資料３－１－７

既存化学物質の人健康影響に関する情報（第一種監視化学物質評価関係）

（平成 17 年 11 月 18 日）

Bis(1-methylethyl)naphthalene

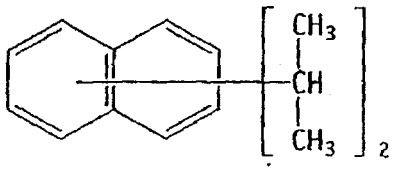
ビス(1-メチルエチル)ナフタレン

[CAS No. 38640-62-9]

Diisopropylnaphthalene

ジイソプロピルナフタレン

Molecular formula: $C_{16}H_{20}$ Molecular weight: 212.33



ABSTRACT

A single oral dose toxicity test in rats revealed an LD_{50} value of more than 2000 mg/kg for bis(1-methylethyl)naphthalene in both sexes.

Bis(1-methylethyl)naphthalene was studied for oral toxicity in rats in a 28-day repeat dose toxicity test at doses of 0, 30, 100, 300, and 1000mg/kg/day. Five of the 12 males and 6 of the 12 females died in the 1000 mg/kg group.

With regard to general signs, adoption of a lateral position, decrease in locomotor activity, abnormal gait, piloerection, and soiled fur were noted in males of the 1000 mg/kg group, and soiled fur was noted in females of the 1000 mg/kg group. Suppression of body weight gain and decreased food consumption were also noted in both sexes of the 1000 mg/kg group.

On hematological examination, the following changes were noted: increases in APTT and PT in males of the 300 mg/kg group; an increase in APTT in females of the 300 mg/kg group; increases in the platelet count, PT, APTT, and fibrinogen concentration and decreases in the red blood cell count and hematocrit in males of the 1000 mg/kg group; and increases in the white blood cell count, APTT, fibrinogen concentration, and neutrophil ratio and a decrease in the lymphocyte ratio in females of the 1000 mg/kg group.

On blood chemical examination, the following changes were noted: increases in total cholesterol in females of the 30 and 100 mg/kg groups; an increase in total bilirubin and a decrease in triglyceride in males of the 300 mg/kg group; increases in total bilirubin and total cholesterol in the females of the 300 mg/kg group; increases in GPT, γ-GTP, total bilirubin, and total cholesterol and a decrease in triglyceride in males of the 1000 mg/kg group; and increases in GPT, γ-GTP, total bilirubin, urea nitrogen, creatinine, total cholesterol, and triglyceride in females of the 1000 mg/kg group.

At necropsy, hypertrophy of the liver was noted in both sexes of the 300 and 1000 mg/kg groups. With regard to organ weights, the following changes were noted: increases in the absolute and relative liver weights in males of the 100, 300, and 1000 mg/kg groups and in females of the 300 and 1000 mg/kg groups; increased relative kidney weights in males of the 1000 mg/kg group; increased absolute and relative kidney weights in females of the 300 and 1000 mg/kg groups; and increased absolute and relative adrenal weights in females of the 1000 mg/kg group.

On histopathological examination, the following changes were noted: centrilobular hypertrophy of hepatocytes in females of the 300 mg/kg group; whole lobular hypertrophy of hepatocytes in males of the 1000 mg/kg group; centrilobular hypertrophy of hepatocytes in both sexes of the 1000 mg/kg group; renal basophilic tubules in males of the 1000 mg/kg group; and neutrophil infiltration in the renal papilla, renal basophililc tubules, and dilatation of renal tubules in females of the 1000 mg/kg group.

Therefore, the NOELs for the 28-day repeat dose oral toxicity are considered to be 30 mg/kg/day for males, and less than 30 mg/kg/day for females.

Bis(1-methylethyl)naphthalene was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 *uvrA*, with or without an exogenous metabolic activation system.

Bis(1-methylethyl)naphthalene induced structural chromosomal aberrations in CHL cells after short-term treatment with an exogenous metabolic activation system.

SUMMARIZED DATA FROM THE STUDIES

1. Single Dose Oral Toxicity [1)]

Purity	:	98.44 %
Test species/strain	:	Rat/Crj:CD(SD)IGS
Test method	:	OECD Test Guideline 401
Route	:	Oral (gavage)
Doses	:	0 (vehicle), 500, 1000, 2000 mg/kg/day
Number of animals/group	:	Males, 5; females, 5
Vehicle	:	Corn oil
GLP	:	Yes

Test results:

No deaths occurred in any group.

Based on the above results, the LD_{50} value of bis (1-methylethyl) naphthalene was concluded to be more than 2000 mg/kg for both sexes.

2. Repeat Dose Toxicity [1)]

Purity	:	98.44 %
Test species/strain	:	Rat/Crj:CD(SD)IGS
Test method	:	Guidelines for 28-Day Repeat Dose Toxicity Testing of Chemicals (Japan)
Route	:	Oral (gavage)
Doses	:	0 (vehicle), 30, 100, 300, 1000 mg/kg/day
Number of animals/group	:	Males, 12; females, 12 (0, 1000 mg/kg) Males, 6; females, 6 (30, 100, 300 mg/kg)
Vehicle	:	Corn oil

Administration period : Males and females, 28 days
Terminal kill : Males and females, days 29 or 43
GLP : Yes

Test results:

Five of 12 males and 6 of 12 females died in the 1000 mg/kg group.

In males, increases in absolute and relative liver weights were noted in the 100 mg/kg group. Increases in APTT, PT, and total bilirubin, a decrease in triglyceride, and increases in the absolute and relative liver weights were noted in the 300 mg/kg group. A lateral position, decrease in locomotor activity, abnormal gait, piloerection, soiled fur, suppression of body weight gain, decreases in platelet count, PT, APTT, fibrinogen concentration, GPT, γ-GTP, total bilirubin, and total cholesterol, decreases in red blood cell count, hematocrit level, and triglyceride, increases in the absolute and relative liver weight and relative kidney weights, whole lobular hypertrophy of hepatocyte, centrilobular hypertrophy of hepatocyte, and renal basophilic tubules were noted in the 1000 mg/kg group.

In females, increases in total cholesterol were noted in the 30 and 100 mg/kg groups. Increases in APTT, total bilirubin, and total cholesterol, the absolute and relative liver and kidney weights, and centrilobular hypertrophy of hepatocyte were noted in the 300 mg/kg groups. Soiled fur, suppression of body weight gain, a decrease in food consumption, increases in the white blood cell count, APTT, fibrinogen concentration, neutrophil ratio, GPT, γ-GTP, total bilirubin, urea nitrogen, creatinine, total cholesterol, and triglyceride, a decrease in the lymphocyte ratio, increases in the absolute and relative liver, kidney, and adrenal weights, centrilobular hypertrophy of hepatocytes, neutrophil infiltration in the renal papilla, and dilatation of renal tubules were noted in the 1000 mg/kg group.

Therefore, the NOELs for the 28-day repeat dose oral toxicity are considered to be 30 mg/kg/day for males, and less than 30 mg/kg/day for females.

3. Genetic Toxicity

3-1. Bacterial test [2)]

Purity : 98.44 %
Test species/strain : *Salmonella typhimurium* TA100, TA1535, TA98, TA1537, *Escherichia coli* WP2 *uvrA*
Test method : Guidelines for Screening Mutagenicity Testing of Chemicals (Japan)
Procedures : Pre-incubation method
Solvent : Acetone
Positive controls : −S9 mix, 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, TA98, WP2 *uvrA*), Sodium azide (TA1535) and 9-Aminoacridine (TA1537)
+S9 mix, 2-Aminoanthracene (all strains)
Doses : −S9 mix; 0, 312.5, 625, 1250, 2500, 5000 μg/plate
+S9 mix; 0, 312.5, 625, 1250, 2500, 5000 μg/plate
S-9 : Rat liver, induced with phenobarbital and 5,6-benzoflavone
Plate/test : 3
Number of replicates : 2
GLP : Yes

Genotoxic effects:

	clastogenicity			polyploidy		
	+	?	-	+	?	-
Without metabolic activation:	[ ]	[ ]	[*]	[ ]	[ ]	[*]
With metabolic activation:	[*]	[ ]	[ ]	[ ]	[ ]	[*]

1) The test was performed by Nihon Bioresearch Inc., Hashima Laboratory, 6-104 Majima, Fukuju-cho, Hashima, Gifu, 501-6251, Japan. Tel +81-58-392-6222 Fax +81-58-392-1284

2) The test were performed by the Research Institute for Animal Science in Biochemistry and Toxicology, 3-7-11 Hashimotodai, Sagamihara-shi, Kanagawa, 229-1132, Japan. Tel +81-42-762-2775 Fax +81-42-762-7979

Administration period	:	Males and females, 28 days
Terminal kill	:	Males and females, days 29 or 43
GLP	:	Yes

Test results:

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In females, increases in total cholesterol were noted in the 30 and 100 mg/kg groups. Increases in APTT, total bilirubin, and total cholesterol, the absolute and relative liver and kidney weights, and centrilobular hypertrophy of hepatocyte were noted in the 300 mg/kg groups. Soiled fur, suppression of body weight gain, a decrease in food consumption, increases in the white blood cell count, APTT, fibrinogen concentration, neutrophil ratio, GPT, γ-GTP, total bilirubin, urea nitrogen, creatinine, total cholesterol, and triglyceride, a decrease in the lymphocyte ratio, increases in the absolute and relative liver, kidney, and adrenal weights, centrilobular hypertrophy of hepatocytes, neutrophil infiltration in the renal papilla, and dilatation of renal tubules were noted in the 1000 mg/kg group.

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Procedures	:	Pre-incubation method
Solvent	:	Acetone
Positive controls	:	-S9 mix, 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, TA98, WP2 *uvrA*), Sodium azide (TA1535) and 9-Aminoacridine (TA1537) +S9 mix, 2-Aminoanthracene (all strains)
Doses	:	-S9 mix; 0, 312.5, 625, 1250, 2500, 5000 μg/plate +S9 mix; 0, 312.5, 625, 1250, 2500, 5000 μg/plate
S-9	:	Rat liver, induced with phenobarbital and 5,6-benzoflavone
Plate/test	:	3
Number of replicates	:	2
GLP	:	Yes