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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Subject: I.D. No. 003125-URU: NTN 33893 Technical. Proposed Dose Levels for Subchronic Neurotoxicity Screening Study (82-7SS) in Rats

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CONCLUSION

The dose levels proposed for the Subchronic Neurotoxicity Screening Study (0, 150, 675 and 3000 ppm) are acceptable. It is recommended, however, that the mid-dose level be raised from 675 ppm to 1000 ppm, since 600 ppm produced very minimal effects in other subchronic studies.

ACTION REQUESTED

Toxicology Branch I was asked to review the dose levels proposed by Miles Corp. in support of registration of NTN-33893 technical (94%) and four formulations (75%, 21%, 2.5% and 0.62%).

COMMENT -

Miles Corp. used the data from a Subchronic Rat study (MRID No. 422563-27) and a Pilot Range-finding Rat study (MRID No. 422563-34) to support the dose levels chosen for the Subchronic Neurotoxicity screen they are about to conduct (see attached rationale).

All three dose levels chosen are supported by existing data. However, in the Pilot Rangefinding study (MRID 422563-34), 600 ppm produced a small decrease in body weight gain in males only, as well as morphologic evidence of liver enzyme induction. Females were not affected at this dose level. In the Subchronic study (MRID 422563-27) body weights were significantly ($p \leq 0.05$) reduced in both sexes (males 6 - 7%, females 10%) intermittently throughout the study. Body weight gain data were not provided.

These findings suggest that 600 ppm may be very close to the threshold for subchronic toxicity. Therefore, it may be better to test at a higher mid-dose level, at 1000 ppm, where clearer evidence of systemic toxicity is expected, in an effort to produce as much useful data as possible from the study.

Attachment

Dose Selection for a Subchronic Neurotoxicity Screening Study (82-7SS) in Rats

NTN 33893 (Imidacloprid)

Imidacloprid is a nitroguanidine compound that is being developed by Miles as an insecticide. Its insecticidal activity is attributed to its action as an agonist at the nicotinic acetylcholine receptor. It has no inhibitory effect on cholinesterase activity.

The rationale for the selection of doses is primarily based on the results of two subchronic dietary exposure studies [1,2]. The highest dietary levels used in those two studies (i.e., 2400 and 3000 ppm, respectively) produced a 10-20% decrease in body weight gain in both sexes but did not produce overt clinical signs. Males that received either 2400 or 3000 ppm exhibited hepatotoxicity and liver enzyme induction (evident as an increase in the incidence of hepatocellular necrosis, round cell infiltrates, swollen cell nuclei and cytoplasmic changes and slightly elevated alkaline phosphatase and ALAT activities). A diet of 3000 ppm produced similar hepatotoxic effects in females and males also exhibited low-grade degenerative changes in the epithelium of the testicular tubules. A slight decrease in body weight gain and some morphologic evidence of liver enzyme induction occurred in males at the 600 ppm dietary exposure level. The NOEL was 600 ppm for females and 150 ppm for males.

Based on these results, 0, 150, 675 and 3000 ppm were selected as the dietary levels for the subchronic neurotoxicity screening study. The 3000 ppm dietary level was selected as a dose that produces clear evidence of toxicity (primarily hepatotoxicity) without causing mortality. The 150 ppm dietary exposure was selected to produce no evidence of toxicity and 675 ppm was chosen to produce an intermediate level of toxicity.

References

1. R. Eiben, "NTN 33893 - Subchronic Toxicity Study on Wistar Rats (Administration in the Feed for 96 Days)", Miles Inc., Agriculture Division Report Number 100036, MRID Number 42256327, 1989.

2. R. Eiben, "NTN 33893 - Pilot Range-Finding Study for a Chronic Toxicity Study on Wistar Rats (Ninety-Eight Day Feeding Study)", Miles Inc., Agriculture Division Report Number 99672, MRID Number 42256334, 1988.