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DATA EVALUATION RECORD – Supplemental
See TXR 0012290, 0012624, 0014415 for the original, supplemental 1, and supplemental 2 DERs

STUDY TYPE: Developmental Neurotoxicity Study [diet] – rats; OCSPP 870.6300 (§83-6); OECD 426.

PC CODE: 129121 **DP BARCODE:** D455516

TEST MATERIAL (PURITY): Fipronil (96.1% a.i.)

SYNONYMS: MB 46030

CITATION: Mandella, R. C. (1995) A Developmental Neurotoxicity Study of Fipronil in the Rat via Dietary Administration. Pharmaco LSR (Huntingdon Life Sciences as of 11/21/95), East Millstone, NJ. Laboratory Report No. 93-4508, December 28, 1995. MRID 44039002. Unpublished

Mandella, R. C., D.E. Rodwell (1998) Historical Control Data in Support of Study No. 93-4508: A Developmental Neurotoxicity Study of Fipronil in the Rat via Dietary Administration. Pharmaco LSR (Huntingdon Life Sciences as of 11/21/95), East Millstone, NJ. Laboratory Report No. 93-4508, 27-FEB-1998, MRID 44501102. Unpublished

Bieler, G.S. (1998) Analysis of Mean Pup Body Weights for the Fipronil Neurotoxicology Study. Research Triangle Institute, RTP, NC, RTI Project Number 6161-3, 26-FEB-1998, MRID 44501103. Unpublished

SPONSOR: Rhone-Poulenc

EXECUTIVE SUMMARY:

In a developmental neurotoxicity study (MRID 44039002, 44501102, 44501103), fipronil (96.1% a.i.) was administered to 30 female Sprague-Dawley rats/group in the diet at dose levels of 0, 0.5, 10 or 200 ppm (0, 0.05, 0.90 or 15 mg/kg/day, respectively) from Gestation Day 6 to Lactation Day 10.

There was no evidence of a treatment-related effect on maternal survival or clinical signs of

toxicity. Two females in the 15 mg/kg/day group died during lactation, but there was no evidence that the deaths were treatment-related. Mean maternal body weight values for the 15 mg/kg/day group were reduced 15.5%, 10.0% and 8.6% in comparison to the controls on Gestation Days 10, 15 and 20, respectively. Mean body weight gain was statistically decreased for Gestation Day interval 6-10, but increased for interval 10-15. Statistically significant reductions in mean body weight were seen in the 15 mg/kg/day group on Lactation Days 0 and 4. Mean body weight gain was statistically increased on Lactation Days 4-11. A statistically significant reduction in group mean food consumption was noted in the 15 mg/kg/day group for Gestation Days 6 to 10 but was comparable to the controls for other intervals. Pregnancy rate and gestation length for treated animals were comparable to the control group. There was no evidence of a treatment-related effect on gross necropsy findings. **The maternal LOAEL is 15 mg/kg/day (200 ppm), based on decreased body weight, body weight gain and food consumption. The maternal NOAEL was 0.90 mg/kg/day (10 ppm).**

At 15 mg/kg/day, litter size was not affected by treatment, but the live birth index was decreased (not statistically significant). The pup viability index (survival from Postnatal Days 0-4) for the 15 mg/kg/day group was significantly decreased (98.9% for control vs. 75.5% for 15 mg/kg/day group). The weaning index (survival from Postnatal Days 4-21) was decreased for this group, but the difference was not statistically significant. Pup sex distribution was not affected. There was a statistically significant decrease in group mean body weights of both males and female offspring at all recorded intervals during lactation (9.2-34.1% and 8.1-33.8% decrease in males and females, respectively) and for various periods post-weaning. Statistically significant increases in the mean day of achieving pinna detachment, upper and lower incisor eruption, vaginal patency and preputial separation were noted; however, preputial separation was the only developmental landmark that was delayed long enough (+4.8 days) to be considered adverse. *At 0.90 mg/kg/day* there was a statistical decrease in pup weight and delayed preputial separation; however, neither was considered to be of a magnitude that indicated an adverse response to treatment. *At 0.05 mg/kg/day* there were no treatment related effects. **The developmental toxicity LOAEL is 15 mg/kg/day (200 ppm), based increased pup mortality, decreased pup weight, and a significant increase in time of preputial separation in males. The NOAEL for developmental toxicity is 0.90 mg/kg/day (10 ppm).**

At 15 mg/kg/day auditory startle testing on Postnatal Day 22 demonstrated a statistically significant decrease in the maximum response for males and females. There was no significant difference in the time to maximum response or average response. There were no changes in this parameter on Postnatal Day 60. Swimming direction scores on Day 6 were reduced for the males and females, although only the males were statistically significant. On Day 14, the scores were comparable. Water "Y" maze time trials for learning and memory showed a statistically significant increase in time required to complete the maze for females in Trials 5 and 6 on Day 24. There were no statistically significant differences for either sex on Days 25, 30, 60, 61 or 65. Statistically significant decreases in absolute brain weights for both sexes, compared to control values, were found on Postnatal Days 11 (20% and 11% decrease in males and females, respectively) and 60 (≈ 7% decrease in males and females). Terminal body weights were also decreased for this group on these days. On Day 11, the relative brain weights for both sexes were significantly increased in comparison to the controls. On Day 60, the values for the control and 15 mg/kg/day groups were comparable. There was no evidence of a treatment-related effect

on the gross macroscopic or microscopic examinations (including the central and peripheral nervous systems) of the pups sacrificed on Postnatal Days 11 and 60. *At doses ≤0.90 mg/kg/day* there were no treatment related developmental neurotoxicity effects. **The developmental neurotoxicity LOAEL is 15 mg/kg/day (200 ppm) based on: decreased maximum auditory startle response; reduced direction scores and group mean angle measurements in swimming evaluations; increased time to complete water "Y" maze time trials; and decreased absolute brain weights. The NOAEL for developmental neurotoxicity is 0.90 mg/kg/day (10 ppm).**

The developmental neurotoxicity study in the rat is classified **Acceptable/Guideline** and **does satisfy** the guideline requirement for a developmental neurotoxicity study (OCSPP 870.6300) in the rat.

COMMENTS: The Executive Summary was revised to update the offspring NOAEL/LOAEL. Previously, the developmental NOAEL and LOAEL were set at 0.05 mg/kg/day and 0.90 mg/kg/day, respectively, based on a marginal but statistically significant decrease in pup body weight and a significant increase in time of preputial separation. After further review of these findings, it was determined that neither the pup body weight decreases nor the increased time to preputial separation were adverse at 0.90 mg/kg/day. Although statistically significant, the pup body weight decrements (3-9%) in the 0.90 mg/kg/day treatment group were within the coefficient of variation of the controls (10%) at all time points for both sexes. In addition, rat pup weight decrements were not observed in the 2-generation reproduction (MRID 42918647) study or comparative thyroid assay (CTA; MRID 50815201) at similar or slightly higher dose levels (2.5 mg/kg/day and 1.0-3.0 mg/kg/day, respectively) and the absolute pup weights for the 0.90 mg/kg/day group were within the range of the historical controls that were reported for multi-generation reproduction studies conducted at the performing lab. Consequently, the pup body weight decreases at 0.90 mg/kg/day were not considered adverse. Likewise, the delay in preputial separation was slight at this dose level (+1.4 days) and was not considered evidence of an adverse response to treatment. At 15 mg/kg/day, the pup weight decreases (8-34%) and increased time to preputial separation (+4.8 days) were significant, substantial, and, in the case of the pup body weight, outside of the provided historical control ranges after PND 0. Although time to preputial separation was within the historical control range (39.0-49.7 days) from the performing lab, the nearly 5-day delay compared to concurrent controls was considered evidence of an adverse response to treatment. In addition, a substantial increase in mortality and multiple neurotoxicity effects were observed in offspring (Note: the neurotoxicity effects are captured in the developmental neurotoxicity LOAEL) in the 15 mg/kg/day treatment group. The developmental NOAEL and LOAEL were thus updated to 0.90 mg/kg/day and 15 mg/kg/day, respectively, based on the increased pup mortality, decreased pup weight, and increased time to preputial separation. The maternal and developmental neurotoxicity NOAEL/LOAELs were not updated.

In addition to revising the NOAEL/LOAEL, the pup body weight (Table 1) and developmental hallmarks (Table 2) tables from the original DER were updated to include historical control data. Those tables are included below.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

Table 1: Mean Pup Weights(±SD)During Lactation (g)[a]

	Fipronil Treatment Level (mg/kg/day)				Historical Control Mean (Range) (MRID 44501102)[c]
	0	**0.05**	**0.90**	**15**	
Males					
Day 0	6.5±0.5	6.5±0.4 (100.0)[b]	6.3±0.4 (97.0)	5.9±0.5** (90.8)	6.1 (5.7-6.4)
Day 4 (Pre-cull)	10.7±1.0	10.4±1.0 (97.2)	10.0±1.1* (93.5)	7.7±1.0** (72.0)	9.3 (8.6-10.5)
Day 4 (Post-cull)	10.7±1.1	10.3±1.0 (96.3)	10.0±1.1* (93.5)	7.8±0.9** (72.9)	NR
Day 11	27.4±3.0	26.1±2.8 (95.3)	25.6±3.3 (93.4)	18.0±3.6** (65.7)	NR
Day 17	41.7±3.7	41.2±4.5 (98.8)	38.9±5.1* (93.3)	31.3±3.6** (75.1)	NR
Day 21	53.9±5.2	52.1±6.8 (96.7)	50.4±6.3 (93.5)	41.3±4.6** (76.6)	48.2 (42.9-54.1)
Females					
Day 0	6.2±0.5	6.1±0.3 (98.4)	5.9±0.3* (95.2)	5.7±0.5** (91.9)	6.1 (5.7-6.4)
Day 4 (Pre-cull)	10.3±0.9	9.7±1.0 (94.2)	9.4±1.1** (91.3)	7.5±0.8** (72.8)	9.3 (8.6-10.5)
Day 4 (Post-cull)	10.3±1.0	9.7±1.0* (94.2)	9.4±1.1** (91.3)	7.5±0.8** (72.8)	NR
Day 11	26.3±2.3	24.9±3.0 (94.7)	24.3±3.1* (92.4)	17.4±3.2** (66.2)	NR
Day 17	40.3±3.0	39.2±4.7 (97.3)	36.7±4.9** (91.1)	29.5±4.6** (73.2)	NR
Day 21	51.6±4.3	49.4±6.3 (95.7)	47.8±6.2* (92.6)	38.5±6.3** (74.6)	48.2 (42.9-54.1)

a Extracted from Table 9 (pages 73 and 74) of the study report.
b Percentage of control value, calculated by reviewer
c Historical control data reported in addendum to the DNT. Based on 12 multi-generation reproduction studies conducted between 1989 and 1995 at Huntingdon Life Sciences.
NR = not reported
* Statistically different from controls, $p<0.05$
** Statistically different from controls, $p<0.01$

Table 2: Developmental Landmark Data[a]

Observation (Mean Day to Criteria)	Treatment Levels (mg/kg/day)				**Historical Control Mean (Range for all Litters)** (MRID 44501102)[bcd]
	0	0.05	0.90	15	
Pinna Detachment	2.5±0.6	2.6±0.6[@@]	2.5±0.6	3.0±0.6**	2.6 (1.3-4.0)
Upper Incisor Eruption	10.3±0.9	10.5±0.9[@@]	10.4±1.0	10.9±1.2**	9.9 (8.5-12.3)
Lower Incisor Eruption	11.4±0.9	11.6±0.9[@@]	11.4±0.9	12.1±0.9**	11.2 (9.3-12.7)
Eye Opening	13.9±0.6	13.9±0.7	13.8±0.7	14.0±0.7	13.8 (13.0-15.1)
Vaginal Patency	31.4±1.1	32.0±1.4[0]	31.6±1.3	32.9±1.7[00]	31.9 (29.3-34.3)
Preputial Separation	44.0±2.5	44.7±2.5	45.4±2.9[00]	48.8±3.3[00]	43.8 (39-49.7)

a Data extracted from revised Table 12 (page 82) of the study report.
b Historical control data for pinna detachment, upper/lower incisor eruption, and eye opening reported in Appendix U of the DNT study report. Based on 2 developmental neurotoxicity studies (14-23 litters/study) conducted at Huntingdon Life Sciences (formerly Pharmaco LSR). Date of the study was not reported.
c Historical control data for vaginal patency reported in Appendix U of the DNT study report. Based on 1 developmental neurotoxicity study (23 litters) conducted at Huntingdon Life Sciences (formerly Pharmaco LSR). Date of the study was not reported.
d Historical control data for preputial separation reported in addendum to the DNT and in Appendix U of the DNT study report. Based on 3 developmental dietary studies (number of litters not reported for all studies) conducted between 1993-1998 at Huntingdon Life Sciences.
NR = not reported
** $p<0.005$ by logit regression and multivariate profile analysis
[@@] $p<0.01$ by logit regression
[00] $p<0.01$ by Cox regression
[0] $p<0.065$ by Cox regression