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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

TXR No. 0053239

MEMORANDUM

DATE: April 26, 2005

SUBJECT: **Pirimicarb:** Qualitative Risk Assessment Based On Alpk:APfSD Rat, Alderley Park Swiss-derived Mouse and C57BL/10J;CD-1 Alpk Mouse Dietary Studies

P.C. Code: 106101

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BACKGROUND

The 104-Week Alpk:APfSD Rat Carcinogenicity Study (MRID 44883802)

A combined chronic toxicity/carcinogenicity study in Alpk:APfSD rats was conducted by Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, for Zeneca Ag Products, Wilmington, Delaware, and dated February 28, 1992 (Report No. CTL/P/3040, MRID No. 44883802).

The study design allocated groups of 52 rats per sex to dose levels of 0, 75, 250 or 750 ppm (0, 3.7, 12.3 or 37.3 mg/kg/day for males; 0, 4.7, 15.6 or 47.4 mg/kg/day for females) of Pirimicarb for 104 weeks. An additional 12 rats per sex per dose were designated for interim sacrifice at 53 weeks.

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The 94-Week Alderley Park Swiss-Derived Mouse Carcinogenicity Study (MRID 44883803)

A carcinogenicity study in Alderley Park Swiss-derived mice was conducted by Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, for Zeneca Ag Products, Wilmington, Delaware, and dated December 24, 1980 (Report No. CTL/P/491, MRID No. 44883803).

The study design allocated groups of 60 mice per sex to dose levels of 0, 200, 400 or 1600 ppm (approximately equal to 0, 10, 20 or 80 mg/kg/day for males and females) of Pirimicarb 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.

The 80-Week C57BL/10J,CD-1 Alpk Mouse Carcinogenicity Study (MRID 44883901)

A carcinogenicity study in C57BL/10J,CD-1 Alpk mice was conducted by Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, for Zeneca Ag Products, Wilmington, Delaware, and dated November 27, 1998 (Study No. PM1035, MRID No. 44883901).

The study design allocated groups of 55 mice per sex to dose levels of 0, 50, 200 or 700 ppm (0, 6.7, 26.6 or 93.7 mg/kg/day for males; 0, 9.0, 37.1 or 130.3 mg/kg/day for females) of Pirimicarb for 80 weeks.

ANALYSES

The 104-Week Alpk:APfSD Rat Carcinogenicity Study (MRID 44883802)

Survival Analyses

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

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

Tumor Analyses

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

Female rats had significant increasing trends for uterine stromal cell polyps, and polyps

and/or sarcomas combined, both at $p < 0.05$. There was a significant difference in the pair-wise comparison of the 750 ppm dose group with the controls for uterine stromal cell polyps and/or sarcomas combined at $p < 0.05$. The statistical analyses of the female rats were based upon Fisher's Exact Test and the Exact Test for Trend (Table 3).

The 94-Week Alderley Park Swiss-Derived Mouse Carcinogenicity Study (MRID 44883803)

Survival Analyses

There were no statistically significant incremental changes in mortality with increasing doses of Pirimicarb in male mice (Table 4). 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 $p < 0.05$ (Table 5).

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

Tumor Analyses

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, and lung adenomas, 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, of the 400 ppm dose group for liver adenomas and/or carcinomas combined, and of the 1600 ppm dose group for lung adenomas and/or carcinomas combined, all at $p < 0.05$. There was also a significant increasing trend for lung adenomas and/or carcinomas combined at $p < 0.01$. Individual histopathology information was missing for 2 males, one in the control group and one in the 200 ppm dose group. One animal in the 400 ppm dose group was recorded as having 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. The statistical analyses of the male mice were based upon Fisher's Exact Test and the Exact Test for Trend (Tables 6 and 7).

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, lung adenomas and adenomas and/or carcinomas combined, ovarian papillary cystadenomas, and mammary gland adenocarcinomas and adenomas and/or adenocarcinomas 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 statistical analyses of the female mice were based upon Peto's Prevalence Test (Tables 8 through 11).

The 80-Week C57BL/10J,CD-1 Alpk Mouse Carcinogenicity Study (MRID 44883901)

Survival Analyses

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 12). Female mice showed a significant increasing trend in mortality with increasing doses of Pirimicarb at $p < 0.05$ (Table 13).

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

Tumor Analyses

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 statistical analyses of the male mice were based upon Peto's Prevalence Test (Table 14).

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 statistical analyses of the female mice were based upon Peto's Prevalence Test (Table 15).

Table 1. Pirimicarb - Alpk:APfSD 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 104/105.

( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Pirimicarb - Alpk:APfSD 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 104/105.

( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

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

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

	Dose (ppm)			
	0	75	250	750
Polyps (%) p =	5/62 (8) 0.04824*	6/64 (9) 0.52239	9[a]/64 (14) 0.21617	11/63 (17) 0.09544
Sarcomas (%) p =	0/62 (0) 0.06126	0/64 (0) 1.00000	0/64 (0) 1.00000	2[b]/63 (3) 0.25200
Combined (%) p =	5/62 (8) 0.01383*	6/64 (9) 0.52239	9/64 (14) 0.21617	13/63 (21) 0.03920*

+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 $p < 0.01$.

Table 4. 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 95/96.
[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 5. 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 95/96.

( )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)
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 7. 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 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)

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 (10)
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 $p < 0.01$.

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Table 9. 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 10. 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 11. 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 $p < 0.01$.

Table 12. Pirimicarb - C57BL/10J,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 13. Pirimicarb - C57BL/10J;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 $p < 0.01$.

Table 14. 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 15. 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 $p < 0.01$.

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