

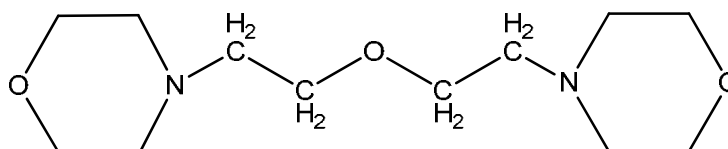
Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test(OECD TG422) -Data Sheet-

Japan Bioassay Research Center
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The data sheet was reviewed and created by Hazard-Data Evaluation Committee of National Institute of Technology and Evaluation in fiscal year 2011 based on the study report obtained by Ministry of Economy, Trade and Industry.

Test substance

MITI No.	: 5-6265
CAS No.	: 6425-39-4
Chemical name	: Bis(2-morpholinoethyl)ether
Synonym	: 4,4'-(3-oxapentane-1,5-diyl)bismorpholine
Molecular weight	: 244.33
Molecular formula	: C ₁₂ H ₂₄ N ₂ O ₃
Structural formula	:



Appearance	: Colorless transparent liquid
Solubility	: Soluble in water
Purity	: 94.8%

Experimental Method

Test animals	: CrI:CD (SD) male and female rats, 10 weeks old (initiation of dosing)
Number of animals	: M; 7 rats/group (control and high dose groups of main study) +5 rats/group (control and high dose groups of recovery). 12 rats/group (low and middle dose groups of main study). F; 12 rats/group (all groups of main study) + 5 rats/group (control and high dose groups of recovery).(RF)
Dosing period	: M; 42days F; 42-48 days (from 14 days before mating to day 4 of lactation)
Administration	: Oral gavage
Vehicle	: Water for injection (dissolved)
Dosing volume	: 5 mL/kg
Dose level	: 0, 30, 100, 300 mg/kg/day

Rationale for selection of dosage: In the 14 days range finding study dosed at 0, 100, 300, 600, 1000 mg/kg/day, following findings were noticed.

1000: death or killed in extremis (5/5; MF), abnormal respiration, increase in irritability of touch response, edema of limbs, edema/reddish change in lung, exudates in thoracic cavity (MF)

600: death or killed in extremis (5/5; MF), abnormal respiration, increase in irritability of touch response, edema of limbs, edema/reddish change in lung, exudates in thoracic cavity (MF)

300: generalized reddening, suppression of body weight gain, decrease in food consumption, decrease in absolute spleen weight, increase in absolute kidney weight (F), decrease in leukocyte count (MF)

100: there were no abnormal changes (MF).

Results

dose (mg/kg/day)	30	100	300
Repeated dose toxicity			
mortality	MF: 0/12	MF: 0/12	M: 1/12(day10), F: 1/12 (day 41,under parturition)
Clinical signs	NE	NE	Flash of skin, edema of limbs, a lot of spilled food(MF), stooping position, piloerection, irregular respiration, loss of fur, erythema/ purpura/ crust formation of tail and/or pinnae (F)
FOB	NEW	Locomotor activity↓(M)	Irritability of touch response↑, locomotor activity↓ (M, RF),
Body weight	NE	NE	Weeks 1: ↓ (MF) , Dosing period: ↓ (MF)
Food consumption	NE	Week 1:↓(M)	Week 1:↓(MF) Recovery Period:↑(MF)
Urinalysis (M)	NE	NE	NE
Hematology	NE	Eosinophil %↓(F)	Neutrophil %↑, eosinophil %↓(MF), lymphocyte %↓(M tendency,F), Hgb↓, PT↓, APTT↓(M), WBC↓, RET%↓, monocyte %↑(F)
Blood chemistry	NE	NE	Alb↓, A/G↓, (F)
Organ weight	NE	Kidney R ↑, liver R↑(F)	Kidney A,R↑, Lung R↑(MF), testis R↑(M),liver R↑, spleen A↓,brain R↑(F)

Necropsy	NE	NE	<u>Dead</u> (M1, F1) edema/reddening of lung enlargement of kidney(M), no abnormality(F) <u>survival</u> whitish patch in the lung, enlargement of kidney, scab at tail(F), no abnormality(M)
Histopathology	NE	NE	<u>Dead</u> edema/congestion/perivascular edema in the lung(MF), vacuolation of epididymal duct epithelium (M), vacuolation of renal distal tubule, vacuolation of blood vessel at tail subcutis (F) <u>Survival</u> Kidney; vacuolation of distal tubule (M7/7,F11/11) Tail; vacuolation of blood vessel of subcutis (M6/7,F10/11), hemorrhage (F1/11)/scab(F1/11)/muscle atrophy(F2/11) Epididymis: vacuolation of epididymal duct epithelium (M5/7) Lung; edema (F1/11), perivascular edema (F1/11)、accumulation of formy cell (F6/11), thickening of alveolar wall (F6/11)
Target organ	Peripheral blood vessel(tail, pinnae), kidney, lung, epididymal duct epithelium		
NOAEL	M: 30 mg/kg/day F: 100 mg/kg/day ¹⁾		
Reason for NOAEL	M100: decrease in locomotor activity F300: found dead, vacuolation of blood vessel of tail subcutis, vacuolation of renal distal tubule, accumulation of formy cell in lung, etc.		

NOEL	M: 30 mg/kg/day F: 30 mg/kg/day		
Reason for NOEL	M100: decrease in locomotor activity F100: kidney R↑, liver R↑		
Reproductive and developmental toxicity			
dose(mg/kg/day)	30	100	300
Parent	NE	NE	Prolonged estrus cycle
offspring	NE	NE	NE
NOAEL	100 mg/kg/day		
Reason for NOAEL	Parent 300: Prolonged estrus cycle		
NOEL	100 mg/kg/day		
Reason for NOEL	Maternal 300: Prolonged estrus cycle		

NE; No effect ; increase ; decrease M; male F; female
A; absolute organ weight R; relative organ weight

Note

- 1) Though repeated dose toxicity NOAEL of female was described to be 30 mg/kg/day based on the increase in relative weights of kidney and liver at 100 mg/kg/day in the summary report, NOAEL was considered to be 100 mg/kg/day, because these organs showed no histopathological changes at this dosage.
- 2) The decrease in serum creatinine was not regarded as the toxic effect, because the mean value of it in the 300 mg/kg/day group was comparable with control.