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

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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Malathion Registration Standard: Dose Level Proposal for Malaoxon Chronic Toxicity/Oncogenicity Study

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Ms. Diane Allemang of Jellinek and Associates, representing Cheminova Agro A/S, communicated to SRRD via letter of August 10, 1992, results of the 14-day dose range-finding study on malaoxon preliminary to the required 2-year chronic toxicity/oncogenicity study in the F344 rat (see attachment).

Originally it had been proposed that the two year study employ dosages of 0, 15, 1500 and 3000 ppm malaoxon in the diet. As a result of this 14-day study,

The Registrant now proposes doses of 0, 20, 1000 and 2000 ppm for the definitive study. Rational for the revision in recommended dosing is discussed as follows:

As background information we should recall that in the 1979 NCI 2-year study of malaoxon in the rat, dosage levels employed were 0, 500 and 1000 ppm in the diet. In that study, there was inadequate evidence that an MTD had been reached. For example, there was no compound related increased mortality, and there were no clinical signs, effects on body weight or food consumption. It would thus appear that a higher level of the test material should have been evaluated. Data from a 13-week study in the rat preliminary to the NCI study found no mortality at 2000 ppm, but complete mortality at the next higher dose of 4000 ppm.

In the current 14-day dose range-finding study, mortality was clearly an effect at 3500 ppm in females but not in males. Clinical signs were seen in males at 3500 ppm and possibly at 2500 ppm. Clinical signs were clearly present in females at 2500 ppm and were reported for some females at 100 ppm. Food consumption was decreased in rats of both sexes at the two highest doses. Body weight gain for females was decreased at the two high doses and for males at the highest dose.

At one week into the study, plasma cholinesterase was statistically significantly inhibited in males and females at 100, 2500 and 3500 ppm. Erythrocyte cholinesterase was statistically significantly inhibited in males at the three top doses and in females only at 3500 ppm.

At study termination, brain cholinesterase was statistically significantly inhibited at 2500 ppm in males and females, and at 3500 ppm in males. Though not assayed for females in the 3500 ppm group due to early mortality, brain cholinesterase presumably would also have been substantially inhibited in this group. At 2500 ppm the inhibition apparently was more pronounced in females (67%) than in males (37%). Erythrocyte cholinesterase was inhibited in males at the two highest doses, but the degree of inhibition was not great, 24% at 2500 ppm and 17% at 3500 ppm. Erythrocyte cholinesterase was not statistically significantly inhibited at any dose level for which it was assayed in females, though it was not assayed in the high dose group for the reason previously indicated. Plasma cholinesterase was remarkably inhibited at term in rats of both sexes at 2500 ppm, in males at 3500 ppm and presumably so in females at 3500 at the time of death.

It would appear that plasma and brain cholinesterase inhibitions are better correlates of toxicity in females than is erythrocyte cholinesterase inhibition.

CONCLUSION:

In consideration of all these findings we view the Registrant's selection of 0, 20, 1000 and 2000 ppm as dosages for the definitive 2-year chronic toxicity/oncogenicity study on malaoxon to be reasonable. We must remind the Registrant that while we will offer comment on dose selection, the decision as to which doses will be used rests with the Registrant.

Attachment