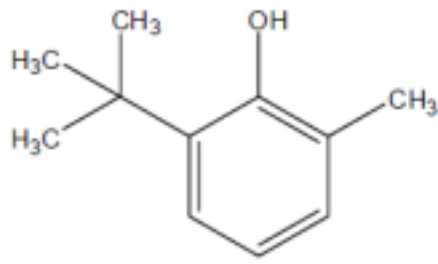


# **Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test(OECD TG422) -Data Sheet-**

MITI No.	3-521		CAS No.	2219-82-1
Test substance	Chemical name	: 2-(1,1-Dimethylethyl)-6-methyl-phenol		
	Synonym	: 6-tert-Butyl-o-cresol 2-tert-Butyl-6-methylphenol		
	Molecular weight	: 164.24		
	Molecular formula	: C <sub>11</sub> H <sub>16</sub> O		
	Structural formula	:		
				
Appearance	White liquid			
Solubility	101.3 mg/L (in water, 25 degC, Calculated value by WSKOW)			
Biodegradation	Non-biodegradable (Official Bulletin of Economy, Trade and Industry dated November 8, 2002)			
Bioconcentration	Low bioconcentration (Official Bulletin of Economy, Trade and Industry dated November 8, 2002)			
Purity	99.8%			
Range finding study	Dose level	0, 40, 200, 1,000 mg/kg/day		
	Dosing period	14 days		
	Results	1,000 (necropsy on Day 3): Death/moribundity (M 2/3 Death, F 3/3 Moribundity), Decrease in locomotor activity, Abnormal gait, Prone position, Lateral position, Lacrimation, Smudge of perinasal ares, Soiled perineal region (M, F), Dark red mottle in the glandular stomach mucosa, Thickening in the glandular stomach wall (M, F), Abnormal contents in the ileum (M, F), Fecal impaction in the cecum (M, F), Distention of the urinary bladder (M, F), Adhesion of the spleen to the stomach (M, F), Distention of the stomach (M, F), Salivation (M, F), Adhesion of the stomach to the liver (M, F), Anemia (M, F) 200: Liver R ↑ (M, F), Thickening in the glandular stomach wall (M, F), Hgb ↓ (M), Hct ↓ (M), Plt ↑ (M), WBC ↓ (M), Soiled perineal region (F), MCHC ↓(F), RET ↑ (F), Heart R ↑ (F) 40: Hgb ↓ (M), Hct ↓ (M), WBC ↓ (M)		
Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test(OECD TG422)				
Experimental Method	Test animals	CrI:CD (SD) male and female rats, 9 weeks old (initiation of dosing)		
	Administration	Oral gavage    Vehicle: 1 w/v% Tween 80 solution		
	Dose level	0, 8, 40, 200 mg/kg/day,    Recovery 0, 200 mg/kg/day (R200)		
	Dosing period	M: 42days F: 42 - 50 days (from 14 days before mating to day 4 of lactation)		
Results of Repeated dose toxicity	Clinical signs	F: Abnormal gait (200), Irregular respiration (200)		
	FOB	NE		

	Body weight	M: Body weight ↓(tendency) (200, R200) F: Body weight ↓ (tendency) (200), Body weight on day 4 of lactation ↓ (200)
	Food consumption	NE
	Urinalysis	NE
	Hematology	M: RET ↑ (200), PT ↑ (200), APTT ↑ (200) F: RET ↑ (200, R200), RBC ↓ (200, R200), Hgb ↓ (200), MCHC ↓ (200), MCV ↑ (200, R200), MCH ↑ (200, R200)
	Blood chemistry	M: T-Cho ↑ (200), gamma-GTP ↑ (200), AST ↑ (tendency) (200), ALT ↑ (tendency) (200), TG ↑ (tendency) (200) F: T-Cho ↑ (200)
	Organ weight	M: Liver A,R ↑ (200), Liver R ↑ (40, R200), Spleen R ↑ (R200) F: Liver A,R ↑ (200), Liver A ↑ (40), Spleen A,R ↑ (200)
	Histopathology	M: Centrilobular hypertrophy of hepatocytes in the liver (200), Increase in extramedullary hematopoiesis in the spleen (200, R200), Increase in hemosiderin deposition in the spleen (R200), Hyperplasia of squamous limiting ridge in the forestomach (200), Eosinophil cell infiltration of the glandular stomach (200), Increase in globule leukocyte (200) F: Centrilobular hypertrophy of hepatocytes in the liver (200), Increase in extramedullary hematopoiesis in the spleen (200), Increase in hemosiderin deposition in the spleen (R200)
	Target organ	Liver, Stomach, Erythroid series (including coagulation system)
Results of Reproduction and developmental toxicity	Parent	F 200: Prolonged gestation length
	Offspring	200: Death ↑, Number of live offspring on day 0 ↓ (tendency), Number of live offspring on day 4 ↓ (tendency), Live birth index ↓, Viability index on day 4 ↓
NOAEL		Repeated dose toxicity: M 40, F 40 Reproductive and developmental toxicity: 40
	Basis for NOAEL	Repeated dose toxicity: M, F 200: Effects on the spleen, erythroid series and liver function  Reproductive and developmental toxicity: F <sub>0</sub> F 200: Prolonged gestation length F <sub>1</sub> 200: Number of live offspring on day 0 ↓ (tendency), Number of live offspring on day 4 ↓ (tendency), Live birth index ↓, Viability index on day 4 ↓
NOEL		Repeated dose toxicity: M 8, F 8 Reproductive and developmental toxicity: 40
	Basis for NOEL	Repeated dose toxicity: M 40: Liver R ↑ F 40: Liver A ↑  Reproductive and developmental toxicity: F <sub>0</sub> F 200: Prolonged gestation length F <sub>1</sub> 200: Number of live offspring on day 0 ↓ (tendency), Number of live offspring on day 4 ↓ (tendency), Live birth index ↓, Viability index on day 4 ↓
Note		

↑; increase, ↓; decrease

M; male, F; female

A; absolute organ weight, R; relative organ weight

The data was reviewed by Hazard-Data Evaluation Committee of National Institute of Technology and Evaluation in fiscal 2008.