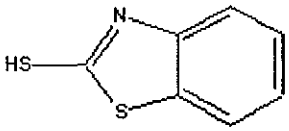
The National Toxicology Program

Abstract for TR-332 2-Mercaptobenzothiazole

TR-332
Toxicology and Carcinogenesis Studies of 2-Mercaptobenzothiazole (CAS No. 149-30-4) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies)



Chemical Formula: $C_7H_5NS_2$ - 3D Structure*

*To view structure, download free Chemscape Chime Plug-in

Toxicology and carcinogenesis studies of technical-grade 2-mercaptobenzothiazole (96%-97% pure), a rubber accelerant and preservative, were conducted by administering the chemical by gavage in a corn oil vehicle to groups of F344/N rats and B6C3F$_1$ mice of each sex for 16 days, 13 weeks, or 2 years. 2-Mercaptobenzothiazole was nominated for study by the National Institute of Environmental Health Sciences and the National Institute for Occupational Safety and Health.

Sixteen-Day and Thirteen-Week Studies:

In 16-day studies, mean body weight gains of rats receiving 2,500 mg/kg were 6-7 g lower than those of vehicle controls; 4/5 male and 5/5 female mice dosed with 3,000 mg/kg and 4/5 female mice dosed with 1,500 mg/kg died; lethargy and prostration occurred in most of these animals after gavage. Based on these results, doses were selected for both species in the 13-week studies were 0, 94 (mice only), 188, 375, 750, and 1,500 mg/kg.

In the 13-week studies, no chemical-related deaths occurred in rats, but body weight gains in males dosed with 1,500 mg/kg and in females dosed with 750 or 1,500 mg/kg were lower than those in the vehicle control groups. Hepatomegaly occurred at the two highest doses in males and at all doses in females; however, no microscopic pathologic changes were noted in any tissue. More than half the mice dosed with 1,500 mg/kg died, but no compound-related body weight changes occurred. Clinical signs in mice were dose related and included lethargy in animals dosed with 375 mg/kg and lacrimation, salivation, and clonic seizure in some dosed with 750 or 1,500 mg/kg. No association between these clinical signs of toxicity and gross or microscopic pathologic effects were observed. Doses selected for the 2-year studies were 0, 375, and 750 mg/kg for male rats and for mice of each sex and 0, 188, or 375 mg/kg for female rats.

Body weight and Survival in the Two-Year Studies:

Fifty animals of each species and sex were administered 2-mercaptobenzothiazole in corn oil by gavage 5 days per week for 103 weeks. Administration of 2-mercaptobenzothiazole resulted in decreased survival in dosed male rats (vehicle control, 42/50; low dose, 22/50; high dose, 20/50) and in the high dose group of female mice (37/50; 39/50; 22/50) but not in female rats (28/50; 31/50; 25/50) or in male mice (38/50; 33/50; 30/50). No effect on body

weight gain in dosed rats was observed; in dosed mice, minor reductions occurred between weeks 3 and 64, withrecovery thereafter. Postgavage lethargy and prostration occurred frequently in dosed rats and mice.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies:

The severity of nephropathy was increased in dosed male rats. Ulcers and inflammation of the forestomach were prevalent in dosed rats, as were increased incidences of epithelial hyperplasia and hyperkeratosis in male rats, but no neoplasms of the forestomach were observed. There were no increases of nonneoplastic lesions in mice which were considered to be compound related.

The incidences of a variety of tumors were increased in rats dosed with 2-mercaptobenzothiazole; some of the increased incidences were not dose related. In low dose male rats, increased incidences ($P<0.01$) were observed for mononuclear cell leukemia (7/50; 16/50; 3/50) and pancreatic acinar cell adenomas (2/50; 13/50; 6/49). Increased tumor incidences with dose-related trends ($P<0.05$) included pituitary gland adenomas in females (15/49; 24/50; 25/50), preputial gland adenomas or carcinomas (combined) in males (1/50; 6/50; 5/50), adrenal gland pheochromocytomas or malignant pheochromocytomas (combined) in males (18/50; 27/50; 24/49), and pheochromocytomas in females (1/50; 5/50; 6/50). These tumors were observed at significantly greater incidences ($P<=0.05$) in the high dose groups than in the vehicle controls.

An increased incidence ($P=0.028$) of hepatocellular adenomas or carcinomas (combined) was observed only in low dose female mice (4/50; 12/49; 4/50). No significant increases in tumor incidences were seen in male mice.

Genetic Toxicology:

2-Mercaptobenzothiazole was not mutagenic in Salmonella typhimurium strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation. In the presence of rat liver S9, 2-mercaptobenzothiazole increased the frequency of chromosomal aberrations and sister chromatid exchanges (SCEs) in Chinese hamster ovary (CHO) cells, as well as mutations at the TK locus of mouse L5178Y lymphoma cells.

Audit:

The data, documents, and pathology materials from the 2-year studies of 2-mercaptobenzothiazole were audited at the NTP Archives. The audit findings show that the conduct of the studies is documented adequately and support the data and results given in this Technical Report.

Conclusions:

Under the conditions of these 2-year gavage studies, there was some evidence of carcinogenic activity of 2-mercaptobenzothiazole for male F344/N rats, indicated by increased incidences of mononuclear cell leukemia, pancreatic acinar cell adenomas, adrenal gland pheochromocytomas, and preputial gland adenomas or carcinomas (combined). There was some evidence of carcinogenic activity for female F344/N rats, indicated by increased incidences of adrenal gland pheochromocytomas and pituitary gland adenomas. There was no evidence of carcinogenic activity of 2-mercaptobenzothiazole for male$B6C3F_1$ mice dosed with 375 or 750 mg/kg. There was equivocal evidence of carcinogenic activity for female $B6C3F_1$ mice, indicated by increased incidences of hepatocellular adenomas or carcinomas (combined).

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Levels from TR-332 2-Mercaptobenzo-Thiazole

Target Organs and Levels of Evidence
NTP Technical Report Number 332

Produced from Chemtrack Database 09/19/01

CHEMICAL/ CAS NUMBER	PEER REVIEW DATE	PRIMARY USES	ROUTE/EXPOSURE LEVELS	STUDY LABO
2-MERCAPTOBENZOTHIAZOLE 149-30-4	03/04/87	RUBBER VULCANIZATION ACCELERATOR. SALTS USED AS FUNGICIDE. CORROSION INHIBITOR FOR COPPER IN AQUEOUS SYSTEMS,CUTTING OILS AND PETROLEUM PRODUCTS. ADDITIVE IN EXTREME-PRESSURE GREASES. (TDB)	Gavage FR: 0,188,375, MR&M: 0,375,750 MG/KG/50 PER GROUP	Physiol· Researc Laborat

LEVELS OF EVIDENCE OF CARCINOGENICITY--ORGAN/TISSUE (NEOPLASM):

MR: SOME EVIDENCE	HEMATOPOIETIC SYSTEM: LEUKEMIA 7/50 16/50 3/50
	PANCREAS ACINAR CELL: ADENOMA 2/50 13/50 6/50
	ADRENAL GLAND MEDULLA: PHEOCHROMOCYTOMA 18/50 25/50 22/49 OR MALIGNANT PHEOCHROMOCYTOMA 0/50 2/50 2/49 COMBINED 18/50 27/50 24/49
	PREPUTIAL GLAND: ADENOMA 0/50 4/50 4/50 OR CARCINOMA 1/50 2/50 1/50 COMBINED 1/50 6/50 5/50
FR: SOME EVIDENCE	ADRENAL GLAND MEDULLA: PHEOCHROMOCYTOMA 1/50 5/50 6/50
	PITUITARY GLAND: ADENOMA 15/49 24/50 25/50
MM: NO EVIDENCE	
FM: EQUIVOCAL EVIDENCE	LIVER: ADENOMA 3/50 7/49 4/50 OR CARCINOMA 1/50 5/49 0/50 COMBINED 4/50 12/49 4/50