

APPENDIX 12

RESULTS OF REPRODUCTIVE TOXICITY STUDIES WITH OMETHOATE

Standard reproductive toxicity studies in omethoate

EPA and PMRA have also evaluated the available data related to pup survival from two reproductive toxicity studies in omethoate. The purpose of this evaluation is to further characterize available pup mortality/survival data and related ChE inhibition in pup/offspring and/or maternal animals. Two omethoate reproductive toxicity studies are available; one administered in the feed and one administered in drinking water. The following tables (1 & 2) provide viability and lactation indices and, when available, side by side comparison of brain ChE inhibition.

A drinking water study (Tables 1 & 2) found pup mortality at the highest dose tested (1 mg/kg/day), most notably in the second generation. In a feeding study conducted at doses up to 0.5 mg/kg/day of omethoate, small increases in pup mortality were noted in the second generation (note: significant deficiencies were noted in the study protocol of the feeding study). In studies with omethoate, the dose-response for maternal ChE inhibition appears more steep than that of the pups—i.e., maternal animals exhibited higher levels of brain ChE inhibition.

Table 1. Comparison of results from omethoate reproductive toxicity studies. F ₁ Generation									
Omethoate Feeding (MRID 46195301)					Omethoate Drinking water (MRID 45806201)				
F ₁ Generation									
Dose	Index	Breeding F _{1A}	Breeding F _{1B}	Brain Cholinesterase Inhibition	Dose ^b	Index	Breeding F _{1A}	Brain Cholinesterase Inhibition (μmol-SH/mL) ^a	
								Parental	F ₁ Pups LD 21
Control	Viability	81.7 ± 2.6	91.2 ± 2.0	NA: Not measured in feeding study	Control	Viability	98.0	4.11 ± 0.32 F 4.61 ± 0.25 M	6.33 ± 0.45 F 6.05 ± 0.67 M
	Lactation	95.3 ± 1.7	97.1 ± 1.4			Lactation	100		
1 ppm	Viability	93.2 ± 1.8**	93.7 ± 1.8		0.5 ppm (0.04 mg/kg/day)	Viability	99.0	4.00 ± 0.23 F	6.30 ± 0.57 F

Table 1. Comparison of results from omethoate reproductive toxicity studies. F₁ Generation

Omethoate Feeding (MRID 46195301)				Omethoate Drinking water (MRID 45806201)					
(0.05 mg/kg/day)	Lactation	95.7 ± 1.6	98.6 ± 1.0		Lactation	100	4.56 ± 0.51 M	5.92 ± 0.74 M	
3 ppm (0.15 mg/kg/day)	Viability	89.1 ± 2.1*	93.7 ± 1.8		3 ppm (0.23 mg/kg/day)	Viability	97.1	3.26** ± 0.13 (21) ^a F 3.80** ± 0.24 (18) M	6.33 ± 0.53 F 6.25 ± 0.52 M
	Lactation	93.4 ± 1.9	97.2 ± 1.4			Lactation	97.9		
10 ppm (0.5 mg/kg/day)	Viability	87.8 ± 2.4	96.5 ± 1.5		18 ppm (1.2 mg/kg/day)	Viability	95.9	2.70** ± 0.18 (34) F 2.83** ± 0.16 (39) M	5.56** ± 0.56 (12) F 5.80 ± 0.45 M
	Lactation	91.3 ± 2.3	96.7 ± 1.6			Lactation	86.4		

Table 1. Comparison of results from omethoate reproductive toxicity studies. F₁ Generation

Omethoate Feeding (MRID 46195301)	Omethoate Drinking water (MRID 45806201)
<p>* p<0.05, ** p<0.01, *** Dunnett test based on pooled variance. ^aNumber in parentheses is percent inhibition calculated by the reviewer. ^bDose expressed as minima of range for male animals Viability index = No. live pups at birth/No. live pups at day 4 or 5 (pre-cull) × 100 Lactation index = No. live pups on day 4 or 5 (post-cull)/No. live pups day 21 or 28 × 100</p>	

Table 2. Comparison of results from omethoate reproductive toxicity studies. F ₂ and F ₃ Generations										
Omethoate Feeding (MRID 46195301)					Omethoate Drinking water (MRID 45806201)					
F ₂ Generation										
Dose	Index	Breeding F _{2A}	Breeding F _{2B}	Brain Cholinesterase Inhibition	Dose ^b	Index	Breeding F _{2A}	Brain Cholinesterase Inhibition (μmol-SH/mL) ^a		
								Adult	Pups LD 21	
Control	Viability	93.1 ± 1.7	78.6 ± 3.7	NA: Not measured in feeding study	Control	Viability	90.3	6.75 ± 0.55 F	8.08 ± 0.56 F	
	Lactation	92.8 ± 2.0	83.1 ± 4.1			Lactation	98.9	7.55 ± 0.68 M	7.77 ± 0.41 M	
1 ppm (0.05 mg/kg/day)	Viability	94.2 ± 1.5	85.3 ± 2.4		0.5 ppm (0.03 mg/kg/day)	Viability	96.8	5.68** ± 0.54 (16) ^a F	7.67 ± 0.61 F	
	Lactation	90.3 ± 2.2	88.4 ± 2.7			Lactation	98.9	6.84* ± 0.50 (9) M	7.57 ± 0.45 M	
3 ppm (0.15 mg/kg/day)	Viability	80.0 ± 2.6**	64.2 ± 3.4**		3 ppm (0.2 mg/kg/day)	Viability	96.3	4.72** ± 0.48 (30) F	6.86** ± 0.95 (15) F	
	Lactation	90.7 ± 2.4	76.3 ± 4.0			Lactation	100	5.32** ± 0.53 (29) M	7.60 ± 0.69 M	
10 ppm (0.5 mg/kg/day)	Viability	85.6 ± 2.5*	62.5 ± 4.2**		18 ppm (1.06 mg/kg/day)	Viability	84.8	3.04** ± 0.16 (55) F	6.45** ± 0.77 (20) F	
	Lactation	88.2 ± 2.7	67.1 ± 5.4*			Lactation	85.8	3.35** ± 0.60 (56) M	6.44** ± 0.74 (17) M	
F ₃ Generation										
Dose	Index	Breeding F _{3A}	Breeding F _{3B}		Brain Cholinesterase Inhibition	Dose ^b	Index	Breeding F _{3A}	Brain Cholinesterase Inhibition (μmol-SH/mL) ^a	
									Adults	Pups
Control	Viability	95.7 ± 1.9	94.0 ± 1.9		NA: Not measured in feeding study	NA: Only 2 generations in drinking water study.				
	Lactation	97.9 ± 1.5	96.3 ± 1.6							
1 ppm (0.05 mg/kg/day)	Viability	94.1 ± 1.6	97.6 ± 1.1							
	Lactation	91.8 ± 2.1	98.2 ± 1.0							
3 ppm (0.15 mg/kg/day)	Viability	94.5 ± 1.6	97.2 ± 1.4							
	Lactation	91.3 ± 2.3	86.7 ± 3.1*							
10 ppm (0.5 mg/kg/day)	Viability	93.3 ± 1.9	92.5 ± 2.0							
	Lactation	82.7 ± 3.3**	92.6 ± 2.2							

* p<0.05, ** p<0.01,
^a Number in parentheses is percent inhibition calculated by the reviewer.
^b Dose expressed as minima of range for male animals
Viability index = No. live pups at birth/No. live pups at day 4 or 5 (pre-cull) × 100
Lactation index = No. live pups on day 4 or 5 (post-cull)/No. live pups day 21 or 28 × 100