

SEP 27 1988

Mr. A. Eimanis
Makhteshim-Agan (America), Inc.
Two Park Avenue
New York, NY 10016

Dear Mr. Eimanis:

Subject: Toxicology Data
Pyrinex (Chlorpyrifos) Insecticide
EPA File Symbol 11678-UL
Your Application Dated December 2, 1987

We have reviewed the toxicology data of the above subject letter and conclude the following:

1. Toxicity in Dietary Administration to Rats for 13 Weeks (Study No. MAK/058/PYRA) (82-1) MRID No. 404364-06.

Classification: Supplementary

2. Pyrinex, Teratogenicity Study in the Rat (Study No. MAK/101/PYR) (83-3) MRID No. 404364-07.

Classification: Minimal

3. Pyrinex, Teratogenicity Study in the Rabbit (Study No. MAK/103/PYR) (83-3) MRID No. 404364-08.

Classification: Supplementary

4. Evaluation of Pyrinex in the Ames Mutagenesis Assay (Study No. 59487-AMKA) MRID No. 404364-11.

Classification: Acceptable

5. In Vitro Chromosomal Aberration Assay on Pyrinex (Chlorpyrifos) (Study No. 59487-CAA) MRID No. 404364-09.

Classification: Acceptable

52849:I:Edwards:209807:LE-08:KENCO:09/15/88:09/26/88:aw:VO:AS

CONCURRENCES

SYMBOL							
SURNAME							
DATE							

6. CHO/HGPRT In Vitro Mammalian Cell Mutation Assay on Pyrinex (Chlorpyrifos) (Study No. 59487-CMA) MRID No. 404364-10.

Classification: Acceptable

Conclusions and Recommendations for the Studies Listed Above

1. 13-Week Dietary Subchronic Study

The Cholinesterase No-Observed-Effect Level (NOEL) was not attained in males (increased inhibition at 0.5 part per million [ppm] - lowest dose tested [LDT]) and was 0.5 ppm in females. The Systemic Toxicity NOEL was 10 ppm and the Systemic Toxicity Lowest-Observed-Effect Level (LOEL) was 200 ppm based on a decrease in body weight gain and possible anemia.

This study may be upgraded depending upon your response regarding the female cholinesterase values.

2. Teratogenicity - Rat

The Cholinesterase Maternal NOEL was not attained as the lowest dose (0.5 mg/kg/day) caused a statistically significant increase in plasma cholinesterase inhibition. The Cholinesterase Maternal LOEL was 0.5 mg/kg/day. The Maternal Systemic NOEL was 2.5 mg/kg/day regarding a decrease in food consumption (during only the first few days of dosing) and a decrease in body weight gain (during the days of dosing). The Maternal Systemic LOEL was 15 mg/kg/day.

The Developmental Toxicity NOEL was 2.5 mg/kg/day (mid-dose). The LOEL was 15 mg/kg/day where postimplantation loss occurred.

Core Classification: Minimal

Cholinesterase Maternal Toxicity NOEL = Not attained
Cholinesterase Maternal Toxicity LOEL = 0.5 mg/kg/day (LDT)
Maternal Systemic Toxicity NOEL = 2.5 mg/kg/day
Maternal Systemic Toxicity LOEL = 15 mg/kg/day
Developmental Toxicity NOEL = 2.5 mg/kg/day
Developmental Toxicity LOEL = 15 mg/kg/day

3. Teratogenicity - Rabbit

The Cholinesterase Maternal NOEL was not attained as the LDT, 12 mg/kg/day, caused a statistically significant increase in plasma cholinesterase inhibition. The Cholinesterase Maternal LOEL was 1 mg/kg/day (LDT).

The Maternal Systemic Toxicity NOEL and LOEL will be determined after review of your response to the Agency's request for information. There was a decrease in food consumption (gestation Days 15-19) and a body weight loss (during the dosing period) followed by a compensatory weight gain in the 140 mg/kg/day group.

The Developmental Toxicity NOEL and LOEL will be determined after review of your response to the Agency's request for information.

Core Classification: Supplementary

This study may be upgraded depending upon your response to the Agency's request.

Maternal Cholinesterase NOEL = Not attained
Maternal Cholinesterase LOEL = 1 mg/kg/day (LDT)

You are requested to provide the following information:

There are rabbits in each group which were said to be "non-pregnant." Please indicate how "non-pregnancy" was determined. Necropsy sheets for "non-pregnant" animals should be submitted.

Explain the value of N on Table 5 of this review, Group 4, mean fetal weight and SD where the value is 14 and for all other parameters N=15 (Table 6, page 40 of the report).

Individual fetal data for litter No. 880 (Group 4, 81 mg/kg/day) as this is missing from the report (Appendix 11, typed page No. D-80 is missing).

4. Ames Mutagenesis Assay

Pyrinex (Chlorpyrifos) was tested in Salmonella strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 (in the presence and absence of S-9) at concentrations of 30, 100, 300, 1000, 3000, and 10,000 ug/plate. DMSO was the solvent and negative control; positive controls were sodium azide, 9-aminoacridine, 2-nitrofluorene, and 2-anthramine. Pyrinex was not toxic nor did it appear to increase over control values the number of revertant colonies/plate. Positive controls caused appropriate mutagenic responses.

5. In Vitro Chromosomal Aberration Assay

Pyrinex (Chlorpyrifos) was tested in an in vitro chromosomal aberration assay with and without S-9 activation. Concentrations assayed were: nonactivation - 10 hour assay = 1.56, 3.12, 5.2, 10.4, 15.6, 31.2, 52, 104 and 156 ug/mL; 19 to 20 hour assay = 0.975, 1.47, 2.93, 4.89, 9.75, 14.7, 29.3, 48.9, 97.5 and 147 ug/mL - activation; two 10-hour assays = 1, 1.5, 3, 5, 10, 15,

30, 50 and 100 ug/mL and 2.95, 4.95, 9.85, 14.8, 29.6, 49.4, 98.5 and 296 ug/mL; 19 to 20 hour assay = 9.75, 14.7, 29.3, 48.9, 97.5, 147 and 293 ug/mL. Positive controls were Mitomycin C (nonactivation) and cyclophosphamide (activation). Cytotoxicity was shown in both nonactivated as well as in activated assays. Pyrinex did not appear to cause chromosomal aberrations. Positive controls caused appropriate mutagenic response.

6. CHO/HGPRT In Vitro Mammalian Cell Mutation Assay

Pyrinex (Chlorpyrifos) was tested in the mammalian cell CHO/HGPRT gene mutation assay at concentrations of 5 to 75 ug/mL in the nonactivation study and 30 to 1000 ug/mL in the activation study. Cytotoxicity assays were performed in both the non-activation and activation studies (1.5-3748 and 1.5-5000 ug/mL, respectively). DMSO (solvent) and the medium were negative control groups. Positive controls were ethylmethanesulfonate (nonactivated) and dimethylnitrosamine (activated). Pyrinex showed cytotoxicity only in the nonactivated study (at 150 ug/mL). "Pitting" of the plastic culture vessels occurred at 50 or 150 ug/mL (nonactivated or activated, respectively). It appeared that the assay tested concentrations that were at the limits of solubility. There was no evidence that Pyrinex caused mutation in either the nonactivated or activated studies. Positive controls caused appropriate mutagenic responses.

I have enclosed a copy of our review for your information.

Sincerely yours,

Dennis H. Edwards, Jr.
Product Manager (12)
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

Enclosure