UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 23 1992

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM:

SUBJECT: Review of data for chlorpyrifos (pyrinex) for Data Call-In notice

EPA IDENTIFICATION NUMBERS: Caswell No.: 219AA
P.C. Code: 059101
HED Project Number: 2-1170

FROM: Robert F. Fricke, Ph.D. Robert F. Fricke 3 Sept 92.
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THRU: Elizabeth Doyle, Ph.D. E.A. Doyle 9/3/92
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and

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Chief, Toxicology Branch II

Registrant: Makhteshim-Agan (America)

Chemical: Chlorpyrifos (Pyrinex)

Action Requested: Review toxicology studies on chlorpyrifos (pyrinex) submitted by Makhteshim-Agan (America) in response to a Data Call In.

Conclusions: The data package consisted of five studies to be reviewed as part of a data call-in. Two studies, a range-finding and definitive oral toxicity in dogs, met the applicable core guidelines. The LOEL was based upon significant decreases in plasma and RBC cholinesterase activities. In the subchronic range-finding inhalation study in rats, the highest achievable aerosol concentration was only 23 ppb, which was generated by vaporizing the chlorpyrifos. This concentration was not high enough to elicit significant toxic effects, other than decreased

RBC cholinesterase activity in the female rats. The two-generation reproduction study in rats was technically acceptable, but supplementary data are required to upgrade the study. The oncogenicity study met the core guidelines; the systemic LOEL was based on increased incidence of non-neoplastic lesions in females and decreased body weights in both sexes.

Following are summaries of the submitted studies.

1. Chlorpyrifos Oral Dose Range Finding Toxicity Study in Beagle Dogs, EPA Accession No.: 421449-08, Huntingdon Research Centre, Ltd., MBS 30/88675, 3 May 1989

Male and female dogs were treated orally with the test article (0, 0.01, 0.03, 0.5 and 5.0 mg/kg/day) for 4 weeks. The test article inhibited plasma, RBC and brain cholinesterase at dosages of 0.03, 0.5 and 5 mg/kg/day, respectively.

NOEL 0.01 mg/kg/day (LDT)

LOEL 0.03 mg/kg/day (MDT)

LOEL based on inhibition of plasma cholinesterase.

CLASSIFICATION: core - Supplementary (This is not a guideline study)

2. A Five Day Nose-Only Inhalation Toxicity Study of Chlorpyrifos (Pyrinex) in the Rat, EPA Accession No.: 421449-09, Bio/dynamics, Inc, 88-8057, 22 December 1988

Male and female rats were exposed to the test article at either 0 ppb (control) or 23 ppb (0.0034 μg/l) for 6 hours/day for five days in a nose-only apparatus. The only significant finding was a significant decrease in RBC cholinesterase activity of female rats in the treatment group. No other signs of toxicity were observed.

LC_{50} > 23 ppb (0.0034 μg/l)

Toxicity category I

CLASSIFICATION: core - Supplementary (This is not a guideline study)

3. Chlorpyrifos Oral Toxicity Study in Beagle Dogs (Repeated Daily Dosage for 13 Weeks) (82-1), EPA Accession No.: 421728-01, Huntingdon Research Centre, Ltd., MBS 31/88999, 3 May 1989

Male and female pure-bred Beagle dogs were given the test article daily for 13 weeks at dosages of 0, 0.01, 0.22 or 5.0 mg/kg/day. The primary toxic effect was the inhibition of plasma, RBC and brain cholinesterase.

	MALE	FEMALE
NOEL	0.01 mg/kg/day (LDT)	0.01 mg/kg/day (LDT)
LOEL	0.22 mg/kg/day (MDT)	0.22 mg/kg/day (MDT)

LOEL is based on significant inhibition (> 20% of control value) of both plasma and RBC cholinesterase.

CLASSIFICATION: core - Guideline (This study satisfies guideline requirements (82-1) for a 90-day feeding study in dogs.)

4. Pyrinex Technical Oncogenicity Study in the Rat (83-2), EPA Accession No.: 421728-02, Life Science Research Israel, Ltd., MAK/095/PYR, 12 July 1990.

This study evaluated the oncogenic potential of test compound, at dietary concentrations of 0, 0.2, 5.0, or 100 ppm (equivalent to approximately 0, 0.0132, 0.33, or 6.99 mg/kg/day for males and 0, 0.0146, 0.365, or 7.78 mg/kg/day for females, respectively) when administered to rats for 104 weeks. Results of the study showed that the test compound was not carcinogenic.

	NOEL	LOEL
Systemic	5.0 ppm (MDT)	100 ppm (HDT)
ChE (males)	0.2 ppm (LDT)	5.0 ppm (HDT)
ChE (females)	< 0.2 ppm (LDT)	0.2 ppm (LDT)

The systemic LOEL is based on decreased body weights in both males and females, increased incidence of non-neoplastic lesions (cataracts and diffuse retinal atrophy) in females.

CLASSIFICATION: core - minimal (This study satisfies guideline requirements (83-2) for an oncogenicity study in rats.)

5. The Effect of Pyrinex (Chlorpyrifos) on Reproductive Function of Two Generations in the Rat, EPA Accession No.: 421728-03, Huntingdon Research Centre, Ltd., MBS 29/881452, 17 August 1989.

The effect of dietary administration of test compound, at dosages of 0, 2, 10 or 50 ppm (mg/kg/day equivalents are 0.13, 0.64, 3.21 (F_0 males); 0.19, 1.03, 5.05 (F_1 males); 0.14, 0.71, and 3.58 (F_0 females); 0.21, 1.08, and 5.44 (F_1 females), respectively) on the reproductive performance of rats over two generations was studied. Although inhibition of cholinesterase activity was noted in the range-finding study, no significant, treatment-related effects were noted in the definitive study (cholinesterase activity was not measured in the definitive study). Supplementary data (body weight gain data, relative organ weight data and fertility indices) are needed, however, to assign NOELs and LOELs.

The Sponsor needs to clarify an apparent discrepancy in the dates between approval dates by the Sponsor and the Study Director. On page 3 of the study the Study Director approved the study on 17 August 1989, which was over three months after it was approved by the Sponsor on 27 April 1989.

CLASSIFICATION: core - supplementary (This study does not satisfy the guideline (83-4) for reproductive and fertility effects in rats.)