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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: **MOLINATE** - Developmental Neurotoxicity Study **UPDATE**

TO: Wilhelmena Livingston
Reregistration Branch, SRRD (7508W)

FROM: Linda L. Taylor, Ph.D Linda Lee Taylor 10/28/98
Reregistration Branch I
Health Effects Division (7509C)

THRU: Whang Phang, Ph.D. W Phang 10/28/98
Branch Senior Scientist, Reregistration Branch I
Health Effects Division (7509C)

Registrant:	Zeneca
Chemical:	S-ethyl hexahydro-1H-azepine-1-carbothioate
Synonym:	Molinate, Ordram
Caswell No.:	444
PC Code:	041402
MRID No.:	44079201

At the October 1, 1998 HIARC meeting on Molinate, the Committee agreed with the TOX SAC conclusion that the effects observed at the low-dose level could not be discounted, and the NOAEL was changed to the LOAEL; i.e., there is no NOAEL for developmental neurotoxicity in this study [MRID 44079201]. This decision was based on the significant decrease in the startle amplitude at all dose levels on day 23 *post partum*. Although it was noted that this effect was the only effect observed at the low dose and that it occurred in only one sex at one time point at this dose level, based on the weight of the evidence on Molinate with respect to neurotoxicity, the occurrence at the low dose is considered treatment-related.

EXECUTIVE SUMMARY: In a developmental neurotoxicity study (MRID 44079201), Molinate [96.8% a.i.] was administered to 30 female Alpk:AP$_f$SD rats/group in the diet at dose levels of 0, 20, 75, and 300 ppm (0, 1.8, 6.9, and 26.1 mg/kg/day, respectively) from gestation day 7 through lactation day 11 [with the day of parturition designated as postnatal day 1].

MATERNAL TOXICITY: There was no evidence of a treatment-related effect on maternal survival or clinical signs of toxicity. Mean maternal body weight values for the 300 ppm group were decreased slightly [93%-94% of control] from day 10 of gestation and throughout lactation [89%-95% of control] compared to the controls. Mean body weight gain at the 300 ppm dose level was decreased prior to dosing [days 1-4 of gestation (88% of control)] and during gestation days 7-22 [76% of control] and 1-22 [80% of control]. During the first 3 days of dosing, dams at the 300 ppm dose level displayed a negative body-weight gain. During lactation, the 300 ppm dose group displayed a negative body-weight gain during days 1-7, and the overall body-weight gain for both the mid- and high-dose groups was decreased [70% and 73% of control, respectively] compared to the control. A statistically significant reduction in group mean food consumption was noted in the 300 ppm group throughout gestation [73%-94% of control] and lactation [75%-87% of control] compared to the control group.

Litter size and the number of pups born live/dead were comparable among the groups, and the mean number of total pups born and live birth index were unaffected by treatment. The mid- and high-dose groups displayed the lowest percent of litters with all pups born live compared to the controls. At 300 ppm, there was an increase in the number of litters with small female pups, a slightly higher mortality rate during days 1 to 5 *post partum*, and the number of missing and presumed dead pups [both sexes] was increased compared to the controls. Whole litter losses occurred at the control [2 litters] and high-dose [4 litters] levels only.

There were no treatment-related findings observed in the dams at necropsy [brain weights were not measured].

SELECTED F1 OFFSPRING: At the high-dose level [300 ppm], there was an increase in preweaning mortality, and a higher number of 300 ppm pups were reported missing/presumed dead compared to the controls. There was a significant decrease in birth weight and an increase in the number of small pups of both sexes at 300 ppm compared to the control group. There was no effect on the sex ratio [percent males].

Decreased body weight was observed at the 300 ppm dose level for both sexes [males 73%-84%/females 72%-82% of control] from day 5-29 of lactation, and the decrease continued post weaning [days 29-63], although the magnitude of the decrease in both sexes [males 81%-88%/females 84%-91% of control] decreased with time. Decreased body-weight gains were observed mainly during the preweaning period in both sexes [64%-84% of control] at 300 ppm.

There was a delay in both preputial separation and vaginal opening at 300 ppm compared to the control groups.

On day 23 *post partum*, there was a significant decrease in the startle amplitude for both sexes at 300 ppm at all 5 intervals, and the females at this time point displayed a dose-related decrease in the startle amplitude, which was statistically significant at all dose levels in 3 of 5 intervals. Males at all dose levels and females at the low- and mid-dose levels displayed comparable responses to those of the controls on day 61, but the high-dose females continued to display a decrease in startle amplitude on day 61. Time to maximum amplitude was increased on day 23 in the high-dose males only and only during the second interval. On day 61, females at 300 ppm displayed a significant increase in the time to maximum amplitude during 4 of the 5 intervals.

Motor activity was comparable among the female groups, but an effect on this parameter cannot be ruled out for males at the 300 ppm dose level because of the initial [day 14] decrease and subsequent, sustained [days 22 and 60 *post partum*], increase in motor activity observed.

Straight-channel swimming time was increased at 300 ppm in both sexes on day 21 *post partum* compared to the controls but comparable among the groups at all other time points. In both the initial learning [day 21] and memory [day 24] phases of the Y-shaped water maze test, both sexes at 300 ppm had a lower percentage of successful trials compared to the controls throughout the test. In the subsequent learning [day 59] and memory [day 62] phases of the Y-shaped water maze test, comparable successes were observed among the groups [both sexes].

There was a treatment-related decrease in absolute brain weight for both sexes at 300 ppm at both the day 12 and day 63 sacrifice times. Brain length was decreased in both sexes at 300 ppm on day 12, and the females of this group also displayed a decrease in brain width. At day 63, slight decreases in both length and width were observed in both sexes at 300 ppm, but statistical significance was not attained.

There were no treatment-related findings at necropsy on either day 12 or day 63, no microscopic abnormalities in the brains of any pups on day 12, and there were no changes in the central or peripheral nervous systems on day 63 that could be attributed to treatment. With respect to morphometric measurements, treatment–related changes in the cortex and/or cerebellum of the brain [decreased structural measurements and decreased thickness of cellular layers] were observed at the mid- and high-dose levels on day 12, and similar treatment-related changes in the cortex, hippocampus, and/or cerebellum were observed at the 300 ppm dose level on day 63.

The NOAEL for maternal toxicity is 75 ppm [6.9 mg/kg/day], and the LOAEL for maternal toxicity is 300 ppm [26.1 mg/kg/day], based on decreased body weight/gain and food consumption.

The NOAEL for developmental neurotoxicity was not determined, based on a reduction in startle amplitude in the auditory startle test in females [day 23] at all dose levels. The developmental neurotoxicity LOAEL is 20 ppm [1.8 mg/kg/day]. At 75 ppm [6.9 mg/kg/day], in addition to the reduction in startle amplitude in the auditory startle test, there were treatment-related reductions in some morphometric measurements in areas of the cerebellum of the brain [day 12] in both sexes.

At 300 ppm [26.1 mg/kg/day], (1) increased mortality, (2) decreased body weight, (3) a delay in the appearance of developmental landmarks [preputial separation and vaginal opening], (4) an increase in swimming time in the straight channel test at day 21 and reduced performance in the learning and memory tests on days 21 and 24, respectively, (5) a reduction in startle amplitude, (6) an increase in the time to maximum amplitude [days 23 and/or 61], (7) a possible increase [slight] in mean motor activity level in males, (8) reduced brain weight [both sexes on days 12 and 63], brain length [both sexes on day 12], and brain width [females on day 12], and (9) reductions in several morphometric measurements in areas of the cortex, hippocampus, and cerebellum of the brain were observed.

The guideline developmental neurotoxicity study in the rat is classified **Acceptable**, and it satisfies the guideline requirement for a developmental neurotoxicity study in the rat (§83-6; OPPTS 870.6300).