PP 2H
PMR-1326

in file

001326/ 359C
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JUL 8 1975

TO: PM

SUBJECT: Request for a Tolerance of 0.1 ppm for 2-(dimethylamine)-5, 6-dimethyl-4-pyrimidinyl dimethylcarbamate and its two major metabolites 5,6-dimethyl-2-(formylmethylamino)-4-pyrimidinyl dimethylcarbamate and 5,6-dimethyl-2-(methylamino)-4-pyrimidinyl dimethylcarbamate in or on potatoes.

Pesticide Petition No: 5F1603

Recommendation: Establish Tolerance

Petitioner: ICI United States Inc.

Chemical Name: 2-(dimethylamino)-5,6-dimethyl-4-pyrimidinyl dimethylcarbamate

Common Name: Pirimicarb

Code Number: PP 062

Related Petitions: None

Established Tolerances: None

Formulation: Pirimor 50 WP

Active Ingredient

50% 2-(dimethylamino)-5,6-dimethyl-4-pyrimidinyl dimethylcarbamate

Inert Ingredient

[redacted]

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Use: Control aphids on potatoes

Application Rate: 4 to 8 ozs. per acre

Application Frequency: 7 to 10 days or as needed.

Application Method: Ground spray.

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*cleared under 40 CFR 180.1001(d).

**cleared under 40 CFR 180.1001(c).

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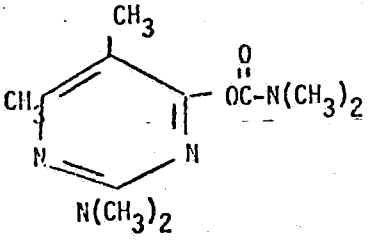
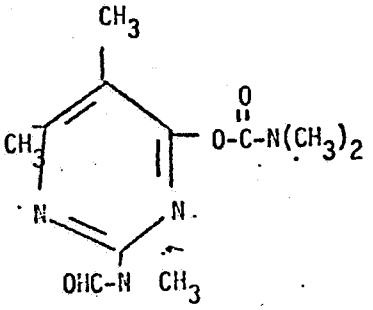
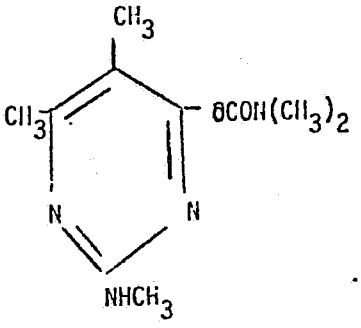
Chemical Structures:



2-(dimethylamino)-5,6-dimethyl-4-pyrimidinyl dimethylcarbamate



(Metabolite) 5,6-dimethyl-2-(formylmethylamino)-4-pyriminyl dimethylcarbamate



(Metabolite) 5,6-dimethyl-2-(methylamino)-4-pyrimidinyl dimethylcarbamate

Pirimicarb toxicology review

Page 3 is not included in this copy.

Pages _____ through _____ are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

X Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

___ FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

- The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

The following toxicity data were submitted earlier under EPA file number 10182-T.

Studies made with Technical Grade Material

Acute:

Oral	Rat (female)	LD_{50}	147 mg/kg
Oral	Mouse (female)	LD_{50}	107 mg/kg
Oral	Dog	LD_{50}	100-200 mg/kg
Intraperitoneal	Rat	LD_{50}	25 mg/kg

Oral Rats (following storage of material at 37°C)

0 storage time	LD_{50}	168 mg/kg
3 mos storage time	LD_{50}	165 mg/kg
6 mos storage time	LD_{50}	221 mg/kg

Skin Irritation Rabbit - not irritating with 25% soln.

Eye Irritation Rabbit - not irritating with 1 drop 50 mg/ml.

Dermal Rats - LD_{50} >500 mg/kg

Neurotoxicity Hens - 25 mg/kg caused no neurotoxic symptoms.

Oral Rats - 10 day study - 50 mg/kg showed no toxic signs but had slowed growth rate and slight depression.

Dermal Rabbits - 14 days - 500 mg/kg no toxic signs

Subacute:

Inhalation Rats - 3 wks actual exposure gave an LC_{50} of 300 mg/m^3 500 mg/kg total. This study did not include a ChE determination.

Inhalation Rats - 3 wks saturated vapour (0.4 mg/m^3 0.04 ppm) at room temperature revealed no toxic effects and produced no significant plasma or RBC ChE depression.

Studies made with 50% W.P. Formulation

Acute:

Oral Rats (female) - LD_{50} 356 mg/kg

Skin Irritation Rabbit - 50% paste mildly irritating (Draize)

Eye Irritation Rabbit - 0.1 ml of 100 mg/ml was slightly irritating (Draize)

Inhalation Rats - 20 g/m^3 no toxic symptoms with 40% plasma ChE depression and no significant RBC-ChE depression.

The following toxicity data were submitted in this petition in support of the tolerance on potatoes.

Acute Rat Oral LD_{50}(Tech) Imperial Chemical Industries 11/67

The test material was identified as PP062. The report number was IHR/224.

Groups of six female rats were tested at different levels during three different times a day, i.e.: 9:00 A.M., 5:00 P.M. and overnight fast.

Results:
9:00 A.M. LD_{50} = 210 mg/kg
5:00 P.M. LD_{50} = 147 mg/kg
Fasted LD_{50} = 68 mg/kg

Guinea Pig Sensitization

The test materials were identified as Pirimicarb (2-dimethylamino-5, 6-dimethylpyrimidin-4-yl dimethylcarbamate and Pirimor (JF2538-50% dispersible powder of pirimicarb). Both materials were prepared for testing as solutions in dimethylformamide.

Each material was applied as a 10% w/v solution to both ears of four male guinea pigs for three days. Four days later, the animals were challenged by applying 10%, 1% and 0.1% w/v solutions in DMF to the shaved flank skin.

Results: Pirimor produced no response. Pirimicarb produced trace of erythema.

Neither test material is judged to be a sensitizer.

Acute Rabbit Eye Irritation (Tech) 8/10/73

The test materials were identified as technical grade pirimicarb (PP062: 2-dimethylamino 5,6-dimethylpyrimidin-4-yl dimethylcarbamate) and a 50% of powder formulation of PP062 (JF2538)*.

[redacted]

One drop of the test material was placed in the conjunctival sac of the left eye of six rabbits. Eyes were not washed. Scoring was by the Draize scale.

Results: The technical material produced mild irritation. The 50% formulation produced slight irritation.

Operation Experience During Formulation

At the early stages of formulation of pirimicarb, as either a 50% wettable powder or as a 50% dispersible grain, reduction in plasma and erythrocyte cholinesterase activities was observed in some operators. At ambient temperatures (20-30°C), these effects were produced by exposure to dusts containing pirimicarb. At elevated temperatures (eg 65°C) inhibition arose after inhalation of pirimicarb vapour. The hazards were successfully contained by plant modifications and it is concluded that pirimicarb can be formulated safely provided that adequate standards of personal hygiene and of plant design and maintenance are observed.

Pirimicarb-induced cholinesterase inhibition in operators occurred within hours of exposure, particularly in plasma. However, in all instances enzyme activities showed complete, and usually rapid, recovery on cessation of exposure to pirimicarb and no longer-term toxicological effects have been noticed amongst the operators involved.

Mice Dominant Lethal (Tech) Inveresk Research International 7/74

The test material was identified as compound PP062 and the dilutent [redacted]

Five groups of 15 male mice of proven fertility were treated immediately before test mating began in the following ways:

Group 1 10 ml. [redacted]/kg body weight/day by gastric intubation for 5 days.

Group 2 10 mg PP062 in [redacted]/kg body weight/day by gastric intubation for 5 days.

Group 3 20 mg PP062 in [redacted]/kg body weight/day by gastric intubation for 5 days.

Group 4 150mg ethylmethanesulphonate in water/kg body weight by intraperitoneol injection once, on the day before test mating.

Group 5 100 mg ethylmethanesulphonate in distilled water/kg body weight/day by gastric intubation for 5 days.

Groups 4 and 5 were positive control groups; the ethylmethanesulphonate was diluted immediately before use with glass distilled water to give concentrations of 15 mg/ml (Group 4) and 10 mg/ml (Group 5).

After treatment, two virgin females were introduced to each treated male. After seven days, the males were transfered to fresh cages and mated with a second batch of virgin female mice. This process was repeated until the treated male mice had been mated for eight weeks. The female mice were killed 13 days after the assumed date of fertilization.

Observations and tests for effects included mortality, number of live implantations, early deaths, late deaths, number corpora lutea graviditalis, male body weights and number of pregnancys.

Results: No mutagenic effects could be detected in the results of this study. The positive control animals did exhibit a mutagenic effect.

This material does not display mutagenic activity up to the highest fed level of 20 mg/kg/day for 5 days.

90 Day Rat Oral (Tech) - Imperial Chemical Industries 7/68 ✓

The test material was identified as PP062.

Outline of Investigation

Group	Number of test animals Male	Female	Dose level of PP.062
I	25	25	None
II	25	25	25 mg/kg per OS
III	25	25	0.025% in diet (250ppm)
IV	25	25	0.075% in diet(750ppm)

Five of each sex from each group were continued for an additional 28 days past the 90 day test period.

Observations and tests for effects included mortality, food consumption and weekly body weights. The following hematology studies were conducted on five rats of each sex on day 0 and day 90:

reticulocyte counts
hemoglobin conc.
PCV
mean corpuscular diameter
WBC
differential white cell count
platelet count
prothrombin index

Plasma and RBC cholinesterase activity was measured once a week for five weeks predosing and then at one and two weeks after dosing, followed by sampling at four day intervals until the study was terminated. Samples for the ChE determinations were taken one hour after dosing. ChE determinations were also conducted at one and four weeks after cessation of dosing. Brain ChE determinations were also conducted on five rats from each level.

Terminal studies included absolute organ weights and organ to body weight of the liver, heart, lungs, adrenals, kidneys and spleen from five rats of each sex of each group. The following tissues were also examined microscopially:

liver	adrenal	stomach	colon
kidney	gonads	duodenum	salivary gland
spleen	thymus	jejunum	mesenteric lymph node
heart	thyroid	caecum	brain
lung	pancreas	ileum	spinal cord

Results: Seven rats were removed from Group II due to death from trauma of repeated cannulation.

The body weights, food consumption, hematology and pathology of the test animals were comparable to the control animals.

The brain, RBC and plasma ChE activity of the 0.025 and 0.075% diet groups were considered normal.

The RBC and brain ChE activity of the 25 mg/kg per 03 group were considered within normal biological variations. A marked inhibition of plasma ChE activity among the male rats of this level and a general inhibition amoung the females were the only effects noted. These effects disappeared after cessation of dosing.

The no effect level for the intubation part of the study is less than 25 mg/kg. The feeding part of the study exhibited a NEL of $\geq$ 750 ppm.

Two Year Rat Feeding (Tech) Imperial Chemical Industries 3/72 ✓

The test material was identified as Pirimicarb (PP062). Report No. MO/IH/P/24.

Forty-eight Wistar derived rats were used par level of 0, 250, 500 and 750 ppm.

Observations and tests for effects included behavior, mortality, body weights, food consumption, hematology as listed below from six rats of each sex from each group at 0, 26, 52, 78, 91 and 104 weeks.

hemoglobin conc.	platelet count
PCV	differential WBC
mean corpuscular diameter	MBC
reticulocyte count	RBC

prothrombin index at 104 weeks, RFC and plasma ChE activity were determined from six rats of each sex from the 0 and 750 ppm levels at the intervals of 0, 6, 12, 18 and 24 months and brain cholinesterase activity at termination of the study. Terminal observations consisted of the microscopic examination of the following tissues:

salivary gland	pancreas
thyroid	spleen
thymus	stomach
heart	duodenum
lungs	jejunum
liver	ileum
adrenals	caecum
kidneys	colon
gonads	epididymus
uterus	seminal vessicles
prostate	urinary bladder
abnormal lymphnodes.	

In addition, the brain and spinal cord were examined from 25% of the rats in each group. The weights of the liver, kidneys, adrenals, lungs, heart and spleen were also recorded.

Results: The 500 and 750ppm level females exhibited a body weight gain inhibition, a reduction in overall food consumption and an increase in the food conversion factor. The 750ppm females also exhibited a significant reduction in spleen weight. The other parameters investigated produced findings which were considered to be within normal biological variations.

The no effect level is 250 ppm.

80 Week Mice Carcinogenic - ICI United States Inc. 7/74 ✓

The material tested was identified as Pirimicarb (PP062; 2-dimethyl-4, 5-dimethypyrimidin-6-yl dimethylcarbamate) with a purity of 97.3%.

Fifty Specific Pathogen Free mice of each sex of the Alderlay Park strain were used per level of 0, 300 and 1500 ppm.

Observations and tests for effects included mortablity, body weight, food consumption, clinical abnormalities and histological examination of the following issues:

salivary gland	pancreas
thyroid	spleen
thymus	stomach
heart	duodenum
lungs	jejunum
liver	ileum
adrenal	caecum
kidney	colon
gonad	uterus
epidiymis	urinary bladder
seminal vessicles	voluntary muscle
prostate	abnormal tissues

Results: Slight body weight gain inhibition was evident among both sex at the 1500 ppm level. The histological examination did not show any increase in tumor formation among the test animals.

90 Day Dog Feeding - Imperial Chemical Industries 9/68

The material tested was identified as PP062 (5,6-dimethyl-2-dimethylamino-4-dimethylcarbamoyloxypyrimidine.

Four beagles of each sex were tested per level of 0, 4, 10 and 25 mg/kg/da Half the dogs were continued for an additional 28 days undosed.

Observations and tests for effects included mortality, body weights, clinical studies as listed below from each dog at 0 and 90 days

hemoglobin	leucocyte count
PCV	platelets
MCHC	clotting function
mean cell diameter	blood glucose
reticulocytes	blood urea
bone marrow cytology	
plasma alkaline phosphatase	
BSP	
urine analysis	

and RBC and plasma ChE activity from four dogs from each group once a week for five weeks prior to dosing and then at weeks 1, 2, 4, 6, 8, 10, 12 and 14. The blood samples were taken one hour after administration of the dose.

Terminal studies consisted of brain ChE activity, weights of the following organs:

heart	adrenals
liver	spleen
kidneys	thyroid
testis	brain
lungs	

and microscopic examination of the following tissues:

pituitary	thymus
salivary gland	heart
thyroid	lungs
aorta	liver
stomach	spleen
duodenum	bone marrow
jejunum	kidney
ileum	bladder
colon	adrenal
lymph nodes	testis
ovary	epididymus
uterus	brain
spinal cord	sciatic nerve

Results: Slight inhibition of plasma ChE activity was evident at the 10 mg/kg level and marked inhibition at the 25 mg/kg level. Delayed red cell maturation was evident at all dose levels with three animals showing megaloblastic anemia. The presence of immature red cells in the bone marrow of all treated dogs suggest that anemia would have occurred in more dogs if treatment had been continued. Complete recovery from anemia and partial recovery from the bone marrow abnormality followed cessation of dosing.

No effect level is less than 4 mg/kg/day.

90 Day Dog Feeding - Industrial Hygiene Research Lab 1/69

These data were presented in report number IHR/248. The test material was identified as PP062.

The testing outline is as follows:

Group	Dose of PP062 per day	Duration	No. of animals Male	Female
I	None	90 days	4	4
II	0.4 mg/kg body weight	90 days	4	4
III	1.8 mg/kg body weight	90 days	4	4
IV	4.0 mg/kg body weight	180 days	4	4

Observations and tests for effects include mortality, body weight, hemoglobin, PCV, MCHC, MCD, reticulocyte, platelets clotting function, serum iron, bone marrow cytology, ChE activity at the 4.0 mg/kg and brain ChE activity at the 4.0 mg/kg.

Terminal studies consisted of the organ to body weight ratio of the liver, spleen, kidneys, adrenals, testes, heart, thyroid, brain and lung, and a microscopic examination of the lung, liver, spleen, kidneys, bladder, epididymis, pituitary, lymph node, uterus, thymus, thyroid, parathyroid and mammary gland.

Results: The occurrence of megaloblasts were unremarkable at the 0.4 mg/kg, insignificantly increased at 1.8 mg/kg and significantly increased at the 4.0 mg/kg/day level. No anemia was reported.

Other areas of investigation were unremarkable. The no effect level is 1.8 mg/kg/day (54ppm). 12ppm

2 Year Dog Feeding -- Industrial Hygiene Research Lab 12/71

These data were presented in report number HO/IH/R/337. The material tested was identified as PP062.

Four young beagle dogs of each sex were tested per level of 0, 0.4, 1.8 and 4.0 mg/kg.

Observations and tests for effects included mortality, body weights, and the following hematology at 0, 3, 6, 9, 12, 15, 18, 21 and 24 months:

hemoglobin	differential
PCV	mean cell diameter
MCHC	platelets
MBC	RBS sedimentation rate

bone marrow cytology was conducted at 0, 6, 12, 16, 20 and 24 months. The following biochemistry at 0, 3, 6, 9, 12, 15, 18, 21 and 24 months:

glucose	urea
alkaline phosphatase	sodium
potassium	BSP retention

urinalysis at three month intervals, ChE activity at three month intervals and electrocardiography at three month intervals. Terminal studies included the absolute weights of the heart, liver, spleen, kidneys, adrenals, thyroids, testis, epididymis, lungs and brain, and microscopic examination of the following tissues:

pituitary	sciatic nerve
salivary gland	ileum
liver	colon
spleen	bladder
pancreas	gonad
kidneys	thyroid
adrenals	thymus
stomach	lung
duodenum	heart
jejunum	aorta
	voluntary muscle

Results: The only adverse finding was a slight increase in the myeloid-erythroid ratio as reported by the testing laboratory.

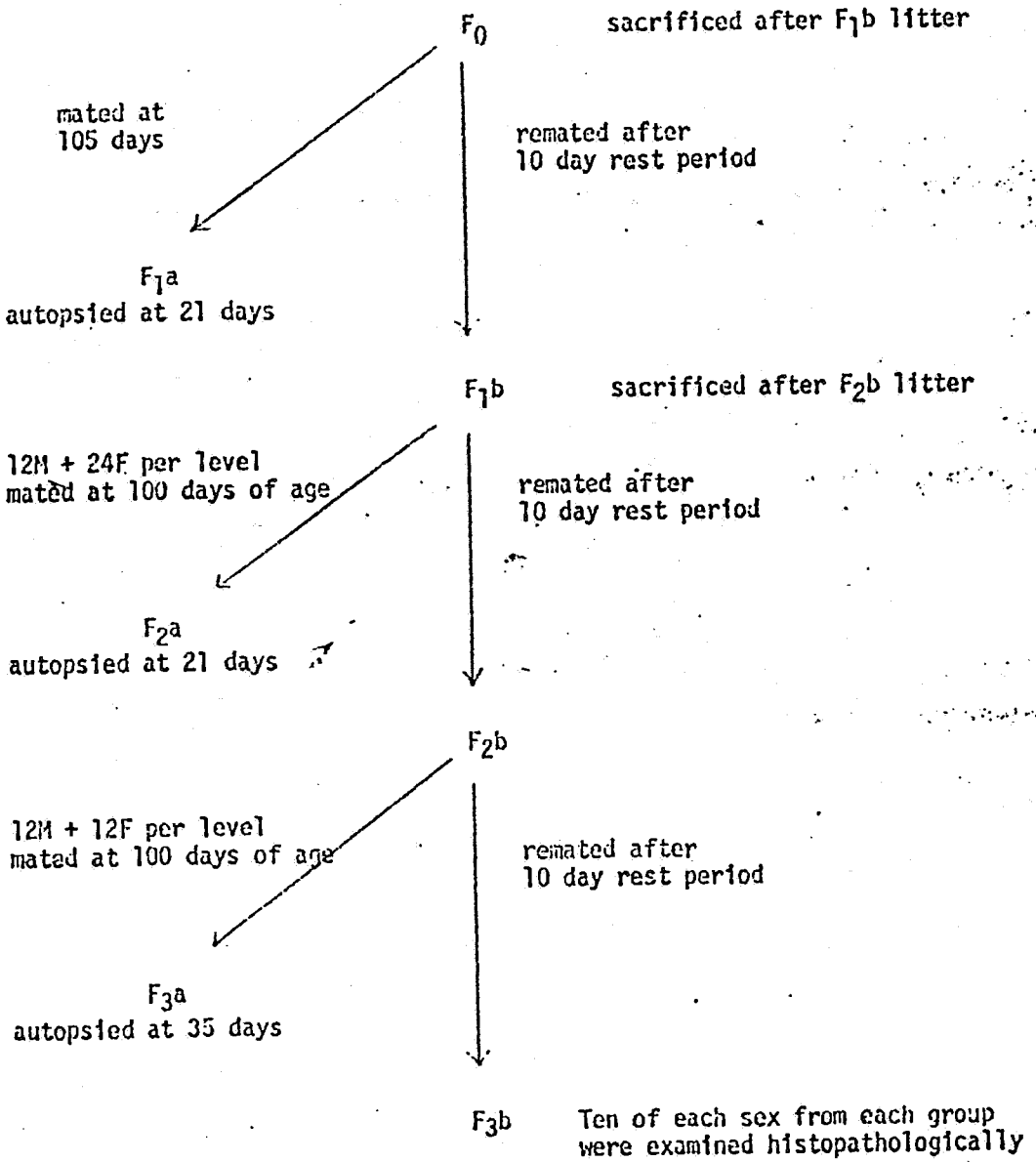
The no effect level is 1.3 mg/kg.

Three Generation Rat Reproduction Study - Industrial Hygiene Research 12/71

These data were presented in report number HO/III/R/339. The material tested was identified as FP062.

Twelve males and twenty-four females were tested per level of 0, 250 and 750 ppm.

The testing outline is as follows:



Observations and tests for effects included mortality, body weight gain, food consumption, behavior, number of pregnancies, litter size, sex, pup weight fertility index, stillbirths and pup abnormalities.

Results - Body weight inhibition was noted among the 750 ppm males and females of the F_1b and F_2b parents. These same rats also showed a reduced food consumption level.

The data resulting from the other parameters were found to be within acceptable limits. Thus, no adverse effects were producted in the reproduction parameters at 750 ppm.

Teratogenic Study in Rabbits 7/74

These data were contained in report number HO/CTL/P/115. The test material was identified as PP062.

Sixteen pregnant female Dutch rabbits were tested per level of 0, 1.25, 2.5, and 5.0 mg/kg. The animals were dosed from day 1 to day 28 inclusive. The inert suspendium medium was [redacted] On day 29, the does were killed by air embolism.

Observations and tests for effects included mortality, body weights, early resorption sites,, late resorption sites, pup viability, pup weight, sex, skeletal abnormalities and internal examination of the pups.

Results - A significant amount of body weight gain inhibition was evident at the 5.0 mg/kg level. There was also a slight reduction in fetal weights at the 5.C mg/kg level. No fetal abnormalities were reported.

Dog and Rat Metabolism Study - Industrial Hygiene Res. Lab. 9/71

These data were presented in report number HO/IH/R/322.

Part I

Two beagle dogs were given a gelatin capsule containing pirimicarb (110 mg) and [nuclear-^{14}C] pirimicarb (4.5μCi), another two beagle dogs were given pirimicarb (110 mg) and [carbonyl-^{14}C] pirimicarb (3.5μCi) as a solution in corn oil. Excreta were collected at 24 hour intervals for four days.

Part II

Ten male rats were given 48 mg/kg of pirimicarb and [nuclear ^{14}C] pirimicarb (1.0μCi) by stomach tube as a solution in water containing 10% ethanol. The 24 hour combined urine sample was retained.

Part III

A) The biliary excretion of orally administered [nuclear - ^{14}C] pirimicarb (0.37μCi;100 mg) was studied in two male rats with a cannulated bile duct. Bile was collected at 24 and 48 hours.

B) The biliary excretion of 2-dimethylamino-4,5-dimethyl-6-hydroxcy-[2-^{14}C]-pyrimidine (0.28μCi) was studied.

Part IV

The anticholinerterase activity was measured in rats administered orally 80 mg/kg pirimicarb and [carbonyl-^{14}C] pirimicarb (0.8μCi). Urine was collected at 24 hours and was compared to a urine sample taken 24 hours post treatment.

Part V

The half-life of pirimicarb was determined in rats by measuring the rate of excretion of $^{14}CO_2$ given [carbonyl-^{14}C] pirimicarb (1μCi) both by stomach tube and by intraperitoneal injection.

Results - Approximately 86% and 94% of the radioactivity from the [nuclear ^{14}C] pirimicarb was recovered in the urine and feces over four days.

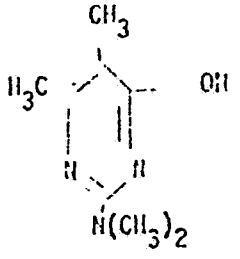
With [carbonyl ^{14}C] pirimicarb, 26% and 14% of the radioactivity was recovered from the urine and feces over four days.

The half-life of pirimicarb in rats was 3-6 hours irrespective of the route of administration.

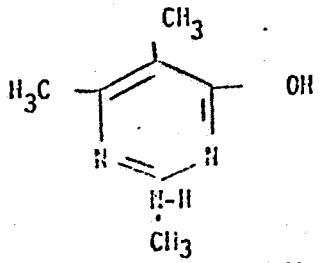
After oral administration of [nuclear ^{14}C] pirimicarb, 8.3% was excreted in the bile in 24 hours.

The metabolic pathway of pirimicarb in the dog and rat are essentially similar. The four major metabolites are:

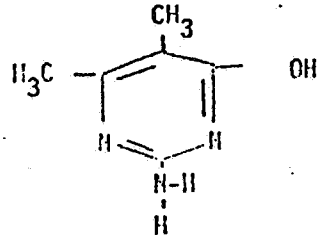
1) 2-dimethylamino-4,5-dimethyl-6-hydroxypyrimidine



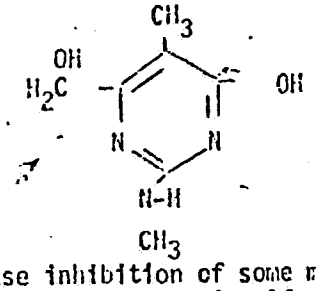
2) 2-methylamino-4,5-dimethyl-6-hydroxypyrimidine



3) 2-amino-4,5-dimethyl-6-hydroxypyrimidine



4) 2-methylamino-4-hydroxymethyl-5-methyl-6-hydroxypyrimidine



The cholinesterase inhibition of some metabolites showed that the most potent inhibitor is pirimicarb itself.

Absorption and Excretion of PP062 by Rats 8/68

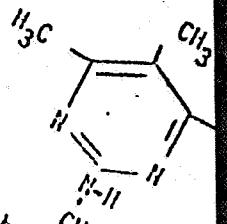
These data were presented in report number IHR/239. The materials tested were identified as 2[^{14}C]-dimethylamino-4,5-dimethyl pyrimidinyl dimethyl carbamate ([nuclear-^{14}C]PP062), specific activity 3.54 mc/mM, and 2-dimethylamino-4,5 dimethyl pyrimidinyl dimethyl [^{14}C] carbamate ([carbonyl-^{14}C]PP062), specific activity 2.3 mC/mM.

Adult male Wistor rats were intubated with 0.19 mg (2.8μC) of nuclear-^{14}C PP062 or 0.22 mg (7μC) of carbonyl-^{14}C PP062. Another rat received an intraperitoneal injection of [carbonyl-^{14}C] PP062.

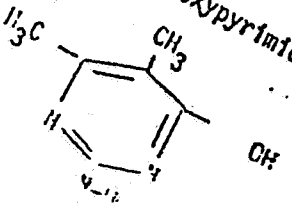
The collected urine was immediately frozen. The expired air was scrubbed with 2N-NaOH for at least 24 hours for determination of $^{14}CO_2$. The tissues from two of the animals fed [nuclear-^{14}C] PP062 were removed and the residual radioactivity determined.

2) 2-methylamino-4,5-dimethyl-6-

3) 2-amino-4,5-dimethyl-6-hydroxypyrimidine



4) 2-methylamino-4-hydr



Proposed Metabolic Breakdown of Pirimicarb

Results - Th test material was rapidly absorbed by and excreted from the body after oral administration. With the [carbonyl-^{14}C]PP062, about 77% of the label was excreted in the expired air as $^{14}CO_2$ 16% in the urine and 1-2% in the feces in 48 hours. With the [nuclear-^{14}C] PP062, about 88% and 3.5% of the label was excreted in the urine and feces respectively in 48 hours.

No significant retention of radioactivity was detected in tissues.

Accumulation Study In Rats - Industrial Hygiene Res. Lab. 1/72

These data are contained in report number HO/IH/P/5. The material tested was identified as pirimicarb labeled with ^{14}C.

Eight female rats were given [2-^{14}C]-pirimicarb orally in corn oil (50 mg/kg; 0.25μCi). Two control animals were given the vehicle only. Two of the test and both controls were killed after 24 hours and portions of abdominal fat removed. The remaining animals were redosed and the procedure repeated at 24 hourly intervals until all the animals had been killed.

Results - The values of the label found were only just above the background. It is concluded that there is no accumulation of pirimicarb or any of its metabolities in fat.

Metabolite Toxicity

Acute Rat Oral LD_{50} - R34885*	female =	50-100 mg/kg
Acute Rat Oral LD_{50} - R34836**	female =	200-400 mg/kg
Acute Rat Oral LD_{50} - R31805***	female =	800-1600 mg/kg
Acute Rat Oral LD_{50} - R34865****	female =	2000-2500 mg/kg
Acute Rat Oral LD_{50} - R31680[1]	female	>2500 mg/kg
Acute Rat Oral LD_{50} - R35140[2]	female	79 mg/kg

1) 2-amino-5,6-dimethyl-4-hydroxy-pyrimidine

2) 2-amino-5,6-dimethyl-pyrimidine-4-yl dimethylcarbamate

* 2-formylmethylamino-5,6-dimethylpyrimidin-4-yl dimethylcarbamate (plant)

** 2-mehtylamino-5,6-dimethylpyrimidin-4-yl dimethylcarbamate (plant)

*** 2-dimethylamino-4,5-dimethyl-6-hydroxpyrimidine (plant and animal)

**** 2-dimethylamino-4,5-dimethyl-6-hydroxypyrimidine (plant and animal)

14 Day Rat Intubation - R34885 - Industrial Hygiene Res. Lab. 8/31/71

These data are contained in report number HO/IH/T/343. The test material was identified as 5,6-dimethyl-2-methyl-formamidopyrimidin-4-yl dimethylcarbamate (a plant metabolite)

Ten rats of each sex were given 25 mg/kg/day for 5 days/wk for 2 weeks. Propylene glycol was the vehicle.

Observations and Tests for effects included mortality, body weights, food consumption and determination of ChE activity 24 hours after the last dose. Terminal studies included the following hematology:

Hemoglobin	Reticulocytes
PCV	WBC
MCHC	platelets
MCD	differential
Howell Jolly Bodies	prothrombin
Kaolin-Cephalin	

and the microscopic examination of the following tissues from four rats of each sex:

kidney	duodenum
liver	jejunum
stomach	ileum
testis	ovary
epididymis	uterus

Results - no significant adverse effects were reported. The NEL is equal to or greater than 25 mg/kg/day.

14 Day Rat Intubation - R34836 - Industrial Hygiene Res. Lab. 8/31/71

These data were presented in report number HO/III/T/842. The plant metabolite was identified as 5,6-dimethyl-2-methylamino-pyrimidin-4-yl dimethylcarbamate

Ten rats of each sex were dosed with a level of 100 mg/kg of the plant metabolite for 5 days per week for two weeks. The vehicle used was propylene glycol.

Observations and Tests for effects included mortality, body weight and ChE activity. Terminal studies included the following hematology:

hemoglobin	WBC
PCV	differential
MCHC	platelets
MCD	Howell Jolly Bodies
reticulocytes	prothrombin
kaolincephalin	

and the microscopic examination of the following tissues from four rats of each sex:

kidney	lung
liver	thymus
spleen	salivary gland
adrenal	pancreas
heart	bladder
stomach	jejunum
duodenum	ileum
testis	ovary
epididymis	uterus

Results - The ferale plasma ChE activity was inhibited by 25%. The female hypochromic anemia reported by the investigating laboratory is considered a gray area by this reviewer. Reticulocytosis is evident among the males. The testing laboratory also reported increased hemopoietic activity in the spleen (no supportive data provided).

Based on the general finding by the testing laboratory, the no effect level must be considered as less than 100 mg/kg/day.

Impurity Data

Acute Rat Oral LD50 - R42486***	155 mg/kg
Acute Rat Oral LD50 - R32444*	800-1000 mg/kg
Acute Rat Oral LD50 - R33160**	~800 mg/kg

[redacted]

Probable Degradation Products

Acute Rat Oral

Chemical	LD50 mg/kg
Guanidine	1105
Methyl guanidine sulphate	1105
Dimethyl guanidine hydrochloride	1445

Conclusion - These toxicity data show no carcinogenic activity or teratogenic activity at the highest fed levels of 1500 ppm and 5.0 mg/kg respectively. The two year rat and dog no effect levels are 250 ppm and 1.8 mg/kg/day respectively. The reproductive facilities of rats during a three generation cycle were unaffected.

Based on the two year NEL in dogs of 1.8 mg/kg, the ADI for a 60 kg human is 1.0 mg/~~kg~~ day. The proposed use on potatoes and the resulting residue of ~~0.1 ppm~~ 0.01 mg will not exceed the ADI.

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cc: Branch Reading File
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