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MEMORANDUM

SUBJECT: RfD Peer Review Report of Pirimicarb [2-dimethylamino)-5,6-dimethyl-4-pyrimidinyl dimethylcarbamate].

CASRN: 23103-98-2
EPA Chem. Code: 106101
Caswell No.: 359C

FROM: George Z. Ghali, Ph.D.
Manager, RfD/QA Peer Review Committee
Health Effects Division (7509C)

THRU: William Burnam
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Health Effects Division (7509C)

TO: Karen Whitby, PM 14
Insecticide-Rodenticide Branch
Registration Division (7505C)

The Health Effects Division-RfD/Peer Review Committee met on April 18, and again on June 27, 1996 to evaluate the existing and/or recently submitted toxicology data in support of Pirimicarb registration and to establish a Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for chronic toxicity studies in dogs (83-1b), a reproductive toxicity study in rats (83-4), a developmental toxicity study in rats (83-3a), a developmental toxicity study in rabbits (83-3b), a subchronic toxicity study in rats (82-1a), a subchronic toxicity study in dogs (82-1b), 13- and 17-week oral toxicity studies in monkeys, a 21-day dermal toxicity study in rats, and a battery of mutagenicity studies (84-2).

A. Chronic and Subchronic Toxicity:

There were no chronic toxicity studies in rats (83-1a) available for review by the Committee. However, a subchronic toxicity study in rats (82-1a, MRID No. 43641003, HED Doc. No. 012061) was available for review and was considered to be supplementary. This study was conducted as a range-finding study for a long-term toxicity study in rats.

Two chronic toxicity studies in dogs (83-1b, 1971, MRID No. 43641002; 1974, MRID No. 43641004) were available for review by the Committee. The Committee considered the first study (1971) to be acceptable and the second one (1974) to be supplementary data. The second dog study was a non-guideline study designed as a mechanistic study to provide information on the hemolytic anemia observed in the main dog study. The data evaluation records (HED Doc. No. 012061; 001726) were considered to be adequate. Minor revisions to the data evaluation records of the main study were recommended regarding the increased incidence of myeloblast, which was considered by the Committee to be an indication of bone marrow stimulation. The NOEL/LOEL were considered to be 1.8 and 4.0 mg/kg/day, respectively, based on hematological changes. This study demonstrated positive response for the Coomb test. This positive response in the dogs (as well as in monkeys as described later), was a cause for concern by members of the Committee. It was suggested that these findings be confirmed in the new dog study which is currently in progress.

A subchronic toxicity study in dogs (82-1b, MRID No. 00113439, 00113440, 43641001, HED Doc. No. 012061) was available for review by the Committee and was considered to be acceptable. The NOEL/LOEL were considered to be 1.8 and 4 mg/kg/day, respectively, based on hematopoietic effects. The NOEL/LOEL were considered to be 4 and 10 mg/kg/day, respectively, based on plasma and red blood cell cholinesterase inhibition.

Two oral gavage non-guideline studies in monkeys were available for review by the Committee; a 13-week study (1977, MRID No. 00080512, HED Doc. No. 001730, 012061) and a 17-week study (1978, MRID No. 00080513, HED Doc. No. 001730, 012061). The Committee considered the first study (1977) to be unacceptable since an insufficient number of animals was used and the data evaluation record was considered to be inadequate. The study, however, was superseded by a 17-week study in monkeys. The second study (1978) was considered to be supplementary and can not be used for regulatory purposes because of wide variability in the data. The NOEL for both systemic toxicity and cholinesterase inhibition was considered to be 2 mg/kg/day. This study demonstrated positive response in Coomb test. This positive response in monkeys (as well as in the dog study as described earlier), was a cause for concern by members of the Committee.

There was a 21-day dermal toxicity study in the rat (82-2, MRID No. 43896201, HED Doc. No. 012061) available for review by the Committee. The study was considered to be acceptable and the data evaluation record was considered to be adequate. The NOEL for systemic toxicity was considered to be 1000 mg/kg/day or greater. In addition, reduction in plasma and brain cholinesterase activities was observed in males and females at all dose levels. At 1000 mg/kg/day, brain cholinesterase was reduced 18.4% in males and 22.5% in females, while at 200 mg/kg/day, reductions were 10.5% in males and 11.3% in females. Similarly, at 1000 mg/kg/day, plasma cholinesterase activity 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 low dose level (40 mg/kg/day), reductions were less than 5% for brain cholinesterase activity and less than 15% for plasma cholinesterase in both sexes. Therefore, the NOEL/LOEL for cholinesterase inhibition for dermal administration were considered to be 40 and 200 mg/kg/day, respectively.

B. Carcinogenicity:

There were no carcinogenicity studies in rats or mice (83-2a and -2b) available for review by the Committee.

C. Reproductive and Developmental Toxicity:

The Committee considered the reproductive toxicity study in rats (83-4, 1991, MRID No. 42796503) to be acceptable and the data evaluation record (HED Doc. No. 010980, 012061) to be adequate. The Committee recommended redefining the reproductive toxicity observed in this study as developmental/systemic toxicity. The NOEL/LOEL for maternal toxicity were considered to be 22.93 and 88.0 mg/kg/day, respectively, based on decreased body weight gain, decreased food consumption, and decreased food efficiency. The NOEL/LOEL for developmental/systemic toxicity were considered to be 22.93 and 88 mg/kg/day based on decreased pup weights.

The Committee considered the developmental toxicity study in rats (83-3a, MRID No. 42796502) to be acceptable and the data evaluation record (HED Doc. No. 010980) to be adequate. The NOEL/LOEL for maternal toxicity were considered to be 25 and 75 mg/kg/day, respectively, based on reduced body weight gain and reduced feed consumption. The NOEL/LOEL for developmental toxicity were considered to be 25 and 75 mg/kg/day, respectively, based on reduced mean fetal weight, increased incidence of fetal minor skeletal anomalies and increased manus scores.

The Committee considered the developmental toxicity study in rabbits (83-3b, MRID No. 42796501) to be acceptable and the data evaluation records (HED Doc. No. 010980, 011719) to be adequate. The NOEL/LOEL for maternal toxicity were considered to be 10 and

60 mg/kg/day, respectively, based on clinical signs, reduced body weight gain and reduced food consumption during dosing period. The NOEL for developmental toxicity was considered to be more than 60 mg/kg/day, the highest dose level tested.

D. Acute and Subchronic Neurotoxicity:

There were no acute (81-8) or subchronic neurotoxicity studies in rats (82-7) available for review by the Committee.

The Committee recommended that an acute neurotoxicity study in rats (81-8) with cholinesterase activity monitoring be submitted before either non-food or food uses be approved. The Committee did not recommend, however, for a subchronic neurotoxicity study in rats (82-7) since chronic studies with adequate cholinesterase measurements are available.

E. Mutagenicity:

There were four mutagenicity studies (84-2) available for review by the Committee including a gene mutation assay, chromosomal aberrations, and other mutagenic mechanisms. The following studies were considered to be acceptable and the data evaluation records were considered to be adequate.

1) Salmonella typhimurium reverse gene mutation assay (MRID No. 43496005, HED Doc. No. 011605): The test is negative in all strains up to the highest dose tested (2500 µg/plate +/-S9).

2) In vitro cytogenetics in human lymphocytes (MRID NO. 43496006, HED Doc. No. 011605). The test is negative up to a precipitating and cytotoxic level (500 µg/mL +/-S9).

3) Mouse micronucleus assay (MRID No. 43496008, HED Doc. No. 011605): The test is negative in C57B1/CJFCD-1/AlpK mice up to the highest dose tested (69.3 mg/kg, equivalent to ~80% of the median lethal dose) when administered once by oral gavage. The data providing evidence of bone marrow cytotoxicity in high-dose females (24-hour cell harvest) are consistent with the findings from dog studies (MRID Nos. 43641001, 43641002, and 43641004) which indicated that bone marrow is a target tissue for pirimicarb.

4) In vivo and in vitro primary rat hepatocyte unscheduled DNA synthesis (UDS) assay (MRID No. 43496007, HED doc. No. 011605): The test is negative in Sprague-Dawley rats up to clinically toxic doses (200 and 250 mg/kg) when administered once by oral gavage. There was, however, no evidence of test material/target cell interaction.

The Committee overall concluded that the acceptable studies satisfy the pre-1991 mutagenicity initial testing battery

guidelines. Based on the findings of the acceptable studies, there is no concern for mutagenicity at this time.

F. Reference Dose (RfD):

Since the data base was largely inconclusive, the Committee, therefore, recommended that an RfD should not be established for this non-food use chemical based on the existing data.

G. Individuals in Attendance

Peer Review Committee members and associates present were William Burnam (Chief, SAB; Chairman, RfD/Peer Review Committee), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Mike Ioannou (Acting Chief, TB II), Nancy McCarroll, Kit Farwell, Guruva Reddy, William Sette, Henry Spencer, and Rick Whiting. In attendance also were Barbara Madden and Catherine Eiden of HED as observers.

Scientific reviewers (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report)

Guruva Reddy _____

Marion Copley _____

Respective Branch Chief (Committee member; signature indicates concurrence with the peer review unless otherwise stated)

Karl Baetcke _____

CC: Stephanie Irene
Albin Kocialski
Karl Baetcke
Marion Copley
Guruva Reddy
Beth Doyle
Amal Mahfouz (OW)
RfD File
Caswell File

H. Material Reviewed:

1. Hodge, M. C. E. (1971). Pirimicarb (PP062): 2-Year Feeding Study in Beagle Dogs. MRID No. 00113441, 43641002. HED Doc. No. 001323, 001326, 001725, 012061. Classification: Acceptable. This study, in conjunction with the short-term feeding study in dogs MRID No. (00080515, 00113443, 43641004, 43641005) satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.
2. Jackson, J. A. et al. (1974). First Revision to a Pirimicarb-Induced Hemolytic Anemia in Dogs - Report of a Special Study. MRID No. 00080515, 00113443, 43641004, 43641005. HED Doc. No. 001726. Classification: Supplementary data. This study, in conjunction with the long-term feeding study in dogs MRID No. (00113441, 43641002), satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.
3. Moxon, M. E. (1991). Pirimicarb: Multigeneration Study in the Rat. MRID No. 42796503. HED Doc. No. 010980, 012061. Classification: Core Minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.
4. Hodge, M. C. E. (1989). Pirimicarb: Teratology Study in the Rat. MRID No. 42796502. HED Doc. No. 010980. Classification: Core minimum data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.
5. Milburn, G. M. (1989). Teratology Study in the Rabbit. MRID No. 42796501. HED Doc. No. 010980, 011719. Classification: Core minimum data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.
6. Paul, J. D. et al. (1978). Pirimicarb: Growth study to determine a no-effect in the female rat. MRID No. 43641003. HED Doc. No. 012061. Classification: Core Supplementary data. This study was not designed to fulfill a specific data requirement under Subpart F of the Pesticide Assessment Guideline.
7. Hodge, M. C. E. (1968). Subchronic studies with Pirimicarb (PP062) in the Beagle Dog. MRID No. 00113439, 00113440, 43641001. HED Doc No. 012061. Classification:

Acceptable. This study satisfies data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats.

8. Heywood, R. et al. (1977). Pirimicarb: Preliminary oral toxicity study in Rhesus monkeys. MRID No. 00080512, HED Doc. No. 001730, 012061. Classification: Unacceptable. This non-Guideline study was not designed to fulfill a specific data requirement under Subpart F of the Pesticide Assessment Guideline.
9. Heywood, R. et al. (1977). Pirimicarb: Oral toxicity study in Rhesus monkeys (Repeated dosage for 17 weeks, followed by a recovery period of 8 weeks). MRID No. 00080513, HED Doc. No. 001730. Classification: Supplementary. This non-Guideline study was not designed to fulfill a specific data requirement under Subpart F of the Pesticide Assessment Guideline.
10. Lees, D. (1995). 21 Day Dermal Toxicity in the Rat. MRID No. 43896201. HED Doc No. 012061. Classification: Acceptable. This study satisfies data requirement 82-2 of Subpart F of the Pesticide Assessment Guideline for 21-day dermal toxicity testing in rats.
11. Jones, K. and Howard, C. A. (1989). Pirimicarb (Technical): An evaluation in the mouse micronucleus test. MRID No. 43496008, HED Doc. No. 011605. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.
12. Trueman, R. W. (1980). An examination of Pirimicarb for potential mutagenicity using the Salmonella/microsome reverse mutation assay. MRID No. 43496005, HED Doc. No. 011605, HED Doc. No. 011605. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.
13. Wildgoos, J. et al. (1987). Pirimicarb: A cytogenetic in human lymphocytes in vitro. MRID No. 43496006, HED Doc. No. 011605. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.
14. Pirimicarb: Assessment for the induction of unscheduled DNA synthesis in rat hepatocytes in vivo. MRID No. 43496007, HED Doc. No. 011605. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.