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

OFFICE OF PREVENTION, PESTICIDE AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

Date: April 16, 2008

SUBJECT: **Ingredient:** Diazinon. **Title:** Revised Executive Summary for the Developmental Neurotoxicity Study

PC Code: 057801
MRID No.: see table
Petition No.: NA
Assessment Type: NA
TXR No.: 0054847

DP Barcode: D351496
Registration No.: REGREV-057801-27616
Regulatory Action: NA
Reregistration Case No.: NA
CAS No.: 333-41-5

FROM: Marion Copley, DVM, DABT
Science Information Management Branch
Health Effects Division (7509P)

THROUGH: Jessica Kidwell
Science Information Management Branch
Health Effects Division (7509P)

TO: Jude Andreasen/Susan Lewis (RM 51)
Reregistration Branch 1
Special Review and Reregistration Division (7505P)

I. CONCLUSIONS

The executive summary for the Diazinon rat Developmental Neurotoxicity Study in this Supplemental DER (attached) revises and supersedes the one in TXR # 0052434. This revision corrects the maternal systemic NOAEL which was inadvertently reported as 30 ppm but should have been 300 ppm. The remainder of DER for this study is unchanged.

II. ACTION REQUESTED

Revise the executive summary for the Diazinon Developmental Neurotoxicity Study in rats (TXR # 0052434) to correct an error in the maternal systemic NOAEL.

III. MRID Summary Table

Study Type	MRID	Comments
Developmental Neurotoxicity Study	46195601, 45842601	Revised executive summary

Rec'd in RLC 4/15/2008 MS

EPA Reviewer: Marion Copley, D.V.M., D.A.B.T. **Signature:** _____
Science Information Management Branch, Health Effects Division (7509P) Date: _____
EPA Secondary Reviewer: Jessica Kidwell **Signature:** _____
Science Information Management Branch, Health Effects Division (7509P) Date: _____

Template version 02/06

TXR#: 0054847

DATA EVALUATION RECORD – Supplemental
See TXR # 0052434 for original DER

STUDY TYPE: Developmental Neurotoxicity Study - Rat;
OPPTS 870.6300 (§83-6); OECD 426

PC CODE: 057801 **DP BARCODE:** D351496

TEST MATERIAL (PURITY): Diazinon Technical (92.9%)

SYNONYMS: 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether

CITATION: Mandella, R.C. (2003) Diazinon: a developmental neurotoxicity study in rats. Huntingdon Life Sciences, Mettlers Road, East Millstone, New Jersey. Laboratory study no. 01-4532; November 17, 2003. MRID 46195601. Unpublished.

Mandella, R.C. (2002) Diazinon: a dietary range-finding developmental neurotoxicity study in rats. Huntingdon Life Sciences, Mettlers Road, East Millstone, New Jersey. Laboratory study no. 01-4530; November 13, 2002. MRID 45842601. Unpublished.

SPONSOR: Makhteshim-Agan of North America, 551 Fifth Avenue, Suite 1100, New York, NY 10176

EXECUTIVE SUMMARY: In a developmental neurotoxicity study (MRID 46195601), Diazinon technical (92.9% a.i., batch # 9896144) was administered to 27 female Crl:CD® (SD)BR IGS rats/dose in the diet at concentrations of 0, 0.30, 30 or 300 ppm from gestation day (GD) 6 through postnatal (lactation) day (PND) 21. The average daily test article intake was 0, 0.026, 2.36, or 24.2 mg/kg/day during gestation and 0.039, 4.06, or 39 mg/kg/day from GD 6 through PND 21. Dietary concentrations were based on a range-finding developmental neurotoxicity study in the rat (MRID 45842601). A Functional Operational Battery (FOB) was performed on 10 dams/dose on GDs 13 and 20, and on PNDs 7, 14, and 20. On PND day 4, litters were culled to yield five males and five females (as closely as possible). Offspring representing at least 20 litters/dose were allocated for detailed clinical observations (FOB), assessment of motor activity, assessment of auditory startle response habituation, assessment of auditory startle pre-pulse inhibition, assessment of learning and memory, and neuropathology at study termination (day 60 of age). On PND day 21, the whole brain was collected from 10 pups/sex/dietary level for micropathologic examination and morphometric analysis. Pup sexual maturation was assessed by age at vaginal opening for females and at completion of balano-

preputial separation for males. Plasma, RBC, and brain cholinesterase activities were measured in dams on PND 21, and in selected pups on PNDs 4 and 21.

In dams, no treatment-related effects on mortality, clinical signs, body weight, FOB parameters, or necropsy findings were noted. Piloerection in a few high-dose animals (4/20) on one day (PND 20) is not clear evidence of maternal toxicity. There was a slight decrease in body weight gain (nonstatistical - 38%) and food consumption (10%) in the high dose dams during lactation. This is supported by the occurrence of cholinesterase inhibition in all three compartments at the mid dose, and to a greater extent the high dose (discussed below).

In mid- and high-dose dams, cholinesterase activity was significantly inhibited in all three compartments: enzyme activity was inhibited by 67 and 92.6%, respectively, in plasma, by 87.3 and 100%, respectively, in RBC, and by 24.8 and 86.8%, respectively, in brain. No inhibition was measured in low-dose dams.

For maternal systemic toxicity, the NOAEL is 300 ppm (24.2 mg/kg/day), the highest dose tested. A LOAEL was not established.

For maternal cholinesterase inhibition, the NOAEL is 0.3 ppm (0.026 mg/kg/day). The LOAEL is 30 ppm (2.36 mg/kg/day) based decreases in on plasma, RBC and brain cholinesterase activities.

Treatment had no adverse effects on survival, clinical sign, FOB, auditory startle response, brain weights, brain morphology or neuropathology.

No treatment-related effects were noted on body weight or body weight gain for pups in the low- or mid-dose groups. At the high dose, absolute body weights of male and female pups was significantly less ($p \leq 0.05$ or 0.01) than control pups beginning on PND 7 for males and PND 4 for females. Correspondingly, male and female pups from the high-dose group had significantly reduced body weight gain compared with the controls at all intervals throughout lactation. Post-weaning, offspring from the high-dose group had significantly lower body weight compared with the controls through PND 60 for males and PND 42 for females. Weight gain by the high-dose males was significantly less than that of the controls for the first two weeks, but was similar thereafter. Weight gain by the high-dose females was not affected during the post-weaning interval.

Males and females from the high-dose group had significant delays ($p \leq 0.01$) in preputial separation (1.9 days after control) or vaginal opening (1.3 days after control), respectively, compared with the controls. Mean body weight at attainment was similar between the treated and control groups for males and females.

In the assessment of motor activity, there was a possible treatment related effect in the high dose males on PND 17, however, it was difficult to interpret the biological significance of this since it only occurred on one day and there was large variability. It was also noted that activity for PND 21 was highly variable across intervals for both males and females. Overall, it was determined that the motor activity assessment was inadequate and difficult to interpret because of too much variability in the data.

In assessment of learning and memory, males from the high-dose group had significantly longer swimming time and a greater number of errors compared to the controls on the first and second day of testing at both PNDs 24 and 60.

In 4-day old male and female pups from high-dose litters, cholinesterase activity was significantly inhibited in plasma by 50.1 and 48.4%, respectively, in RBC by 41.3 and 37.8%, respectively and in brain by 16.7 and 13.4%, respectively. On PND 21 dose-related inhibition of cholinesterase activity was observed in male and female pups from the mid- and high-dose litters. Plasma enzyme activity was inhibited in the mid- and high-dose offspring by 34.4 and 68.2%, respectively, in males and by 18.6 and 51.2%, respectively, in females. RBC enzyme activity was inhibited in mid- and high-dose males by 23.5 and 58.3%, respectively and in high-dose females by 53.8%. Males and females from the high-dose group had 44.2 and 28.6% inhibition, respectively, of brain enzyme activity.

For offspring systemic toxicity, the NOAEL is 30 ppm (2.36 mg/kg/day). The LOAEL is 300 ppm (24.2 mg/kg/day) based reduced body weight and body weight gain an delayed sexual maturation in males and females.

For offspring cholinesterase inhibition NOAEL is 0.30 ppm (0.026 mg/kg/day). The LOAEL is 30 ppm (2.36 mg/kg/day) based on plasma, and RBC cholinesterase activities both sexes.

This study is classified **Acceptable/NonGuideline** and may be used for regulatory purposes. It does not, however, satisfy the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6); OECD 426 (draft) due to the inadequacies in the assessment of motor activity in the offspring and the pending review of the positive control data.

I. COMMENTS:

- This supplemental data evaluation record (DER) is only for the purpose of correcting an error in the previous DER (TXR # 0052434). The maternal systemic NOAEL was incorrectly given in the executive summary and in the Reviewer's Comments section. This revised executive summary replaces the previous one. The Study Deficiencies section and Appendix remain unchanged but are included for the convenience of the user.

- Although the LOAEL in the range-finding study (MRID 45842601) is 30 ppm, there is more confidence in the results of the definitive study (MRID 46195601) which resulted in a NOAEL of 300 ppm.

    - The N in the definitive study is larger, 27 vs 10 rats/dose.
    - There were no statistically significant effects (other than ChE inhibition) in the definitive study.
    - Maternal ChE was not measured in the range-finding study.

II. STUDY DEFICIENCIES: Dams with whole litter loss should have been included in calculations of some reproductive parameters. There was no information regarding the conditions of the open arena observations.

APPENDIX

STUDY TYPE: Developmental Neurotoxicity Study - Rat
[OPPTS 870.6300 (§83-6)] OECD 426

PC CODE: 057801

TEST MATERIAL (PURITY): Diazinon Technical (94.2%)

SYNONYMS: 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether

CITATION: Mandella, R.C. (2002) Diazinon: a dietary range-finding developmental neurotoxicity study in rats. Huntingdon Life Sciences, Mettlers Road, East Millstone, New Jersey. Laboratory study no. 01-4530; November 13, 2002. MRID 45842601. Unpublished.

SPONSOR: Makhteshim-Agan of North America, 551 Fifth Avenue, Suite 1100, New York, NY 10176

EXECUTIVE SUMMARY: In a range-finding developmental neurotoxicity study (MRID 45842601), Diazinon technical (94.2% a.i., batch # 9896144) was administered to 10 female Sprague-Dawley CD® rats/dose in the diet at concentrations of 0, 0.1, 0.5, 50, or 300 ppm from gestation day (GD) 6 through postnatal day (PND) 21. The average daily test article intake during the study was 0, 0.0125, 0.063, 6.56, and 38.06 mg/kg/day. A Functional Operational Battery (FOB) was performed on 5 dams/dose on GDs 7, 14, and 20, and on PNDs 1, 4, 7, 14, and 20. On PND day 4, litters were culled to yield five males and five females (as closely as possible). The FOB was conducted on 8 pups/sex/group on PND 4, 7, 11, 14, 17, and 20. Blood and brain cholinesterase activities were measured in 8 pups/sex/group on PND 4 and 21, in 2 dams/group on PND 5 or 6, and in 8 dams/group on PND 21.

All dams survived to scheduled sacrifice. During gestation, no effects on body weight or body weight gain were noted. During lactation, body weight gain by the 300-ppm dams was decreased by 25-80% of the control level. Food consumption was similar between the treated groups and the control group during gestation and lactation. At 300 ppm treatment-related observations during the maternal FOB included tremors in two animals and absence of pupil response in two animals. Maternal necropsy was unremarkable.

The maternal systemic LOAEL is 300 ppm (38.06 mg/kg/day) based on clinical signs of toxicity and the NOAEL is 50 ppm (6.56 mg/kg/day).

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R158649

Chemical: Diazinon

PC Code:
057801

HED File Code: 11100 Other Chemistry Documents
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