoma in the male mouse.

The CPRC concluded that there is no need to repeat the mouse study, since there are adequate data for performing Risk Characterization, based on the lung tumors in the mouse¹⁰. In order to fulfill the data gap in the structural chromosomal category, the CPRC recommended that an adequate micronucleus test be submitted.

H. Induces Cancer Call --Fenoxycarb

After a full evaluation of all of the data and supporting information regarding animal carcinogenicity, the Committee concludes that exposure to fenoxycarb resulted in an increased incidence of tumors of the lung (malignant and benign) and Harderian gland (benign only) in the male CD-1 mouse. Data from urethan, which is a possible metabolite of fenoxycarb, and is associated with tumors at the same sites (lung and Harderian gland) in many species, provided additional support. There does not appear to be evidence of genotoxicity for fenoxycarb; however, based on the available evidence from mutagenicity studies, a data gap was identified.

The Committee agrees that fenoxycarb induces cancer in animals.

¹⁰The Registrant, however, did repeat the mouse study, of its own volition.

APPENDIX

EVALUATION OF URETHAN

The following summary is taken primarily from: 1) Chemical Induction of Cancer, Structural Bases and Biological Mechanisms, volume IIIA Aliphatic Carcinogens, by Joseph C. Arcos, Yin-Tak Woo and Mary F. Argus¹¹; 2) J. of Env. Sci. Health, C1(1), 97-133 (1983), "Carcinogenicity, Mutagenicity and Teratogenicity of Carbamates, Thiocarbamates and related compounds: An Overview of Structure-Activity Relationships and Environmental Concerns", by Yin-Tak Woo. Urethan (see Structure Activity Relationship section for structure) is a multi potential carcinogen in mice, rats, and hamsters. The attached table CXVI, taken from the first article above, demonstrates the carcinogenic potential of urethan. The route of treatment does not appear to influence the tumor profile to any great extent, although it may be effected by dose and schedule of treatment.

It has been tested in numerous strains and substrains of mice with the lung effected most frequently. These tumors occur whether exposure is by the oral, i.p., i.v., s.c., topical or inhalation route. Other frequently effected organs are the hematopoietic system and liver, particularly in younger mice. Targets in some specific strains include mammary gland, Harderian gland, forestomach, foot pad, intestines, skin, and salivary gland.

In the rat there is considerable strain difference. The principal tissues affected in young adult Sprague-Dawley rats are mammary gland, the ear duct (Zymbal's gland), and the hematopoietic system, and the kidney.

Syrian hamsters show an increase in melanotic tumors of the skin. The skin tumors occur independent to route of exposure.

Urethan has been extensively tested for mutagenic activity in numerous systems. It appears to be inactive in most gene mutation assays but active in several chromosome damage assays.

In the Fifth Annual Report on Carcinogens (Summary 1989) DHHS¹² considered there to be sufficient evidence for carcinogenicity of urethan in experimental animals (based on IARC V.7, 1974; IARC S.4, 1982). The IARC Monographs on the Evaluation of Carcinogenic Risks to Humans; Overall Evaluations of Carcinogenicity: An Updating of

¹¹Published in 1982 by Academic Press, New York, "5.2.1.6.3.2 Urethan and Related Compounds", pp 499-507.

¹²Prepared for the National Institute of Environmental Health Sciences, "Urethane" (CAS No. 51-79-6) pp286-289.

IARC Monographs Volumes 1 to 42, Supplement 7 (pp 30-32, 73) lists urethan as a 2B carcinogen with sufficient degree of animal evidence for carcinogenicity and no adequate data for evidence for carcinogenicity in humans. The IARC description of a Group 2B is:

"The agent is possibly carcinogenic to humans."

"This category is generally used for agents for which there is limited evidence in humans in the absence of sufficient evidence in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in humans or when human data are nonexistent but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent for which there is inadequate evidence or no data in humans but limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group."

Based on the above information concerning urethan, the HED Cancer Peer Review Committee determined that, if urethan were to be formally presented to the Committee for evaluation, it would most likely be given the classification of B2 (probable human carcinogen).

TABLE CXVI¹³

Carcinogenicity of Urethan in Adult Animals

Species and strain	Route	Principal organs affected	References
Mouse, A	oral, i. p. or i. v.	Lung	(109)
Mouse, A/Jax	i. p.	Lung	(110)
Mouse, AK	i. p.	Lung	(111)
Mouse, AKR	i. p.	Hematopoietic system	(112)
Mouse, Balb/c	i. p.	Lung	(113,114)
Mouse, Bagg	i. p.	Lung	(111,115)
Mouse, BLH	inhalation	Lung	(116)
Mouse, (Bagg X DBA)F ₁	i. p.	Lung	(115)
Mouse, C	s. c.	Lung	(117)
Mouse, C3H	oral	Lung, hematopoietic system, fat pad	(13)
	i. p.	Mammary gland, lung	(10)
	topical	Mammary gland, lung, fat pad	(10)
Mouse, C57	i. p.	Lung	(111)
	i. p.	Liver, intestines	(118)
Mouse, C57BL	inhalation	Lung	(116)
Mouse, C58	i. p.	Hematopoietic system, liver, intestines	(112)
Mouse, (C57 X A/J)F ₁	oral	Lung	(119)
Mouse, (C57 X C3H)F ₁	i. p. or topical	Lung, mammary gland, fat pad, Harderian gland	(10, 12)
	i. p.	Lung, Harderian gland, liver	(120)
Mouse, CBA	i. p.	Lung	(115)
Mouse, CTM	oral	Lung, hematopoietic system, mammary gland, liver, Harderian gland	(121,122)
Mouse, Db	i. p.	Lung, hematopoietic system, liver	(114)
Mouse, DBA	oral, i. p. or topical	Lung, mammary gland, fat pad	(10, 13)
Mouse, DBA/2eBDE	i. p. or topical	Liver, hematopoietic system, lung, fat pad, Harderian gland	(123)
Mouse, dd	oral	Lung	(124)
Mouse, FA	i. p.	None	(115)
Mouse, FB	i. p.	Lung	(115)

(Continued)

¹³Chemical Induction of Cancer, Structural Bases and Biological Mechanisms, volume IIIA Aliphatic Carcinogens, by Joseph C. Arcos, Yin-Tak Woo and Mary F. Argus.

TABLE CXVI (contd.)

Species and strain	Route	Principal organs affected	Reference
Mouse, Hall	s. c.	Lung, liver, hematopoietic system, skin	(125)
Mouse, NH	i. p.	Lung	(115)
Mouse, NMRI	inhalation	Lung	(116)
Mouse, NZO/Bl	i. p.	Skin	(126)
Mouse, Stock albino 'S'	topical	None	(8)
Mouse, Strong A	i. p.	Lung	(115)
Mouse, Swiss	oral	Lung, hematopoietic system	(127,128)
	oral	Forestomach	(9)
	i. p.	Lung	(115)
	s. c.	Lung	(117)
Mouse, "White-footed"	i. p.	None	(111)
Mouse, Zb	i. p.	Lung, hematopoietic system, liver, mammary gland	(114)
Rat, MRC	i. p.	Nervous system, thyroid gland, liver	(129)
Rat, Sprague	oral	Liver, adrenal cortex, hematopoietic system, mammary gland	(130)
Rat, Sprague-Dawley	oral or i. p.	Mammary gland, ear duct (Zymbal's gland), hematopoietic system, kidney	(14)
Hamster, Syrian golden	oral	Skin, forestomach, intestines, lung, mammary gland, liver	(131-133)
	oral or topical	Skin, mammary gland, ovary	(134-137)
	s. c.	Skin, forestomach, intestines	(138,139)
Hamster, European	i. p.	Subcutaneous and peritoneal tissues (with lower incidence: liver, lung, adrenal gland, nasal cavity, kidney, forestomach)	(28)
Guinea pig	oral	None	(140)
Chicken (Brown Leghorn)	oral or i. p.	None	(140)

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