

[82-1a. Pirimicarb Tech. Subchronic - feeding rat/1978]

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DATA EVALUATION REPORT

STUDY TYPE: 8-Week Feeding Study - Rat

OPPTS NUMBER: N/A

GUIDELINE NUMBER: N/A

DP BARCODE: D215390

SUBMISSION CODE: None

P. C. NO: 106101

TOX. CHEM NO: 359C

TEST MATERIAL: PP062; Pirimicarb

SYNONYMS: 2-(Dimethylamino)-5,6-dimethyl-4-pyrimidinyl
dimethylcarbamate

CITATION: Paul, JD., D. Richards, PB. Banham, et al. (1978)
Pirimicarb: Growth study to determine a no-effect in the female
rat. Zeneca Central Toxicology Lab., Alderley Park, Macclesfield,
Cheshire, UK (ICI). CTL/P/408/PR0020. June 1978. MRID 43641003,
Unpublished.

SPONSOR: Zeneca Inc.; Agrochemical products; Wilmington, DE 19897
(formerly ICI).

EXECUTIVE SUMMARY: In a non-guideline subchronic study (MRID# 4364103), 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, therefore, does not fall under 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.

A. MATERIALS:

1. **Test compound:** Crystalline pirimicarb (PP062), Batch # - BX 189, Purity - 97% was used in the study.
2. **Test animals:** Species: female rats, Strain: Wistar derived (Alderly Park), Age: 21 days, Weight: 31 - 47g, Source: Alderly Park, Cheshire, England.

B. STUDY DESIGN:

The objective of the study was to establish the NOEL in females which can be used for designing chronic studies.

1. Animal assignment

Female rats were randomly assigned by litter to the following test groups:

TABLE 1. EXPERIMENTAL DESIGN		
GROUP	Dietary Concentration (ppm)	Number of Animals
1	0 (Control)	20
2	100	20
3	175	20
4	250	20
5	750	20

2. Diet preparation

The compound was dissolved in acetone at 2% v/w, added to PRDE Expanded diet and was mixed in a Hobart mixer resulting a concentration of 3,750 ppm. This premix was diluted with PRDE Expanded diet to give the appropriate test diets. Control diet was prepared identical to the test diet, except without pirimicarb. All diets were pelleted by mixing with tap water 17.5% v/w and air drying at 50°C in a Mitchel hot air oven for 2.5 hours. Diets were prepared at ~ 14 day intervals and pirimicarb levels were determined on premix and pellets after a storage of 20 and 22 days. Homogeneity of premix was determined on samples taken from top, middle and bottom of mixer.

Results - The homogeneity checks performed during the study were found to be within $\pm 6\%$. Analytical concentration of pirimicarb in the premix and pellets was generally within $\pm 10\%$ of the theoretical value. Stability of premix was determined in an earlier study and reported as 14 days but

no supporting data was furnished.

3. Animals had free access to food and water. Food consumption was determined weekly and food wastage was measured daily. Water consumption was determined weekly. Water wastage was minimized using spring loaded valve drinking spout.
4. **Statistics** - Bodyweight gain, food consumption, food wastage and water consumption was analyzed using ANOVA method. Treated group means were compared to control means using Student's 't' test on residual mean square from the ANOVA. For bodyweight gain, food utilization, and food wastage a one-sided test was used, otherwise a two-sided test was used.
5. The studies were done in 1978 i.e., long before the implementation of GLP Guidelines; therefore, does not fall under purview of either GLP or Quality Assurance requirements.

C. METHODS AND RESULTS:

1. Observations:

All animals were checked daily for clinical reactions. A detailed examination was done weekly of all animals during the study.

Results: During week 4 one animal (Group 4) was inadvertently removed from the cage and was not returned to the study. No clinical signs attributable to dosing were observed.

2. Body weight

All animals were weighed upon arrival, at the time of randomization and weekly for 8 weeks.

Results - Table 1 presents mean bodyweight gains during the study. In high-dose (750 ppm) females, bodyweight gains were significantly ($P \leq 0.01$) decreased compared to controls starting week 3 and remained depressed for remainder of the study. Overall decrease of bodyweight gains in the 750 ppm group was 9% compared to controls. The decreased bodyweight gain was associated with decreased food consumption, which suggests palatability may be the factor or toxicity threshold was reached. Significant reduction at week 7 at 100 ppm was considered incidental. **The LOEL for the study is 750 ppm and NOEL = 250 ppm.**

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TABLE 1. MEAN BODYWEIGHT GAIN (g) FROM WEEK 0 ^A					
Period (weeks)	Dose (ppm)				
	Control	100	175	250	750
Mean Week 0 Bodyweight	105.5	107.8	104.8	106.8	112.8
1	31.0	28.6	32.7	29.7	28.0
2	54.8	53.8	54.8	53.6	50.6
3	78.4	75.2	78.0	75.7	67.4**
4	94.4	91.2	93.0	93.4 ¹	82.8**
5	113.2	107.3	114.8	112.6 ¹	101.0**
6	128.4	122.6	127.2	125.8 ¹	115.5**
7	138.8	130.6*	137.2	134.8 ¹	123.4**
8	147.0	141.1	146.8	144.2 ¹	132.8**

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1 N = 19, all others N = 20

** Statistically significant ($P \leq 0.01$)

3. Food consumption

Food Consumption was recorded weekly and food wastage daily. Table 2 shows decreased food consumption in the high-dose animals which are consistent with decreased bodyweight gain presented in Table 1. As suggested above palatability or

TABLE 2. MEAN FOOD CONSUMPTION (g) ^A					
	Control	100 ppm	175 ppm	250 ppm	750 ppm
1	129	133	126	120*	135
2	159	165 ¹	146**	132**	139**
3	154	157	146*	143**	134**
4	160 ¹	165	154	153 ¹	139**
5	153	150	155	160 ¹	141**
6	158	152	145*	166 ¹	146*
7	153	143**	147	154 ¹	150
8	143	150	142	142 ¹	147

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1 N = 19, all others N = 20

* = $P \leq 0.05$, ** = $P \leq 0.01$

toxicity threshold may be the interpretation for reduced bodyweight gain. In the 175 ppm and 250 ppm groups food consumption decreased significantly ($P \leq 0.05$ to 0.01) during the first 3 weeks but rebounded to control levels and is not

considered toxicologically significant. Food consumption in the 100 ppm group was comparable to control levels except for significant ($P \leq 0.01$) which was coincided decreased bodyweight gain; this isolated incidence was considered not treatment-related. The systemic toxicity LOEL is 750 ppm and NOEL is = 250 ppm.

4. Water consumption was not affected.
5. Ophthalmological examination was not performed.
6. Hematology and Clinical chemistry were not done.
7. Urinalysis was not done.
8. Necropsies were not performed.

D. DISCUSSION:

The study was conducted in 1978 prior to implementation of GLP guidelines and therefore, does not meet the guidelines. This study was not designed to meet any specific guideline but to confirm decreased bodyweight gain observed in earlier studies in females fed 750 ppm pirimicarb. The results of this study suggests the effect might be due in part to decreased food consumption associated with palatability. The Systemic Toxicity LOEL is 750 ppm (75 mg/kg/day), based on bodyweight decrement and food consumption. The Systemic Toxicity NOEL is 250 ppm (25 mg/kg/day).

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

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