7-10-96

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

Chemical Name: Pirimicarb

PC Code: 106101

Structure

The Health Effects Division Toxicology Endpoint Selection Committee considered the available toxicology data for Pirimicarb at a meeting held on June 27, 1996. Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

TOXICOLOGIST: Guruva B. Reddy Date: _____

SECTION HEAD: Marion P. Copley Date: _____

BRANCH CHIEF: Karl Baetcke Date: _____

106101.TE1

Dermal absorption: No studies are available. A comparison of LD_{50}s of 147 mg/kg/day in the acute oral toxicity (Merck Index 10th edition) and > 500 mg/kg/day in the acute dermal toxicity study (HED Doc. # 001727) in rats indicate a dermal absorption rate of ≈ 29%. A comparison of the LOEL of 75 mg/kg/day in the developmental rat and the NOEL of 1000 mg/kg/day in the 21-day dermal toxicity study in rats indicated a dermal absorption rate of approximately 7.5%. Based on these values and the available data, the Committee recommended a conservative value of NO more than 25% for dermal absorption.

% absorbed: about 25%

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ACUTE DIETARY ENDPOINT (ONE DAY)

Study Selected: None

MRID No.: N/A

Summary: NA

Dose and Endpoint for use in risk assessment: Not applicable.

Comments about study nd/or endpoint: Existing data base supports only a non-food use.

This risk assessment is NOT required

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SHORT TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 TO 7 DAYS)

Study Selected: 82-2

MRID No.: 43896201

Summary: In a 21-Day dermal toxicity study (MRID [43896201]) Pirimicarb, (97.6 %a.i.) was administered dermally to 5 male and 5 female Alpk:APfSD (Wistar derived) rats per dose group as a paste in distilled water at dose levels of 0, 40, 200 and 1000 mg/kg/day. A total of 15 six-hour applications were made during the 21-day test period. Animals were fitted with plastic collars to prevent oral exposure.

Systemic toxicity was not observed upto and including 1,000 mg/kg/day. **The systemic toxicity LOEL is > 1000 mg/kg and the systemic toxicity NOEL = 1,000 mg/kg/day.**

In addition, reductions in plasma and brain cholinesterase were observed in males and females in a dose related manner at all test levels. At the 1000 mg/kg dose level, brain cholinesterase was reduced 18.4% in males and 22.5% in females while at the 200 mg/kg/day dose level, reductions were 10.5% in males and 11.3% in females. Similarly, at the 1000 mg/kg dose level plasma cholinesterase was reduced 19.6% in males and 39.7% in females while reductions were 17.6% in males and 23.4% in females at the 200 mg/kg dose level. At the low dose level (40 mg/kg) reductions were less than 5% for brain cholinesterase and less that 15% for plasma cholinesterase in both sexes. **Based upon these findings, the ChE LOEL in this study is considered 200 mg/kg/day and the ChE NOEL is the low dose level, 40 mg/kg/day.**

Dose and Endpoint: NOEL = 40 mg/kg/day based on the inhibition of brain and plasma cholinesterase.

Comments about dose/study: None.

This risk assessment is required.

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INTERMEDIATE TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

DERMAL EXPOSURE:

Study Selected: 82-1(b); MRID No.: 43641001

Summary: In a two part dietary subchronic study (MRID# 43641001), 4 beagle dogs/sex/dose received in Part 1 either 0, 4, 10 or 25 mg/kg/day and in Part 2 either 0, 0.4, 1.8 or 4 mg/kg/day of PP062 (94% a.i.). Half of the dogs/dose in Part 1 were sacrificed after 90 days other half was allowed 28 days for recovery. The 0, 0.4 and 1.8 mg/kg/day dose groups were sacrificed after 90 days but the 4 mg/kg/day dose group was continued on the test diet for 180 days. Part 2 was limited to an assessment of the hematological changes noted in Part 1. These studies were done prior to implementation of GLP Guidelines.

Test chemical effects on bone marrow cytology were evident at 4 mg/kg/day in both Parts 1 and 2. In particular in Part 2, **megaloblasts** were increased in both males/females at 30, 60 and 90 days having values of 3.7/3.4, 4.2/5.4 and 6.6/4.9 counts, respectively, compared to counts of 0.5/0.8 in the controls verifying the increases noted in Part 1 at all dose levels. Other indications of bone marrow cytology and hematology also indicated effects (see DER for details). During the course of the study one high-dose male and female and one mid-dose female developed macrocytic anemia. High-dose male died and the death was attributable to anemia and this dog exhibited erythropoietic hyperplasia. There was **decreased body weight** in males (about 4%, $P < 0.05$) at 25 mg/kg/day. The bone marrow effects were said by the study author to be indicative of "a compound-dependent, hemolytic anemia of the 'penicillin type'." **The Systemic Toxicity LOEL is 4 mg/kg/day, based on hematopoietic effects. The Systemic Toxicity NOEL is 1.8 mg/kg/day.**

Part I. Plasma ChE was inhibited in 10 and 25 mg/kg/day dose males/females by approximately 24.8%/1.92% and 34.5%/18.5%, respectively, at 12 weeks; plasma ChE was significantly inhibited in both sexes by second week. RBC AChE activity was inhibited in mid- and high-dose males (16.4% and 27.7%, respectively) and high-dose females (21%). In Part 2, plasma ChE and RBC AChE were not affected. **The LOEL is 10 mg/kg/day, based on plasma ChE and RBC AChE inhibition. The NOEL is 4 mg/kg/day.**

The parts combined are classified as **Acceptable** and **satisfy** the regulatory requirements (82-1b) for subchronic toxicity study in dogs.

Dose and Endpoint: NOEL of 1.8 mg/kg/day is based on hematopoietic effects including bone marrow effects indicative of a compound-dependent hemolytic anemia of the "penicillin type".

Comments about dose/study: None.

This risk assessment is required.

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CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

DERMAL EXPOSURE:

Studies Selected:

1. 90-day - dog

   (see Intermediate Exposure for Summary)

2. 2-year dog

   Summary: In this chronic study (MRID#43641002), 4 beagles/sex/dose, received either 0, 0.4, 1.8 or 4 mg/kg/day PP062 tech. (94% a.i.) in their diet for two (2) years.

   At 4 mg/kg/day there were noted effects on bone marrow cytology as indicated by decrease in the Myeloid:Erythroid (M:E) ratios of 64% in females and 32% males. This change resulted mainly from increases in late normoblasts ($P < 0.01$, 65%) and megaloblasts ($P < 0.01$, 3.5 fold) and the total erythroid mass (41%) in females with two of the four females contributing most of the change. Nonsignificant increases were noted for late normoblasts (29%) and megaloblasts (12%) and total erythroid mass in males. Total myeloids decreased in females (49%) and males (19%). Metamyelocytes (89%, $P< 0.01$ in females and 63%, $P < 0.05$ in males) were most significantly reduced and the associated bands (56%, $P < 0.05$ in females and 39%, not significant in males) were also reduced. Myeloblasts (4 fold in females and 3 fold in males) were increased. Promyelocyte-neutrophils in males ($P < 0.05$, 3 fold) were increased. Metamyelocytes-neutrophils (60%, $P < 0.05$) and metamyelocytes-eosinophils (68%, $P < 0.05$) in females were decreased. **The systemic toxicity LOEL is 4.0 mg/kg/day, based on bone marrow cytology. The NOEL is 1.8 mg/kg/day.**

   The study was done prior to implementation of GLP Guidelines, therefore, does not fall under purview of either GLP or Quality Assurance requirements. The study is classified as **Acceptable** and **satisfy** the regulatory requirements (83-1b) for a chronic toxicity study in dogs.

Dose and Endpoint: The NOEL of 1.8 mg/kg/day is based on hematopoietic effects including bone marrow effects indicative of a compound-dependent hemolytic anemia of the "penicillin type".

Comments about dose/study: The NOELs (1.8 mg/kg/day), the LOELs (4.0 mg/kg/day) and the effects (hematological/bone marrow) were same for both studies.

This risk assessment is required.

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INHALATION EXPOSURE (ANY TIME PERIOD):

Based on the LC50 of 949 μg/L for males and 858 μg/L for females, Pirimicarb is placed in Tox. Cat. III. Therefore, risk via the inhalation route is not a concern at this time.

This risk assessment is NOT required.

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CANCER CLASSIFICATION AND BASIS: Cancer status of Pirimicarb was not determined because of an inadequate data base.

Q_1* = N/A

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RfD AND BASIS: The HED RfD Peer Review Committee (06/07/96) did not establish an RfD, since this is a non-food use chemical.

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ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of Pirimicarb

Guideline No.	Study Type	HED DOC.#.	Results	Toxicity Category
81-1	Acute Oral	001727	LD_{50} = 147 mg/kg	II
81-2	Acute Dermal	001727	LD_{50} > 500 mg/kg	II
81-3	Acute Inhalation	43496001	LC_{50} = 948 μg/l for males and 858 μg/l for females	III
81-4	Primary Eye Irritation	001727	Corneal opacity reversed in 7 days	II
81-5	Primary Skin Irritation	001727	Non-irritant (35 - 50 mg/kg)	III
81-6	Dermal Sensitization	43496002	Moderate-sensitizer	Acceptable