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OVERVIEW

MESOTRIONE (ZA1296) 6/22/2000

Study Type: Non-Guideline; Single Generation Reproductive Study in the Rat

Work Assignment No. 2-01-52CC (amend 1) (MRID 44505112)

Prepared for

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Disclaimer

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6/22/00

OVERVIEW

STUDY TYPE: Correlation of dietary tyrosine and mesotrione with litter size and pup viability
OPPTS Number: N/A OPP Guideline Number: non-GDL

DP BARCODE: D259369 SUBMISSION CODE: S541375
P.C. CODE: 122990 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Mesotrione (96.8% purity)

SYNONYMS: ZA1296; 2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione; 2-(4-mesyl-2-nitrobenzoyl)-cyclohexane-1,3-dione

CITATION: Williams, J., (1997) ZA1296: A Single Generation Reproductive Toxicity Study in the Rat (up to day 5 *post partum*). Central Toxicology Laboratory, Cheshire, UK, Laboratory Report No: CTL/L/8015; Study No: XR6312/F0. November 11, 1997. MRID 44505112. Unpublished.

SPONSOR: Zeneca AG Products, Wilmington, Delaware

EXECUTIVE SUMMARY: The stated objective of this study (MRID 44505112) was to investigate the effects of mesotrione (96.8% purity, batch P17) in conjunction with dietary tyrosine on litter size and pup viability in Alpk:Ap$_f$SD rats. One control group and 7 test groups (20 time-mated females/group) received mesotrione and/or L-tyrosine in the diet as follows: Group 1 was the control group, Group 2 received 0 ppm mesotrione + 0.5% tyrosine, Group 3 received 0 ppm mesotrione + 1% tyrosine, Group 4 received 0 ppm mesotrione + 2% tyrosine, Group 5 received 2500 ppm mesotrione only, Group 6 received 2500 ppm mesotrione + 0.5% tyrosine, Group 7 received 2500 ppm mesotrione + 1% tyrosine, and Group 8 received 2500 ppm mesotrione + 2% tyrosine. Diets were administered continuously beginning on gestation day (GD) 0. Clinical signs, body weights, food consumption, and plasma tyrosine levels were measured in the dams; offspring were counted, examined for clinical signs, and weighed. Any animal which failed to litter by GD 25 or experienced difficulties with parturition was sacrificed and discarded.

The results of this special study are presented as an attachment to this overview (Study Report Tables 1 through 5, pages 9 through 15). There were no differences of toxicological concern in pup body weights.

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At 48 hours after the start of treatment, tyrosine levels in groups 2-8 were increased (↑9-1807%, not analyzed for statistical significance). During clinical observation, the following findings were noted: eye opacity in groups 6 (7/20 treated), 7 (15/20 treated), and 8 (8/20 treated); hunched posture in 5/20 group 8 animals; and piloerection in groups 5 (4/20 treated), 6 (12/20 treated), 7 (16/20 treated), and 8 (14/20 treated). All group 8 females displayed severe corneal lesion which necessitated the termination of the entire group on GDs 8-11. Decreased ($p<0.001$) body weights were observed in group 8 animals on GDs 4 and 7 (↓11-13%).

Increased incidences of whole litter losses between PNDs 1-5 occurred in groups 6 and 7 (4/17 and 8/18, respectively). Decreased litter size on PND 1 was noted in group 7 (↓16%, not statistically significant [NS]). The mean number of pups found dead on PND 1 was increased in group 7 (↑435%, $p<0.05$). In groups 6 and 7, a decreased number of live male pups (mean number live pups litter = 5.35 and 4.83, respectively, vs 7.05 controls, $p<0.05$) and an increased number of dead male pups (mean number dead/litter = 0.35 and 0.67, respectively, vs 0 controls, $p<0.05$) were noted on PND 1. In groups 6 and 7, the following findings ($p<0.05$ or 0.001) were noted on PND 5: decreased number of live pups/litter (↓23 and 53%, respectively); increased percent deaths (↑225 and 525%, respectively); decreased number of male pups/litter (↓44 and 61%, respectively); increased percent deaths in males (↑372 and 946%, respectively); decreased number of female pups/litter (group 7 only, ↓41%); and increased percent deaths in females (group 7 only, ↑192%). An additional finding in group 6 included an increase in percent deaths in the females (↑80%, NS). In group 5 on PND 5 the following findings (NS) were noted: decreased number of live pups/litter (↓13%); increased percent deaths (↑110%); increased percent deaths in the males (↑137%) and in the females (↑111%).

In conclusion, both litter size and pup viability were decreased following treatment of the maternal animals with 2500 ppm mesotrione co-administered with 0.5% and 1% tyrosine; males appeared to be more susceptible to the effects of treatment.

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