(3)

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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

TXR No.: 0053618

MEMORANDUM

DATE: July 13, 2005

SUBJECT: **PIRIMICARB:** Report of the Cancer Assessment Review Committee
PC Code: 106101

FROM: Jessica Kidwell, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509C)

Jessica Kidwell

TO: Guruva Reddy, Toxicologist (RAB1)
George Kramer, Risk Assessor (RAB1)
Health Effects Division (7509C)

George Larocca
Insecticide Branch, Registration Division (7505C)

The Cancer Assessment Review Committee met on May 11, 2005 to evaluate the carcinogenic potential of PIRIMICARB. Attached please find the Final Cancer Assessment Document.

cc: J. Pletcher
Y. Woo

(1)

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF **PIRIMICARB**

PC Code 106101

FINAL
July 13, 2005

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

PIRIMICARB CANCER ASSESSMENT DOCUMENT FINAL

DATA PRESENTATION: Gunuva Reddy, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise stated).

Karl Baetcke

Lori Brunsman

William Burnam

Marion Copley

Vicki Dellarco

Kit Farwell

Abdallah Khasawinah

Nancy McCarroll

Tim McMahon

Esther Rinde

Linda Taylor

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist See attached sheet

OTHER ATTENDEES: Whang Phang (HED/RRB1), P.V. Shah (HED/RAB1), Pramod Terse (HED/RAB1), Karen Whitby (HED/RAB1)

PIRIMICARB CANCER ASSESSMENT DOCUMENT FINAL

DATA PRESENTATION: Guruva Reddy, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise stated).

Karl Baetcke _____

Lori Brunsman _____

William Burnam _____

Marion Copley _____

Vicki Dellarco _____

Kit Farwell _____

Abdallah Khasawinah _____

Nancy McCarroll _____

Tim McMahon _____

Esther Rinde _____

Linda Taylor _____

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist _____

OTHER ATTENDEES: Whang Phang (HED/RRB1), P.V. Shah (HED/RAB1), Pramod Terse (HED/RAB1), Karen Whitby (HED/RAB1)

TABLE OF CONTENTS

EXECUTIVE SUMMARY

On May 11, 2005, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of pirimicarb. This was the first time that this compound was assessed for carcinogenicity by the CARC.

Guruva Reddy of Registration Action Branch 1 presented the chronic toxicity/carcinogenicity studies in Wistar rats and Swiss derived and CD-1 mice. In the rat carcinogenicity study (MRID 44883802), pirimicarb (97.3% a.i.) was administered in the diet to Wistar derived rats (52/sex/dose) at dose levels of 0, 75, 250, or 750 ppm (0, 3.7, 12.3, and 37.3 mg/kg/day in males and 0, 4.7, 15.6, and 47.4 mg/kg/day in females, respectively) for 24 months. In the mouse carcinogenicity study (MRID 44883803), Swiss-derived mice (60/sex/dose) were fed diets containing pirimicarb at dose levels of 0, 200, 400 and 1600 ppm (0, 10, 20, and 80 mg/kg/day for males and females, respectively) for 94 weeks. All animals were sacrificed when overall mortality approached 80% at week 94. Two control groups of 60 mice per sex were combined for these analyses as there were no statistically significant differences in mortality, body weight, body weight gain, food consumption or food utilization between these two control groups. In another mouse carcinogenicity study (MRID 44883901), pirimicarb (97.5% a.i.) was administered to groups of 55 male and 55 female C57BL/10J$_f$CD-1 mice in diet at concentrations of 0, 50, 200, and 700 ppm (0, 6.7, 26.6, and 93.7 mg/kg/day for males and 0, 9.0, 37.1 and 130.3 mg/kg/day for females, respectively) for 80 weeks.

The CARC concluded the following:

Carcinogenicity

Wistar Rat

- Uterine stromal cell sarcomas were observed in female rats at 750 ppm with an incidence of 2/63 (3%) compared to 0/62 (0%) in the controls. Although the incidence of 3% for sarcomas at the high dose exceeded the historical incidence range of 0-2% from Bayer AG and 0-1.82% of the Charles River historical controls, there was no statistically significant increase in tumors at the high dose. In addition, no historical control data from the testing laboratory were provided. Therefore, the CARC did not consider the uterine stromal cell sarcomas to be treatment-related.

- No treatment-related tumors were observed in male rats.

- Adequacy of Dosing: Dosing at the high dose of 750 ppm was considered to be adequate in both sexes to assess the carcinogenicity of pirimicarb in rats. In females, this was based on

6

significantly decreased mean body weights (13% ($p \leq 0.01$)) and body weight gains (9-19%) compared to controls and an increased severity of sciatic nerve demyelination (moderate demyelination -25/52 vs 6/53 controls) and minimal to marked muscle degeneration (15/52 vs 2/53 controls). In males, this was based on decreased body weight gains [6 - 13% from week 1 to 86 ($p \leq 0.05$ or 0.01)] and increased brain necrosis in males at 750 ppm. In the high-dose males, nervous tissue was affected as indicated by increased incidence of minimal to moderate necrosis of brain (6/52 vs 1/52 controls).

Swiss Mouse (MRID 44883803)

- In male mice, the incidences of liver adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 200, 400, and 1600 ppm dose groups, respectively, were as follows:

  Adenoma: 14/104 (13%), 5/51 (10%), 11/48 (23%), 19/52 (37%)
  Carcinoma: 10/104 (10%), 13/51 (25%), 8/48 (17%), 17/52 (33%)
  Combined: 22/104 (21%), 18/51 (35%), 17/48 (35%), 32/52 (62%)

  There were significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 ppm dose group with the controls, for liver adenomas, carcinomas, and adenomas and/or carcinomas combined, all at $p<0.01$. There were significant differences in the pair-wise comparisons of the 200 ppm dose group with the controls for liver carcinomas and adenomas and/or carcinomas combined, and of the 400 ppm dose group for liver adenomas and/or carcinomas combined, all at $p<0.05$. The tumor incidences at all doses for combined adenomas and/or carcinomas (35% for 200 and 400 ppm; 62% for 1600 ppm) exceeded the historical control range of 0-27% for mice reported by the testing laboratory. The CARC considered the liver tumors in male mice to be treatment-related based on the robust tumor response at all dose levels for combined liver adenomas and/or carcinomas, which was driven by the increase in both adenomas and carcinomas.

- In female mice, the incidences of liver adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 200, 400, and 1600 ppm dose groups, respectively, were as follows:

  Adenoma: 4/107 (4%), 3/53 (6%), 7/53 (13%), 4/42 (10%)
  Carcinoma: 2/95 (2%), 3/47 (6%), 3/47 (6%), 5/32 (16%)
  Combined: 5/107 (5%), 6/53 (11%), 9/53 (17%), 9/42 (21%)

  There were significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 ppm dose group with the controls, for liver carcinomas and adenomas and/or carcinomas combined, all at $p< 0.01$. There were significant differences in the pair-wise comparisons of the 400 ppm dose group with the controls for liver adenomas and adenomas and/or carcinomas combined, both at $p< 0.05$. There was also a significant difference in the pair-wise comparison of the 200 ppm dose group with the

controls for liver adenomas and/or carcinomas combined at $p< 0.05$. Historical control data for liver tumors in females were not provided. The CARC considered the liver tumors in female mice to be treatment-related based on the robust tumor response at all dose levels for combined liver adenomas and/or carcinomas, driven by an increase in carcinomas at the high dose.

- In male mice, the incidences of lung adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 200, 400, and 1600 ppm dose groups, respectively, were as follows:

  Adenomas: 17/103 (17%), 9/51 (18%), 8/48 (17%), 19/54 (35%)
  Carcinomas: 1/103 (1%), 0/51 (0), 0/48 (0), 1/54 (2%)
  Combined: 18/103 (17%), 9/51 (18%), 8/48 (17%), 19/54 (35%)

  There was a significant increasing trend, and a significant difference in the pair-wise comparison of the 1600 ppm dose group with the controls, for lung adenomas, both at $p<0.01$. There was a significant increasing trend at $p<0.01$, and a significant difference in the pair-wise comparison of the 1600 ppm dose group with the controls at $p<0.05$, for lung adenomas and/or carcinomas combined. The incidence at 1600 ppm of 35% for lung adenomas, and adenomas and/or carcinomas combined, is outside the historical control range of 0-28% of the testing laboratory for the combined tumors. Combined lung tumors (driven by adenomas) at the high dose of 1600 ppm were considered to be treatment-related.

- In female mice, the incidences of lung adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 200, 400, and 1600 ppm dose groups, respectively, were as follows:

  Adenomas: 13/108 (12%), 9/57 (16%), 11/56 (20%), 18/52 (35%)
  Carcinomas: 1/75 (1%), 0/35 (0), 1/44 (2%), 0/24 (0)
  Combined: 14/108 (13%), 9/57 (16%), 12/56 (21%), 18/52 (35%)

  There were significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 ppm dose group with the controls, for lung adenomas and adenomas and/or carcinomas combined, all at $p<0.01$. The incidences of adenomas and/or carcinomas combined exceeded the historical control range (0 - 15.5%) of the testing laboratory for the combined tumors. Combined lung tumors (driven by adenomas) at the high dose of 1600 ppm were considered to be treatment-related.

- In female mice, the incidence of ovarian papillary cystadenomas was 0/75 (0), 1/35 (3%), 3/44 (7%), and 3/24 (13%) for the control, 200, 400, and 1600 ppm dose groups, respectively. There was a significant increasing trend, and a significant difference in the pair-wise comparison of the 1600 ppm dose group with the controls, for ovarian papillary cystadenomas, both at $p<0.01$. Tumor incidences at mid- and high-doses were outside the range for the historical controls of the testing laboratory (0.7-1.3%). The CARC

8

considered the ovarian papillary tumors seen at the high dose to be treatment-related.

- In female mice, the incidence of mammary gland adenomas, adenocarcinomas, and combined adenomas and/or adenocarcinomas for the control, 200, 400, and 1600 ppm dose groups, respectively, were as follows:

Adenomas:	0/53 (0), 0/27 (0), 2/36 (6%), 0/19 (0)
Adenocarcinomas:	0/94 (0), 1/46 (2%), 0/48 (0), 4/30 (13%)
Combined:	0/94 (0), 1/46 (2%), 2/48 (4%), 4/30 (13%)

  Female mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 ppm dose group with the controls, for mammary gland adenocarcinomas and adenomas and/or adenocarcinomas combined, all at $p < 0.01$. The incidence of combined adenomas and/or adenocarcinomas at 1600 ppm (13%) were outside the historical control range of 1.3 - 4.3% of the testing laboratory. The CARC considered the mammary gland tumors (driven by adenocarcinomas) to be treatment-related.

- Adequacy of Dosing: The CARC considered dosing at the high dose of 1600 ppm to be adequate, and not excessive, based on moderate decreased body weight gains ($p \leq 0.01$) throughout the study in males (10-37%) and females (18-45%), and increased mortality in females which only occurred towards the end of the study (88%, high dose vs. 75%, controls).

CD-1 Mouse (MRID 44883901)

- In male mice, the incidence of harderian gland tumors was 0/52 (0), 2/54 (4%), 1/54 (2%), 4/55 (7%) for the control, 50, 200, 700 ppm dose groups, respectively. There was a significant increasing trend at $p<0.01$, and a significant difference in the pair-wise comparison of the 700 ppm dose group with the controls at $p<0.05$, for harderian gland adenomas. The incidence of 7% at the high-dose group exceeded the mean 1.3% (range 0 - 3.6%) for the historical controls for 80 week studies, but was within the 0-10% for historical controls for 2-year studies. Overall, the CARC did not consider the harderian gland adenomas at the high dose to be treatment-related since there was no dose-response. However, some members of the CARC considered this evidence to be equivocal.

- In female mice, the incidence of lung tumors was 0/53 (0), 0/52 (0), 0/51 (0), and 6/51 (12%) for the control, 50, 200 and 700 ppm dose groups, respectively. There was a significant increasing trend, and a significant difference in the pair-wise comparison of the 700 ppm dose group with the controls, for lung adenomas, both at $p<0.01$. The incidence of 12% in the 700 ppm group is outside the historical control incidence of both the 80-weeks (0 - 2%) studies. The CARC considered the benign lung tumors in female mice to be treatment-related.

- Adequacy of Dosing: The CARC considered the top dose of 700 ppm to be adequate and not excessive in both sexes. This was based on significantly ($p \leq 0.05$) decreased body weight throughout the study with high-dose group males and females weighing less than 6-8% compared to controls. Weight gain was reduced by 22 and 14% in high dose males and females, respectively, during the first 13 weeks of the study and by 14 and 21%, respectively, over the entire study. Furthermore, tumors were present at this dose.

Mutagenicity

Pirimicarb was not mutagenic in bacteria and did not induce a clastogenic response in mammalian cells *in vitro* or micronuclei in the bone marrow of treated mice. Nevertheless, there is clear and reproducible evidence of a positive response in an *in vitro* mammalian cell gene mutation assay with L5178Y mouse lymphoma cells. Mutagenic activity was reproducible, confined to the S9-activated portion of the assay, concentration-related and occurred at severely cytotoxic levels (causing 10% survival) to levels where >50% of the cells survived. Since the micronucleus assay has a low detection rate (43%) for agents that induce liver tumors (Morita *et al.*, 1997), the CARC recommends that an additional *in vivo* assay be performed to determine whether pirimicarb is active in whole animal assays with non-hematopoietic tissue. Therefore, overall there is some concern for mutagenicity.

Structure Activity Relationship

No suitable analogues for pirimicarb were located.

Mode of Action

No mode of action data were submitted.

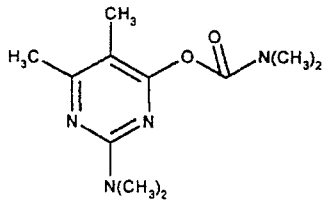
In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified Pirimicarb as **"Likely to be Carcinogenic to Humans"**. This was based on multiple benign and/or malignant tumors (liver, lung, ovary, mammary gland) seen in male and female Swiss mice and lung tumors in female CD-1 mice, at doses that were adequate to assess the carcinogenicity of pirimicarb, and some concern for mutagenicity. The Committee recommended that a linear low-dose extrapolation approach (Q1*), based on the appropriate tumor response in mice, be used to estimate human cancer risk.

I. INTRODUCTION

On May 11, 2005, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of pirimicarb. This was the first time that this compound was assessed for carcinogenicity by the CARC.

II. BACKGROUND INFORMATION

Chemical Name: Pirimicarb (5,6-Dimethyl-2-dimethylamino-4-dimethylcarbamoyl-oxy-pyrimidine) is a carbamate pesticide
Emperical Formula: $C_{11}H_{18}N_4O_2$
CAS Registry No.: 23103-98-2
PC Code: 106101
Structure:



Pirimicarb belongs to dimethylcarbamate group of insecticides and is active against both organophosphate and non-organophosphate resistant aphids. It has been used on a wide range of crops including cereals, sugar beet, potatoes, fruits, vegetables for the control of aphids. It is applied as an aerosol, dispersible granules, dispersible powders, emulsifiable concentrates, smoke generator, or ULV spray.

III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Chronic Toxicity/Carcinogenicity Study in Wistar Rats

Reference: Tinston, D.J. (1992) Pirimicarb-Two Year Feeding Study in Rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Report No. CTL/P/3040. February 28, 1992. MRID 44883802. Unpublished.

A. Experimental Design

Pirimicarb (97.3% a.i.) was administered in the diet to Wistar derived rats (52/sex/dose) at dose levels of 0, 75, 250, or 750 ppm (0, 3.7, 12.3, and 37.3 mg/kg/day in males and 0, 4.7, 15.6, and 47.4 mg/kg/day in females, respectively) for 24 months. In addition, 12 rats/sex/dose were terminated at 53 weeks and 8-12 rats/sex/dose were used for plasma,

erythrocyte, and brain cholinesterase activity determinations at 27, 53, 79, and 105 weeks.

B. Discussion of Mortality and Tumor Data

Survival Analysis

There were no statistically significant incremental changes in mortality with increasing doses of Pirimicarb in male (Table 1) or female rats (Table 2) (L. Brunsman, 2005).

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

Table 1. Pirimicarb - Alpk:APfSD Wistar Rat Study (MRID 44883802)

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	2/64	0/62	12/62	4/50	24/46	30/52 (58)
75	0/64	3/64	11/61	4/50	28/46	35/53 (66)
250	1/64	1/63	12/62	4/50	21/46	27/52 (52)
750	0/64	1/64	12/63	6/51	21/45	28/52 (54)

[+]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 104.
( )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. Pirimicarb - Alpk:APfSD Wistar Rat Study (MRID 44883802)

Female 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	2/64	0/62	11/62	2/51	12/49	16/53 (30)
75	0/64	0/64	12/64	7/52	13/45	20/52 (38)
250	0/64	0/64	12/64	9/52	10/43	19/52 (37)
750	1/64	0/63	12/63	3/51	12/48	16/52 (31)

[*]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 104.

( )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 $p < 0.01$.

Tumor Analysis

There were no compound-related increases in tumors in male rats.

As shown in Table 3, female rats had a significant increasing trend for uterine stromal cell polyps (considered to be a non-neoplastic lesion), at $p<0.05$ (L. Brunsman, 2005). Stromal cell polyp incidence was 5/62 (8%), 6/64 (9), 9/64 (14%), and 11/63 (17%) for 0, 75, 250, and 750 ppm, respectively. There were no historical control data reported for uterine stromal polyps.

Uterine stromal cell sarcomas were observed at 750 ppm. The incidence was 2/63 (3%) compared to 0/62 (0%) in the controls (Table 3). The incidence of 3% for sarcomas at high dose exceeded the historical incidence range of 0 -2% from Bayer AG and 0 - 1.82% of the Charles River historical controls. Historical control data were not provided by the testing laboratory. The statistical analyses of the female rats were based upon Fisher's Exact Test and the Exact Test for Trend.

Table 3. Pirimicarb - Alpk:APfSD Wistar Rat Study (MRID 44883802)

Female Uterine Polyps and Stromal Cell Tumor Rates+ and Fisher's Exact Test and Exact Test for Trend Test Results

	Dose (ppm)			
	0	75	250	750
Polyps (%)	5/62 (8)	6/64 (9)	9[a]/64 (14)	11/63 (17)
p =	0.04824*	0.52239	0.21617	0.09544
Sarcomas (%)	0/62 (0)	0/64 (0)	0/64 (0)	2[b]/63 (3)
p =	0.06126	1.00000	1.00000	0.25200

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

[a]First polyp observed in an interim sacrifice animal at week 53, dose 250 ppm.
[b]First sarcoma observed at week 87, dose 750 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 $p < 0.01$.

C. Non-Neoplastic Lesions

At the 12 month sacrifice, no findings of toxicological significance were identified. Increased incidence of (41% vs 0 in controls) hepatocellular hypertrophy was observed in high-dose males, however, no hepatocellular hypertrophy at final necropsy was observed. Therefore, this finding was considered an adaptive response.

When considering animals that died intercurrently or were sacrificed at the terminal sacrifice, an effect on nervous tissue was observed (Table 4). The incidence of minimal to moderate brain necrosis in high dose males increased 11.5% compared to 1.9% in the controls. The incidence was not dose-related. In males, a dose-related increase in slight to marked muscle degeneration was observed. The incidence was 11/52 (21%), 12/53 (23%), 17/52 (33%) and 19/52 (37%) at 0, 75, 250 and 750 ppm, respectively. In high-dose females, the increased incidence of moderate to marked sciatic nerve demyelination was 53.8% vs 11.5% in controls. Further, in the high-dose females, an increased incidence of slight to moderate skeletal muscle degeneration was observed. The incidence was 28.8% compared to 3.8% in the controls. The increased muscle degeneration may be associated with the increased sciatic nerve demyelination observed in high dose females. Sciatic nerve demyelination at lower doses was comparable to controls.

Table 4. Incidences of non-neoplastic histological findings in male and female rats dosed with pirimicarb for up to 104 weeks.[a]

Finding/Necropsy		Dose (ppm)			
		0	75	250	750
MALES					
Intercurrent Deaths and Final Necropsy					
Number examined		52	53	52	52
Voluntary muscle degeneration	Minimal	9	5	6	6
	Slight	4	8	9	13
	Moderate	4	1	8	5
	Marked	3	3	0	1
	Total	**20**	**17**	**23**	**25**
Brain; necrosis	Minimal	0	1	0	1
	Slight	0	1	1	2
	Moderate	1	0	0	3
	Total	**1**	**2**	**1**	**6**
FEMALES					
Intercurrent Deaths and Final Necropsy					
Number examined		53	52	52	52
Sciatic nerve, demyelination	Minimal	11	11	8	4
	Slight	35	33	32	22
	Moderate	6	4	8	25
	Marked	0	1	0	3
	Total	**52**	**49**	**48**	**51**
Voluntary muscle, degeneration	Minimal	0	1	4	3
	Slight	2	1	0	10
	Moderate	0	0	0	2
	Marked	0	0	0	0
	Total	**2**	**2**	**4**	**15**

a Data calculated by the reviewers from data obtained from the Study Report.

D. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing at the high dose of 750 ppm was considered to be adequate in both sexes to assess the carcinogenicity of pirimicarb in rats. In females, this was based on significantly decreased mean body weights (13% ($p \leq 0.01$)) and body weight gains (9-19%) compared to controls and an increased severity of sciatic nerve demyelination (moderate demyelination -25/52 vs 6/53 controls) and minimal to marked muscle degeneration (15/52 vs 2/53 controls). In males, this was based on decreased body weight gains (6 - 13% from week 1 to 86 ($p \leq 0.05$ or 0.01) and increased brain necrosis in males at 750 ppm. In the high-dose males, nervous tissue was affected as indicated by increased incidence of minimal to moderate necrosis of brain (6/52 vs 1/52 controls). Plasma, blood, or brain cholinesterase measurements were not affected.

2. Carcinogenicity Study in Swiss Mice (MRID 44883803)

Reference: Sotheran, M.F, Banham, P.B., Jackson, D.G., *et al.* (1980) Pirimicarb-Lifetime Study in the Mouse. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Report No. CTL/P/491. December 24, 1980. MRID 44883803. Unpublished.

A. Experimental Design

Swiss-derived mice (60/sex/dose) were fed diets containing pirimicarb at dose levels of 0, 200, 400 and 1600 ppm (0, 10, 20, and 80 mg/kg/day for males and females, respectively) for 94 weeks. All animals were sacrificed when overall mortality approached 80% at week 94. Two control groups of 60 mice per sex were combined for these analyses as there were no statistically significant differences in mortality, body weight, body weight gain, food consumption or food utilization between these two control groups.

B. Discussion of Mortality and Tumor Data

Survival Analysis

There were no statistically significant incremental changes in mortality with increasing doses of Pirimicarb in male mice (Table 5) (L. Brunsman, 2005). Female mice showed a significant increasing trend in mortality with increasing doses of Pirimicarb, as well as a significant difference in the pair-wise comparison of the 1600 ppm dose group with the controls, both at $p < 0.01$ (Table 6).

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

Table 5. Pirimicarb - Alderley Park Swiss-Derived Mouse Study (MRID 44883803)

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

Weeks

Dose (ppm)	1-26	27-52	53-78	79-96[f]	Total
0	11/119[m]	10/108	38/98	25/60	84/119 (71)
200	5/59[m]	10/54	13/44	19/31	47/59 (80)
400	6/60	5/52	19/47	14/28	44/60 (73)
1600	1/60	6/59	24/53	16/29	47/60 (78)

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

[f]Final sacrifice at week 95.
[m]There was no histopathology information on mouse #18 in the control group or mouse #177 in the 200 ppm dose group so these animals have been omitted from the analyses.

( )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 6. Pirimicarb - Alderley Park Swiss-Derived Mouse Study (MRID 44883803)

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

Weeks

Dose (ppm)	1-26	27-52	53-78	79-96[f]	Total
0	10/120	8/110	43/102	29/59	90/120 (75)**
200	0/60	8/60	21/52	13/31	42/60 (70)
400	2/60	8/58	12/50	25/38	47/60 (78)
1600	4/60	17/56	18/39	14/21	53/60 (88)**

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

[f]Final sacrifice at week 95.

( )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 $p < 0.01$.

Discussion of Tumor Data

As shown in Table 7, male mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 ppm dose group with the controls, for liver adenomas, carcinomas and adenomas and/or carcinomas combined, all at $p < 0.01$. Pair-wise comparison showed a significant ($p<0.05$) increase in hepatocellular carcinomas (13/51, 25%) and adenomas and/or carcinomas combined (18/51, 35%) at 200 ppm when compared to controls (carcinomas: 10/104, 10%; adenoma/carcinoma 22/104, 21%). Pair-wise comparison showed a significant ($p<0.05$) increase in hepatocellular adenomas and/or carcinomas combined (17/48, 35%) at 400 ppm when compared to controls (22/104, 21%). Pair-wise comparison showed a significant increase ($p < 0.01$) in liver adenomas (19/52, 37%), carcinomas (17/52, 33%) and adenomas and/or carcinomas combined (32/52, 62%) at 1600 ppm when compared to controls (22/104, 21%). The combined incidence of adenomas and/or carcinomas at the 1600 ppm (62%) exceeded historical control range of 0-27% from the testing laboratory (1965-1975) for the combined liver tumors.

As shown in Table 8, male mice had a significant increasing trend, and a significant difference in the pair-wise comparisons of the 1600 ppm dose group with the controls, for lung adenomas ($p < 0.01$). The incidence of lung adenomas was 17/103 (17%), 9/51 (18%), 8/48 (17%), and 19/54 (35%) for 0, 200, 400 and 1600 ppm, respectively. There was a significant ($p < 0.01$) increasing trend for lung adenomas and/or carcinomas combined at 1600 ppm. The incidence was 18/103 (17), 9/51 (18%), 8/48 (17%) and 19/54 (35%) for 0, 20, 400 and 1600 ppm, respectively. At 1600 ppm, pair-wise comparison showed a significant increase in lung adenomas at $p<0.01$ (19/54, 35%), and adenomas and/or carcinomas combined at $p<0.05$ (19/54, 35%) when compared to controls (adenomas: 17/103, 17%; adenomas and carcinomas combined: 18/103, 17%). The incidence of 35% for lung adenomas, and adenomas and/or carcinomas combined, at 1600 ppm is outside the historical control range of 0 -28% of the testing laboratory for the combined tumors. The statistical analyses of the male mice were based upon Fisher's Exact Test and the Exact Test for Trend (Tables 7 and 8).

As shown in Table 9, female mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 ppm dose group with the controls, for liver carcinomas and adenomas and/or carcinomas combined, all at $p< 0.01$. There were significant differences in the pair-wise comparisons of the 400 ppm dose group with the controls for liver adenomas and adenomas and/or carcinomas combined, both at $p < 0.05$. There was also a significant difference in the pair-wise comparison of the 200 ppm dose group with the controls for liver adenomas and/or carcinomas combined at $p < 0.05$. The incidence of adenomas was 4/107 (4%), 3/53 (6%), 7/53 (13%), and 4/42 (10%) at 0, 200, 400, and 1600 ppm, respectively. The incidence of carcinomas was 2/95 (2%), 3/47 (6%), 3/47 (6%) and 5/32 (16%). The incidence of adenomas and/or carcinoma combined was

5/107 (5%), 6/53 (11%), 9/53 (17%) and 9/42 (21%). The incidence of 16% for carcinomas, and 21% for the adenomas and/or carcinomas combined at 1600 ppm exceeded the control incidence of 5%. Historical control data for liver tumors in female mice were not provided.

As shown in Table 10, female mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 ppm dose group with the controls, for lung adenomas and adenomas and/or carcinomas combined, at $p < 0.01$. The incidence of adenomas was 13/108 (12%), 9/57 (16%), 11/56 (20%), and 18/52 (35%) for 0, 20, 400, and 1600 ppm, respectively. The incidence of adenomas and/or carcinomas combined were 14/108 (13%), 9/57 (16%), 12/56 (21%), and 18/52 (35%). The incidences of adenomas and/or carcinomas combined exceeded the historical control range for adenomas and/or carcinomas combined (0-15.5%) of the testing laboratory.

Table 11 provides the ovarian papillary cystadenoma tumor incidence. There was a significant increasing trend, and significant differences in the pair-wise comparison of the 1600 ppm dose group with the controls, for ovarian papillary cystadenomas, at $p < 0.01$. The tumor incidence was 0/75 (0%), 1/35 (3%), 3/44 (7%) and 3/24 (13%) for 0, 200, 400, and 1600 ppm, respectively. Tumor incidences at mid- and high-doses were outside the spontaneous rate of 0%, and outside the range 0.7-1.3% for the historical controls from the testing laboratory.

There were significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 ppm dose group with the controls, for mammary gland adenocarcinomas and adenomas and/or adenocarcinomas combined, at $p < 0.01$ (Table 12). The incidence of adenocarcinoma was 0/94 (0%), 1/46 (2%), 0/48 (0%), 4/30 (13%) for the 0, 200, 400, and 1600 ppm, respectively; and adenoma and/or adenocarcinoma combined was 0/94 (0%), 1/46 (2%), 2/48 (4%), and 4/30 (13%), respectively. The incidence of combined adenomas and/or adenocarcinomas at 1600 ppm (13%) were outside the historical control range of 1.3 - 4.3% of the testing laboratory. The statistical analyses of the female mice were based upon Peto's Prevalence Test (Tables 9 through 12).

Table 7. Pirimicarb - Alderley Park Swiss-Derived Mouse Study (MRID 44883803)

Male Liver Tumor Rates[+] and Fisher's Exact Test and Exact Test for Trend Test Results

	Dose (ppm)			
	0[m]	200[m]	400[n]	1600
Adenomas (%)	14[a]/104 (13)	5/51 (10)	11/48 (23)	19/52 (37)
p =	0.00022**	0.81812	0.11140	0.00113**
Carcinomas (%)	10/104 (10)	13[b]/51 (25)	8/48 (17)	17/52 (33)
p =	0.00153**	0.01025*	0.16296	0.00052**
Combined (%)	22[c]/104 (21)	18/51 (35)	17[c]/48 (35)	32[d]/52 (62)
p =	0.00000**	0.04648*	0.04890*	0.00000**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 45.

[a]First adenoma observed at week 47, dose 0 ppm.

[b]First carcinoma observed at week 45, dose 200 ppm.

[m]There was no histopathology information on mouse #18 in the control group or mouse #177 in the 200 ppm dose group so these animals have been omitted from the analyses.

[n]Animal #199 of the 400 ppm dose group had a liver nodule but autolysis made differentiation impossible so this animal was not included in the total count of those having a liver adenoma or carcinoma.

[c]Two animals in each of the control and 400 ppm dose groups had both an adenoma and a carcinoma.

[d]Four animals in the 1600 ppm dose group had both an adenoma and a carcinoma.

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 8. Pirimicarb - Alderley Park Swiss-Derived Mouse Study (MRID 44883803)

Male Lung Tumor Rates[+] and Fisher's Exact Test and Exact Test for Trend Test Results

	Dose (ppm)			
	0[m]	200[m]	400	1600
Adenomas (%)	17/103 (17)	9[a]/51 (18)	8/48 (17)	19/54 (35)
p =	0.00296**	0.51314	0.57566	0.00799**
Carcinomas (%)	1/103 (1)	0/51 (0)	0/48 (0)	1[b]/54 (2)
p =	0.3780	1.00000	1.00000	0.57104
Combined (%)	18/103 (17)	9/51 (18)	8/48 (17)	19[c]/54 (35)
p =	0.00427**	0.57225	0.63177	0.01205*

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 47.

[a]First adenoma observed at week 47, dose 200 ppm.

[b]First carcinoma observed at week 85, dose 1600 ppm.

[m]There was no histopathology information on mouse #18 in the control group or mouse #177 in the 200 ppm dose group so these animals have been omitted from the analyses.

[c]One animal in the 1600 ppm dose group had both adenoma and carcinoma

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 9. Pirimicarb - Alderley Park Swiss-Derived Mouse Study (MRID 44883803)

Female Liver Tumor Rates[+] and Peto's Prevalence Test Results

	Dose (ppm)			
	0	200	400	1600
Adenomas (%)	4/107 (4)	3/53 (6)	7/53 (13)	4[a]/42 (11)
p =	0.06598	0.23009	0.02649*	0.07957
Carcinomas (%)	2/95 (2)	3/47 (6)	3/47 (6)	5[b]/32 (16)
p =	0.00301**	0.06893	0.18818	0.00577**
Combined (%)	5[c]/107 (5)	6/53 (11)	9[c]/53 (17)	9/42 (21)
p =	0.00052**	0.04377*	0.01780*	0.00092**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 48, dose 1600 ppm.
[b]First carcinoma observed at week 59, dose 1600 ppm.

[c]One animal in each of the control and 400 ppm dose groups had both an adenoma and a carcinoma.

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 10. Pirimicarb - Alderley Park Swiss-Derived Mouse Study (MRID 44883803)

Female Lung Tumor Rates+ and Peto's Prevalence Test Results

	Dose (ppm)			
	0	200	400	1600
Adenomas (%)	13/108 (12)	9[a]/57 (16)	11/56 (20)	18/52 (35)
p =	0.00001**	0.27442	0.14475	0.00001**
Carcinomas (%)	1[b]/75 (1)	0/35 (0)	1/44 (2)	0/24 (0)
p =	0.65477	0.73060	0.33330	0.73060
Combined (%)	14/108 (13)	9/57 (16)	12/56 (21)	18/52 (35)
p =	0.00002**	0.32223	0.11662	0.00002**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 39, dose 200 ppm.
[b]First carcinoma observed at week 72, dose 0 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 11. Pirimicarb - Alderley Park Swiss-Derived Mouse Study (MRID 44883803)

Female Ovarian Papillary Tumor Rates[+] and Peto's Prevalence Test Results

	Dose (ppm)			
	0	200	400	1600
Cystadenomas (%)	0/75 (0)	1/35 (3)	3/44 (7)	3[a]/24 (13)
p =	0.00697**	0.09835	0.06541	0.00128**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First cystadenoma observed at week 72, dose 1600 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 12. Pirimicarb - Alderley Park Swiss-Derived Mouse Study (MRID 44883803)

Female Mammary Gland Tumor Rates[+] and Peto's Prevalence Test Results

	Dose (ppm)			
	0	200	400	1600
Adenomas (%)	0/53 (0)	0/27 (0)	2[a]/36 (6)	0/19 (0)
p =	0.55121	-	0.07633	-
Adenocarcinomas (%)	0/94 (0)	1/46 (2)	0/48 (0)	4[b]/30 (13)
p =	0.00008**	0.10295	-	0.00156**
Combined (%)	0/94 (0)	1/46 (2)	2/48 (4)	4/30 (13)
p =	0.00097**	0.10295	0.05343	0.00124**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 83, dose 400 ppm.
[b]First carcinoma observed at week 60, dose 1600 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 $p < 0.01$.

C. Non-Neoplastic Lesions

There were no significant non-neoplastic histopathologic findings were observed.

D. Adequacy of Dosing for Assessment of Carcinogenicity

The CARC considered dosing at the high dose of 1600 ppm to be adequate, and not excessive, based on moderate decreased body weight gains ($p \leq 0.01$) throughout the study in 1600 ppm males (10-37%) and females (18-45%), and increased mortality by week 94 in females (88%, high dose vs. 75%, controls). No changes of toxicological concern were noted in clinical signs, gross pathology, or non-neoplastic histopathology.

3. Carcinogenicity Study in CD-1 Mice (MRID 44883901)

Reference: Rattray, N. (1998) Pirimicarb: 80-week carcinogenicity study in mice. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Study No. PM1035. November 27, 1998. MRID 44883901. Unpublished

A. Experimental Design

Pirimicarb (97.5% a.i., batch/lot #Y00032/049) was administered to groups of 55 male and 55 female C57BL/10J$_f$CD-1 mice in diet at concentrations of 0, 50, 200, and 700 ppm (0, 6.7, 26.6, and 93.7 mg/kg/day for males and 0, 9.0, 37.1 and 130.3 mg/kg/day for females, respectively) for 80 weeks.

B. Discussion of Mortality and Tumor Data

Survival Analysis

Male mice showed a significant decreasing trend in mortality with increasing doses of Pirimicarb, as well as a significant negative difference in the pair-wise comparison of the 700 ppm dose group with the controls, both at $p < 0.05$ (Table 13). Female mice showed a significant increasing trend in mortality with increasing doses of Pirimicarb at $p < 0.05$ (Table 14).

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

Table 13. Pirimicarb - C57BL/10J$_f$CD-1 Alpk Mouse Study (MRID 44883901)

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

	Weeks			
Dose (ppm)	1-26	27-52	53-82[f]	Total
0	1/55	1/54	6/53	8/55 (15)*[n]
50	0/55	1/55	9/54	10/55 (18)
200	0/55	1/55	3/54	4/55 (7)
700	0/55	0/55	2/55	2/55 (4)*[n]

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

[f]Final sacrifice at week 81.
[n]Negative trend or negative change from control.
( )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 14. Pirimicarb - C57BL/10J$_f$CD-1 Alpk Mouse Study (MRID 44883901)

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

	Weeks			
Dose (ppm)	1-26	27-53	54-82[f]	Total
0	1/55	1/54	5/53	7/55 (13)*
50	1/55	1/54	8/53	10/55 (18)
200	1/55	3/54	4/51	8/55 (15)
700	1/55	2/54	11/52	14/55 (25)

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

[f]Final sacrifice at week 81.
[n]Negative trend or negative change from control.
( )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 $p < 0.01$.

Tumor Analysis

Male mice had a significant increasing trend at $p < 0.01$, and a significant difference in the pair-wise comparison of the 700 ppm dose group with the controls at $p < 0.05$, for harderian gland adenomas. The incidence was 0/52 (0%), 2/54 (4%), 1/54 (2%) and 4/55 (7%) for the 0, 50, 200, and 700 ppm, respectively. The incidence of 7% at the high-dose group exceeded the mean 1.3 (range 0 - 3.6%) for the historical controls for 80 week studies, but was less than 0 - 10% for historical controls for 2-year studies. The statistical analyses of the male mice were based upon Peto's Prevalence Test (Table 15).

Female mice had a significant increasing trend, and a significant difference in the pair-wise comparison of the 700 ppm dose group with the controls, for lung adenomas, both at $p <$

0.01. The incidence was 0/53 (0%), 0/52 (0%), 0/51 (0%) and 6/51 (12%) for the 0, 50, 200, and 700 ppm, respectively. The incidence of 12% in the 700 ppm group is outside the historical control incidence of both the 80-weeks (0 - 2%) studies. The statistical analyses of the female mice were based upon Peto's Prevalence Test (Table 16).

Historical control data was generated between 1984 - 1994 for the 18-month studies and 1988 - 1996 for the 2-year studies.

Table 15. Pirimicarb - C57BL/10J$_f$CD-1 Alpk Mouse Study (MRID 44883901)

Male Harderian Gland Tumor Rates[+] and Peto's Prevalence Test Results

	Dose (ppm)			
	0	50	200	700
Adenomas# (%)	0/52 (0)	2/54 (4)	1[a]/54 (2)	4/55 (7)
p =	0.00102**	0.15866	0.15866	0.01677*

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 58, dose 200 ppm.

#There were no carcinomas observed.

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 16. Pirimicarb - C57BL/10J$_f$CD-1 Alpk Mouse Study (MRID 44883901)

Female Lung Tumor Rates[+] and Peto's Prevalence Test Results

	Dose (ppm)			
	0	50	200	700
Adenomas# (%)	0/53 (0)	0/52 (0)	0/51 (0)	6[a]/51 (12)
p =	0.00008**	-	-	0.00914**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 60, dose 700 ppm.

#There were no carcinomas observed.

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 $p < 0.01$.

Historical control data were generated between 1984 - 1994 for the 18-month studies and 1988 - 1996 for the 2-year studies.

C. Non-Neoplastic Lesions

There were no significant non-neoplastic histopathologic findings were observed.

D. Adequacy of Dosing for Assessment of Carcinogenicity

The CARC considered the top dose of 700 ppm to be adequate and not excessive in both sexes. This was based on significantly ($p \leq 0.05$) decreased body weight throughout the study with high-dose group males and females weighing less than 6-8% compared to controls. Weight gain was reduced by 22 and 14% in high dose males and females, respectively, during the first 13 weeks of the study and by 14 and 21%, respectively, over the entire study. Furthermore, tumors were present at this dose.

IV. TOXICOLOGY

1. Metabolism

Pirimicarb is extensively and rapidly metabolized by entero-hepatic circulation and excreted in the urine, feces and expired air. Total recovery of the administered dose was 92-99% by 96 hours. In biliary excretion group 74-78% of the administered dose was excreted in bile by 48 hours. The metabolic profiles were similar between sexes and doses. Urine was the primary route of excretion (74-84% in the mass balance study groups and 54-64% in the biliary study groups) and feces (6.8-16.6% in non-biliary groups) and bile (13.1-16.5% of dose) were secondary routes of excretion. Expired air accounted for ≤0.1 of the dose in the pirimidyl-[^{14}C]-pirimicarb-treated rats, but 67% of dose in the carbonyl-[^{14}C]-pirimicarb-treated rats, indicating that the carbamate moiety is rapidly metabolized to CO_2. Parent was not isolated in any matrix, indicating complete metabolism of pirimicarb. A total of 30 metabolites, including CO_2, were isolated and 18 of these were identified accounting for 69-88% of the dose. The major proposed route of metabolism was hydrolysis of the carbamate moiety to produce 5,6-dimethyl-2-dimethylamino-4-hydroxypyrimidine (Metabolite IV, 4-16% of dose). This step was followed by N-demethylation to produce the principal metabolite, 5,6-dimethyl-2-methylamino-4-hydroxypyrimidine (Metabolite I, 21-49% of dose), and 2-amino-5,6-dimethyl-4-hydroxypyrimidine (Metabolite II, 3-10% of dose). Alternatively, Metabolite IV could be conjugated with glucuronide to form 1 of 2 isomers (Metabolites III and XVI, 4-14% of dose). Other minor metabolites isolated from urine and feces included 6-hydroxymethyl-2-methylamino-5-methylpyrimidin-4-ol (Metabolite V, 2-7% of doses) and two mercapturate conjugates: 5,6-Dimethyl-2-methylamino-5/6-hydroxypyrimidine-4-mercapturate (Metabolite VI, 2-11% of dose) and 5,6-Dimethyl-2-dimethylamino-5/6-hydroxypyrimidine-4-mercapturate (Metabolite VII, 1-5% of dose). The metabolic pathway is consistent with the available data from the reviewed studies. **MRID Nos.:** 44883828, 44883829, 44883830, 44883836 and 44903001.

2. Mutagenicity

Pirimicarb was not mutagenic in bacteria and did not induce a clastogenic response in mammalian cells *in vitro* or micronuclei in the bone marrow of treated mice. Nevertheless, there is clear and reproducible evidence of a positive response in an *in vitro* mammalian cell gene mutation assay with L5178Y mouse lymphoma cells. Mutagenic activity was reproducible, confined to the S9-activated portion of the assay, concentration-related and occurred at severely cytotoxic levels (causing 10% survival) to levels where >50% of the cells survived. Since the micronucleus assay has a low detection rate (43%) for agents that induce liver tumors (Morita *et al.*, 1997), the CARC recommends that an additional *in vivo* assay be performed to determine whether pirimicarb is active in whole animal assays with

non-hematopoietic tissue.

(i) In an Ames assay, when tested in Salmonella typhimurium strains TA98, TA100, TA1535 and TA1538 at concentrations up to 2500 µg/plate, pirimicarb was nonmutagenic with metabolic activation. This study is classified as acceptable and satisfies the requirements for FIFRA Test Guidelines 84-2 for *in vitro* Mutagenicity (bacterial reverse gene mutation) data (**MRID No.** 43496004).

(ii) In an Ames assay, when tested in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 at concentrations up to 2500 µg/plate, pirimicarb was non mutagenic with or without metabolic activation. This study is classified as acceptable and satisfies the requirements for FIFRA Test Guidelines 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data (**MRID No.** 43496005).

(iii) In an Ames assay, when tested in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 and strains WP2P and WP2PuvrA of *E. coli* at concentrations up to 5000 µg/plate (Limit Dose), pirimicarb was non mutagenic with or without metabolic activation. This study is classified as acceptable and satisfies the requirements for FIFRA Test Guidelines 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data (**MRID No.** 44883810).

(iv) In a *vitro* mammalian cell gene mutation assay at thymidine kinase locus, L5178Y TK +/- mouse lymphoma cells were repeatedly exposed to pirimicarb in DMSO at concentrations ranging from 313 to 5000 µg/mL with S9 and from 10 - 316 µg/mL without S9 activations. Pirimicarb induced dose-related, statistically significant increased in mutant frequencies in the presence of S9. This study is classified as acceptable and satisfies the requirements for FIFRA Test Guidelines 84-2 for *in vitro* mammalian forward gene mutation data (**MRID No.** 44883833).

(v) In an *in vitro* mammalian chromosomal aberration assay with human primary lymphocytes, when tested up to solubility limit of 500 µg/ml, pirimicarb was not mutagenic with or without metabolic activation. This study is classified as acceptable and satisfies the requirements for FIFRA Test Guidelines 84-2 for *in vitro* cytogenetic mutagenicity data (**MRID No.** 43496006).

(vi) In a mouse micronucleus assay, no increase in micronuclei was seen following oral dosing at doses up to and including 69.3 mg/kg to C57B1/CJfCD-1 mouse. This study is classified as acceptable and satisfies the requirements for FIFRA Test Guidelines 84-2 for *in vivo* cytogenetic mutagenicity data (**MRID No.** 43496008).

(vii) In unscheduled DNA synthesis (UDS) assay with rat hepatocytes, Pirimicarb at

concentrations ranging from 200 µg/mL to 250 µg/mL did not induced UDS in primary rat hepatocytes. This study is classified as acceptable and satisfies the requirements for FIFRA Test Guidelines 84-2 for other genotoxic mutagenicity data **(MRID No.** 43496007).

3. Structure-Activity Relationship

There are no suitable structural analogues to pirimicarb were found.

4. Subchronic and Chronic Toxicity

a) Subchronic Toxicity

Rat

MRID 4364103: In a non-guideline subchronic study 20 Wistar derived Alderly Park female rats/dose were fed diets containing 0, 100, 175, 250 or 750 ppm (0, 10, 17.5, 25 or 75 mg/kg) PP062 tech. (94% a.i.) for 8 weeks. The objective of the study was to confirm the NOEL in females for use in chronic studies; only parameters evaluated were clinical signs, food and water consumption and bodyweight gain. The study was done prior to implementation of GLP Guidelines, and therefore, does not fall under the purview of either GLP or Quality Assurance requirements.

Systemic toxicity observed as decreased bodyweight at 750 ppm might be due in part to decreased food consumption associated with palatability. The NOEL = 250 ppm.

The study is classified as **supplementary** and not upgradable, since it was of limited design to answer specific questions. The study **does not satisfy** the requirements (82-1a) for a oral subchronic toxicity study in rats.

MRID 44233103: In a subchronic toxicity study (MRID 44233103), pirimicarb (purity unspecified) was administered to albino Wistar rats (25 rats/sex/dose group) at 250 or 750 ppm in the diet or at 25 mg/kg/day by gavage for 90 days. Following the 90-day treatment period, five rats in each group were maintained without treatment for a 28-day recovery period.

Pirimicarb exerted a cholinergic effect immediately after dosing in rats treated at 25 mg/kg/day by gavage. During the 90-day treatment period, plasma cholinesterase activity levels of gavage-dosed animals were 33-39% lower in males and 26-58% lower in females compared to corresponding control activity levels. During the 28-day recovery period, activity levels in both sexes approached concurrent control levels. No other treatment-related effects were observed in this group. The death or removal of 7 males and 5 females

in the 25 mg/kg/day gavage-dosed group resulted from the trauma from repeated cannulation.

No treatment-related deaths or other effects were observed in any treatment group. No treatment-related effects were observed in rats fed dietary concentrations of 250 or 750 ppm. No treatment-related differences in clinical signs, body weights, food consumption, hematology, erythrocyte or brain cholinesterase activity, absolute or relative organ weights, or gross or microscopic changes were observed. Ophthalmoscopic, clinical blood chemistry, and urinalysis parameters were not measured. No neoplastic tissue was observed. **For the oral dosing (feeding) portion of the study, the NOEL is 750 ppm (75 mg/kg/day), the highest dose tested; a LOEL was not established. For the gavage dosing portion of the study, the LOEL is 25 mg/kg/day, the only dose tested, based on plasma cholinesterase inhibition in both sexes; a NOEL was not established.**

This 90-day subchronic toxicity study is classified **unacceptable (82-1a)** because the test substance was inadequately characterized. The study may be upgraded and found to be acceptable if complete characterization of the test substance is provided.

MRID 00108374: In this subchronic study, groups of 25 male and 25 female Wistar rats were fed Pirimicarb® in diet at concentrations of 0, 250, or 750 ppm (0, 12.5, and 37.5 mg/kg/day, respectively); an additional groups of rats were gavaged 25 mg/kg/day of pirimicarb by stomach tube.

The body weights, food consumption, hematology and pathology of the test animals were comparable to control animals. The brain, RBC and plasma cholinesterase levels in the 250 and 750 ppm groups were not affected. At the 25 mg/kg/day (gavage study), plasma cholinesterase was markedly inhibited in males (27%); these effects disappeared after cessation of dosing. **The LOEL for ChE = 25 mg/kg/day, based on plasma ChE inhibition in males. The NOEL is < 25 mg/kg/day.**

The study is **Acceptable** for the purpose of determining the dose levels ChE inhibition, but **does not satisfy** the requirements (82-1a) for a oral subchronic study in rats.

MRID 44233101: In a subchronic neurotoxicity study, pirimicarb (97.6% a.i.) was administered to Alpk:APfSD (Wistar-derived) rats (12/sex/dose) at dietary concentrations of 0, 75, 250 or 1000 ppm (0, 5.6, 19.2 or 77.1 mg/kg/day for males; 0, 6.6, 21.8 or 84.4 mg/kg/day for females) for 13 weeks. All rats were evaluated by functional observation battery (FOB) and motor activity testing prior to treatment and during weeks 5, 9, and 14. Six rats/sex/group were evaluated for neuropathology and the remaining 6 rats/sex/group were evaluated for cholinesterase activities (plasma, erythrocyte, and brain) at the end of the study.

No rats died during the study. No treatment-related neurotoxicological effects or differences in FOB assessment or motor activity results were observed. The 1000 ppm treatment groups had mean final body weights 8-9% lower than the control body weights. Both sexes consumed less food than the controls; mean weekly food consumption values were ≤6% lower for males and 7-20% lower for females compared to the control values. The 250 ppm treatment groups had mean body weights ≤5-6% lower than the controls that were significantly ($p \leq 0.05$) decreased for males at weeks 7-14, and for females at weeks 9 and 12-14. Food consumption was not affected by treatment. The 75 ppm treatment groups appeared to be unaffected by treatment. For all treatment groups, no treatment-related differences in absolute or relative brain weights or in brain, erythrocyte, plasma cholinesterase or neuropathy target esterase activities were observed. No treatment-related gross pathological abnormalities were observed in any treatment group. No macroscopic or microscopic abnormalities in nervous system tissues from 1000 ppm group rats were observed. The positive control data for the laboratory was considered adequate to assure that the laboratory could interpret the data. **No neurotoxicological effects were observed at 1000 ppm, the highest dose tested. The toxicological LOAEL for this study is 250 ppm (19.2 mg/kg/day), based on decreased body weights in both sexes. The toxicological NOAEL is 75 ppm (5.6 mg/kg/day), based on the lack of effects on body weights and food consumption noted in this study, in conjunction with a lack of gross and/or histopathological findings in a subchronic toxicity study (MRID 44233103) reviewed in conjunction with this study.**

This study is classified **acceptable(guideline)** and satisfies the guideline requirement for a subchronic neurotoxicity study in rodents (§82-7).

b) Chronic Toxicity

Rat

MRID 44883802: In a combined chronic/oncogenicity study, pirimicarb (97.3% a.i.) was administered in the diet for 104 weeks to100 Wistar derived rats/sex/group at levels of 0, 75, 250, or 750 ppm (equivalent to approximately 0, 3.7/4.7, 12.3/15.6, or 37.3/47.4 mg/kg/day [M/F]). Twelve rats/sex/dose were terminated at approximately 53 weeks and 36 rats/sex/group were used for plasma, erythrocyte, and brain cholinesterase activity determinations at 27, 53, 79, and 105 weeks.

No differences of toxicological concern were observed in survival rates in either sex of the treated groups throughout the study when compared to the respective control groups. There were no differences of toxicological concern in food consumption, ophthalmological parameters, hematological parameters, urinalysis, gross pathology, and plasma, RBC, and brain cholinesterase activities.

Hair loss, scaly tail, piloerection, and blackened tip of tail were increased in all treatment groups versus concurrent controls, but the toxicological significance of these findings is not clear.

At 750 ppm, final body weights (week 104) were decreased ($p \leq 0.01$) with respect to concurrent controls in the females (↓13%). Body weight gains were reduced ($p \leq 0.05$ or 0.01) in the females throughout the study (↓9-19%) and in the males from week 1 to 86 (↓6-13%). Thinness was observed in the females and is considered to be related to the decreased body weights. When considering all animals that died intercurrently or were sacrificed at the final necropsy, an effect on nervous tissue was indicated by the increased incidence of minimal to moderate necrosis in the brain of males - 6/52 treated vs 1/52 controls, and an increase in females in the severity of sciatic demyelination (moderate demyelination - 25/52 treated vs 6/53 controls).. An increased incidence of minimal to marked voluntary muscle degeneration observed in females (15/52 treated vs 2/53 controls) may be associated with the observed nerve demyelination.

There were no differences of toxicological concern in the 250 and 75 ppm group.

The chronic toxicity LOAEL is 750 ppm [equivalent to 37.3/ 47.4 mg/kg/day (M/F)], based on increased severity of peripheral nerve demyelination, voluntary muscle degeneration and decreased body weights and body weight gains in females and increased brain necrosis and decreased body weight gains in males. The chronic toxicity NOAEL is 250 ppm [equivalent to 12.3/15.6 mg/kg/day (M/F)].

[See Section III.1.B for discussion of tumor data.]

The submitted study is classified as **acceptable** (**§83-5a**) and does satisfy the guideline requirements for a chronic toxicity study (§83-1) and a carcinogenicity study (§83-2) in rats.

Mouse

MRID 44883803: In a mouse carcinogenicity study, pirimicarb (97.7-98.2% a.i.) was administered to Swiss-derived mice (60/sex/group) for up to 94 weeks at 0, 200, 400, or 1600 ppm (approximately equivalent to 0, 10, 20, and 80 mg/kg/day). After 94 weeks, all surviving animals were sacrificed.

There were no changes of toxicological concern in clinical signs, gross pathology, or non-neoplastic histopathology. At 1600 ppm, overall mortality was increased 20% in females. Final % survival in the females was 11% vs 26% in the combined control groups. Body weight gains were decreased ($p \leq 0.01$) throughout the study in the 1600 ppm males and

females (10-45%) with respect to concurrent controls. There were no findings of toxicological concern in the 200 or 400 ppm groups. In conclusion, the dietary levels employed in this study were adequate to characterize the oncogenic potential of pirimicarb in both sexes of Swiss-derived mice. Chronic toxicity was characterized in mice by decreases in body weight gains and increases in mortality.

The chronic toxicity LOAEL is 1600 ppm [equivalent to 80 mg/kg/day (M/F)], based on increased mortality in females and decreased body weight gains in males and females. The chronic toxicity NOAEL for males and females is 400 ppm (equivalent to 20 mg/kg/day).

[See Section III.2.B for discussion of tumor data for Swiss mice.]

The carcinogenicity study in the mouse is determined to be **acceptable (§83-2(b))** and does satisfy the guideline requirement for an oncogenicity study in mice.

MRID 44883901: In a carcinogenicity study (MRID 44883901), pirimicarb (97.5% a.i., batch/lot #Y00032/049) was administered in the diet to groups of 55 male and 55 female C57BL/10J$_f$CD-1 Alpk mice at concentrations of 0, 50, 200, or 700 ppm (0, 6.7, 26.6, and 93.7 mg/kg/day, for males and 0, 9.0, 37.1, and 130.3 mg/kg/day, respectively, for females) for 80 weeks. The mice were killed during week 81.

No treatment-related effects were observed on clinical signs of toxicity or mortality in male or female mice receiving any dose of the test material. Absolute body weights were significantly decreased in both sexes throughout the study with high-dose group males weighing up to 6% less than controls and high-dose group females weighing up to 8% less. Weight gain was reduced by 22% and 14% in high-dose males and females, respectively, during the first 13 weeks of the study and by 14% and 21%, respectively, over the entire study. Food consumption was significantly reduced by 8% or less in high-dose group males compared with that of controls and was similar between treated and control females. High-dose group males had food efficiency values 37% and 21% less than those of controls for weeks 1-4 and weeks 1-12, respectively, and high-dose group females had food efficiency values 14%, 17%, and 13% less than those of controls for weeks 1-4, 5-8, and 1-12, respectively, showing that the effect on weight gain was not due to reduced food consumption. Erythrocyte parameters (red blood cell count, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration) showed small but significant changes in mid- and high-dose animals in both sexes, but the levels were too small to be considered toxicologically significant. Post-mortem evaluations showed no treatment-related and toxicologically significant effects on organ weight, the incidences of gross lesions, or incidences of non-neoplastic microscopic lesions.

The lowest-observed-adverse-effect level (LOAEL) for pirimicarb in mice was 700 ppm (93.7 and 130.0 mg/kg/day for males and females, respectively) based on decreased weight gain and food efficiency in both sexes. The no-observed-adverse-effect level (NOAEL) was 200 ppm (26.6 and 37.1 mg/kg/day for males and females, respectively).

[See Section III.3.B for discussion of tumor data for CD-1 mice.]

This carcinogenicity study in the mouse is **Acceptable/Guideline** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice. No major deficiencies were noted for this study.

5. Mode of Action Studies

There are no mode of action studies available at this time.

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

The Committee's assessment of the weight-of-the-evidence (WOE) is discussed below:

1. Carcinogenicity

Rat

- Uterine stromal cell sarcomas were observed in female rats at 750 ppm with an incidence of 2/63 (3%) compared to 0/62 (0%) in the controls. Although the incidence of 3% for sarcomas at the high dose exceeded the historical incidence range of 0-2% from Bayer AG and 0 - 1.82% of the Charles River historical controls, the tumors were not statistically significant at the high dose. In addition, no historical control data from the testing laboratory were provided. Therefore, the CARC did not consider the uterine stromal cell sarcomas to be treatment-related.

- No treatment-related tumors were observed in male rats.

- Adequacy of Dosing: Dosing at the high dose of 750 ppm was considered to be adequate in both sexes to assess the carcinogenicity of pirimicarb in rats. In females, this was based on significantly decreased mean body weights (13% ($p \leq 0.01$)) and body weight gains (9-19%) compared to controls and an increased severity of sciatic nerve demyelination (moderate demyelination -25/52 vs 6/53 controls) and minimal to marked muscle degeneration (15/52 vs 2/53 controls). In males, this was based on decreased body weight gains (6 - 13% from week 1 to 86 ($p \leq 0.05$ or 0.01) and increased brain necrosis in males

at 750 ppm. In the high-dose males, nervous tissue was affected as indicated by increased incidence of minimal to moderate necrosis of brain (6/52 vs 1/52 controls).

Swiss Mouse (MRID 44883803)

- In male mice, the incidences of liver adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 200, 400, and 1600 ppm dose groups, respectively, were as follows:

  Adenoma: 14/104 (13%), 5/51 (10%), 11/48 (23%), 19/52 (37%)
  Carcinoma: 10/104 (10%), 13/51 (25%), 8/48 (17%), 17/52 (33%)
  Combined: 22/104 (21%), 18/51 (35%), 17/48 (35%), 32/52 (62%)

  There were significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 ppm dose group with the controls, for liver adenomas, carcinomas, and adenomas and/or carcinomas combined, all at $p<0.01$. There were significant differences in the pair-wise comparisons of the 200 ppm dose group with the controls for liver carcinomas and adenomas and/or carcinomas combined, and of the 400 ppm dose group for liver adenomas and/or carcinomas combined, all at $p<0.05$. The tumor incidences at all doses for combined adenomas and/or carcinomas (35% for 200 and 400 ppm; 62% for 1600 ppm) exceeded the historical control range of 0-27% for mice reported by the testing laboratory. The CARC considered the liver tumors in male mice to be treatment-related based on the robust tumor response at all dose levels for combined liver adenomas and/or carcinomas, which was driven by the increase in both adenomas and carcinomas.

- In female mice, the incidences of liver adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 200, 400, and 1600 ppm dose groups, respectively, were as follows:

  Adenoma: 4/107 (4%), 3/53 (6%), 7/53 (13%), 4/42 (10%)
  Carcinoma: 2/95 (2%), 3/47 (6%), 3/47 (6%), 5/32 (16%)
  Combined: 5/107 (5%), 6/53 (11%), 9/53 (17%), 9/42 (21%)

  Female mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 ppm dose group with the controls, for liver carcinomas and adenomas and/or carcinomas combined, all at $p< 0.01$. There were significant differences in the pair-wise comparisons of the 400 ppm dose group with the controls for liver adenomas and adenomas and/or carcinomas combined, both at $p< 0.05$. There was also a significant difference in the pair-wise comparison of the 200 ppm dose group with the controls for liver adenomas and/or carcinomas combined at $p< 0.05$. Historical control data for liver tumors in females were not provided. The CARC considered the liver tumors in female mice to be treatment-related based on the robust tumor response at all dose levels for combined liver adenomas and/or carcinomas, driven by an increase in carcinomas at the high dose.

- In male mice, the incidences of lung adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 200, 400, and 1600 ppm dose groups, respectively, were as follows:

  Adenomas: 17/103 (17%), 9/51 (18%), 8/48 (17%), 19/54 (35%)
  Carcinomas: 1/103 (1%), 0/51 (0), 0/48 (0), 1/54 (2%)
  Combined: 18/103 (17%), 9/51 (18%), 8/48 (17%), 19/54 (35%)

  Male mice had a significant increasing trend, and a significant difference in the pair-wise comparisons of the 1600 ppm dose group with the controls, for lung adenomas, both at $p<0.01$. There was a significant increasing trend at $p<0.01$, and a significant difference in the pair-wise comparisons of the 1600 ppm dose group for lung adenomas and/or carcinomas combined, at $p<0.05$. The incidence of 35% for lung adenomas, and adenomas and/or carcinomas combined at 1600 ppm, is outside the historical control range of 0-28% of the testing laboratory for the combined tumors. Combined lung tumors (driven by adenomas) at the high dose of 1600 ppm were considered to be treatment-related.

- In female mice, the incidences of lung adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 200, 400, and 1600 ppm dose groups, respectively, were as follows:

  Adenomas: 13/108 (12%), 9/57 (16%), 11/56 (20%), 18/52 (35%)
  Carcinomas: 1/75 (1%), 0/35 (0), 1/44 (2%), 0/24 (0)
  Combined: 14/108 (13%), 9/57 (16%), 12/56 (21%), 18/52 (35%)

  Female mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 ppm dose group with the controls, for lung adenomas and adenomas and/or carcinomas combined, all at $p<0.01$. The incidences of adenomas and/or carcinomas combined exceeded the historical control range (0 - 15.5%) of the testing laboratory for the combined tumors. Combined lung tumors (driven by adenomas) at the high dose of 1600 ppm were considered to be treatment-related.

- In female mice, the incidence of ovarian papillary cystadenomas was 0/75 (0), 1/35 (3%), 3/44 (7%), and 3/24 (13%) for the control, 200, 400, and 1600 ppm dose groups, respectively. Female mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 ppm dose group with the controls, for ovarian papillary cystadenomas, both at $p<0.01$. Tumor incidences at mid- and high-doses were outside the spontaneous rate of 0%, and outside the range 0.7-1.3% for the historical controls of the testing laboratory. The CARC considered the ovarian papillary tumors seen at the high dose to be treatment-related.

- In female mice, the incidence of mammary gland adenomas, adenocarcinomas, and combined adenomas and/or carcinomas for the control, 200, 400, and 1600 ppm dose groups, respectively, were as follows:

  Adenomas: 0/53 (0), 0/27 (0), 2/36 (6%), 0/19 (0)
  Adenocarcinomas: 0/94 (0), 1/46 (2%), 0/48 (0), 4/30 (13%)
  Combined: 0/94 (0), 1/46 (2%), 2/48 (4%), 4/30 (13%)

  Female mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 ppm dose group with the controls, for mammary gland adenocarcinomas and adenomas and/or adenocarcinomas combined, all at $p < 0.01$. The incidence of combined adenomas and/or adenocarcinomas at 1600 ppm (13%) were outside the historical control range of 1.3 - 4.3% of the testing laboratory. The CARC considered the mammary gland tumors (driven by adenocarcinomas) to be treatment-related.

- Adequacy of Dosing: The CARC considered dosing at the high dose of 1600 ppm to be adequate, and not excessive, based on moderate decreased body weight gains ($p \leq 0.01$) throughout the study in males (10-37%) and females (18-45%), and increased mortality in females which only occurred towards the end of the study (88%, high dose vs. 75%, controls).

CD-1 Mouse (MRID 44883901)

- In male mice, the incidence of harderian gland tumors was 0/52 (0), 2/54 (4%), 1/54 (2%), 4/55 (7%) for the control, 50, 200, 700 ppm dose groups, respectively. Male mice had a significant increasing trend at $p< 0.01$, and a significant difference in the pair-wise comparison of the 700 ppm dose group with the controls at $p<0.05$, for harderian gland adenomas. The incidence of 7% at the high-dose group exceeded the mean 1.3 (range 0 - 3.6%) for the historical controls for 80 week studies, but was less than 0 - 10% for historical controls for 2-year studies. Overall, the CARC did not consider the harderian gland adenomas at the high dose to be treatment-related since there was no dose-response. However, some members of the CARC considered this evidence to be equivocal.

- In female mice, the incidence of lung tumors was 0/53 (0), 0/52 (0), 0/51 (0), and 6/51 (12%) for the control, 50, 200 and 700 ppm dose groups, respectively. Female mice had a significant increasing trend, and a significant difference in the pair-wise comparison of the 700 ppm dose group with the controls, for lung adenomas, both at $p < 0.01$. The incidence of 12% in the 700 ppm group is outside the historical control incidence of both the 80-weeks (0 - 2%) studies. The CARC considered the benign lung tumors in female mice to be treatment-related.

- Adequacy of Dosing: The CARC considered the top dose of 700 ppm to be adequate and not excessive in both sexes. This was based on significantly ($P \leq 0.05$) decreased body

weight gains throughout the study with high-dose group males and females weighing less than 6 - 8% compared to controls. Weight gain was reduced by 22 and 14% in high dose males and females, respectively, during the first 13 weeks of the study and by 14 and 21%, respectively, over the entire study. Further, the dosing was considered adequate since tumors were present at the highest dose tested.

2. Mutagenicity

Pirimicarb was not mutagenic in bacteria and did not induce a clastogenic response in mammalain cells *in vitro* or micronuclei in the bone marrow of treated mice. Nevertheless, there is clear and reproducible evidence of a positive response in an *in vitro* mammalian cell gene mutation assay with L5178Y mouse lymphoma cells. Mutagenic activity was reproducible, confined to the S9-activated portion of the assay, concentration-related and occurred at severely cytotoxic levels (causing 10% survival) to levels where >50% of the cells survived. Since the micronucleus assay has a low detection rate (43%) for agents that induce liver tumors (Morita *et al.*, 1997), the CARC recommends that an additional *in vivo* assay be performed to determine whether pirimicarb is active in whole animal assays with non-hematopoietic tissue. Therefore, overall there is some concern for mutagenicity.

3. Structure Activity Relationship

No suitable analogues for pirimicarb were located.

4. Mode of Action

No mode of action data were submitted.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified Pirimicarb as **"Likely to be Carcinogenic to Humans"**. This was based on multiple benign and/or malignant tumors (liver, lung, ovary, mammary gland) seen in male and female Swiss mice and lung tumors in female CD-1 mice, at doses that were adequate to assess the carcinogenicity of pirimicarb, and some concern for mutagenicity.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The Committee recommended that a linear low-dose extrapolation approach (Q1*), based on the appropriate tumor response in mice, be used to estimate human cancer risk.

VIII BIBLIOGRAPHY

MRID No.	CITATION
44883802.	Tinston, D.J. (1992) Pirimicarb-Two Year Feeding Study in Rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Report No. CTL/P/3040. February 28, 1992. Unpublished.
44883803	Sotheran, M.F, Banham, P.B., Jackson, D.G., *et al.* (1980) Pirimicarb-Lifetime Study in the Mouse. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Report No. CTL/P/491. December 24, 1980. Unpublished.
44883901	Rattray, N. (1998) Pirimicarb: 80-week carcinogenicity study in mice. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Study No. PM1035. November 27, 1998. Unpublished
44883836	Gledhill, A.J. (1998). Pirimicarb: Biotransformation in the Rat. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Study No.: UR0528, April 24, 1998. Unpublished.
44883829	Brown, A. (1997). Pirimicarb: Excretion and Tissue Distribution of a Single Oral Dose (50 mg/kg) in the Rat. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Report No.: CTL/P/5381; May 28, 1997. Unpublished.
44903001	Brown, A. (1997). Pirimicarb: Excretion and Tissue Distribution of a Single Oral Dose (1 mg/kg) in the Rat Following Repeat Dosing. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Report No.: CTL/P/5382; April 30, 1997. Unpublished.
44883830	Brown, A. (1997). Pirimicarb: Whole Body Autoradiography in the Rat. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Report No.: CTL/P/5383; April 15, 1997. Unpublished.
44883828	Brown, A. (1997). Pirimicarb: Excretion and Tissue Distribution of a Single Oral Dose (1 mg/kg) in the Rat. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Report No.: CTL/P/5329; March 12, 1997. Unpublished.

43496004 Longstaff, E. (1978) Pirimicarb: Short Term Predictive Tests for Carcinogenicity: Results from the Salmonella/Microsome Reverse Mutation Test. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Lab Project Number: CTL/P/428. Unpublished.

43496005 Trueman, R. (1980) An Examination of Pirimicarb for Potential Mutagenicity Using the Salmonella/Microsome Reverse Mutation Assay. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Lab Project Number: CTL/P/540: Y00032/001/002. Unpublished.

43496006 Wildgoose, J.; Howard, C.; Richardson, C. et al. (1987) Pirimicarb: A Cytogenetic Study in Human Lymphocytes In vitro. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Lab Project Number: CTL/P/1655: Y00032/001/002. Unpublished.

43496008 Jones, K.; Howard, C. (1989) Pirimicarb (Technical): An Evaluation in the Mouse Micronucleus Test. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Lab Project Number: CTL/P/2641: SM0310. Unpublished.

43496007 Kennelly, J. (1990) Pirimicarb: Assessment for the Induction of Unscheduled DNA Synthesis in Rat Hepatocytes In vivo. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Lab Project Number: CTL/P/2824: SR0367. Unpublished.

44883810 Callander, R. (1995) Pirimicarb--An Evaluation of Mutagenic Potential Using S. typhimurium and E. coli. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Lab Project Number: CTL/P/4798: YV3663. Unpublished.

44883833 Clay, P. (1996) Pirimicarb: L5178Y TK+/- Mouse Lymphoma Mutation Assay. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK.. Lab Project Number: CTL/P/5080. Unpublished.

43641003 Paul, J.; Richards, D.; Banham, P.; et al. (1995) Pirimicarb: Growth Study to Determine a No-Effect Level in the Female Rat. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Lab Project Number: CTL/P/408: PR0020. Unpublished.

44233103 Griffiths, D.; Conning, D. (1995) First Revision to Ninety-Day Oral Toxicity of PP062-Albino Rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK.. Lab Project Number: PR0106: CTL/R/237. Unpublished.

00108374 Griffiths, D.; Conning, D. (1968) Ninety-day Oral Toxicity of PP062--Albino Rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK.. Report No. IHR/237. Unpublished.

44233101 Horner, S.A. (1996) Pirimicarb: Subchronic neurotoxicity study in rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK SK10 4TJ. Laboratory Project No. PR1048. November 27, 1996. Unpublished.

43641001 Hodge, M. (1995) Subchronic Studies with Pirimicarb (PP062) in the Beagle Dog: (Reformat of "Ninety-Day Oral Toxicity of PP062--Beagle Dogs" and "Oral Toxicity of PP062--Beagle Dogs"). Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK.. Lab Project Number: CTL/P/4593: PD0107: CTL/R/241. Unpublished.

44903002 Horner, S.A. (1998) Pirimicarb: 1 Year oral toxicity study in dogs. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, U.K.. Laboratory Project ID.: CYL/P/5690, January 21, 1998. MRID 44903002. Unpublished.

43641002 Hodge, M. (1995) Pirimicarb (PP062): 2-Year Feeding Study in Beagle Dogs. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, U.K.. First Revision: Lab Project Number. CTL/R/337: PD0108: HO/IH/R/337. Unpublished.

---------- Brunsman, L. (2005) Pirimicarb: Qualitative Risk Assessment Based on Alpk:APfSD Rat, Alderley Park Swiss-derived Mouse and C57BL/10JfCD-1 Alpk Mouse Dietary Studies. April 26, 2005. TXR No. 0053239.

---------- Morita, T. Asaon, N Awogi, T, Sasaki YF, Sato S-I, Shimada H, Sutou S, Suzuki A, Wakata T, Sofuni T, Hayashi M (1997). Evaluation of the rodent micronucleus assay in the screening of IARC carcinogens (Groups 1, 2A and 2B). The summary report of the 6th collaborative study by CSGMT MMS. MUTAT RES; 389 (1). 3-122.